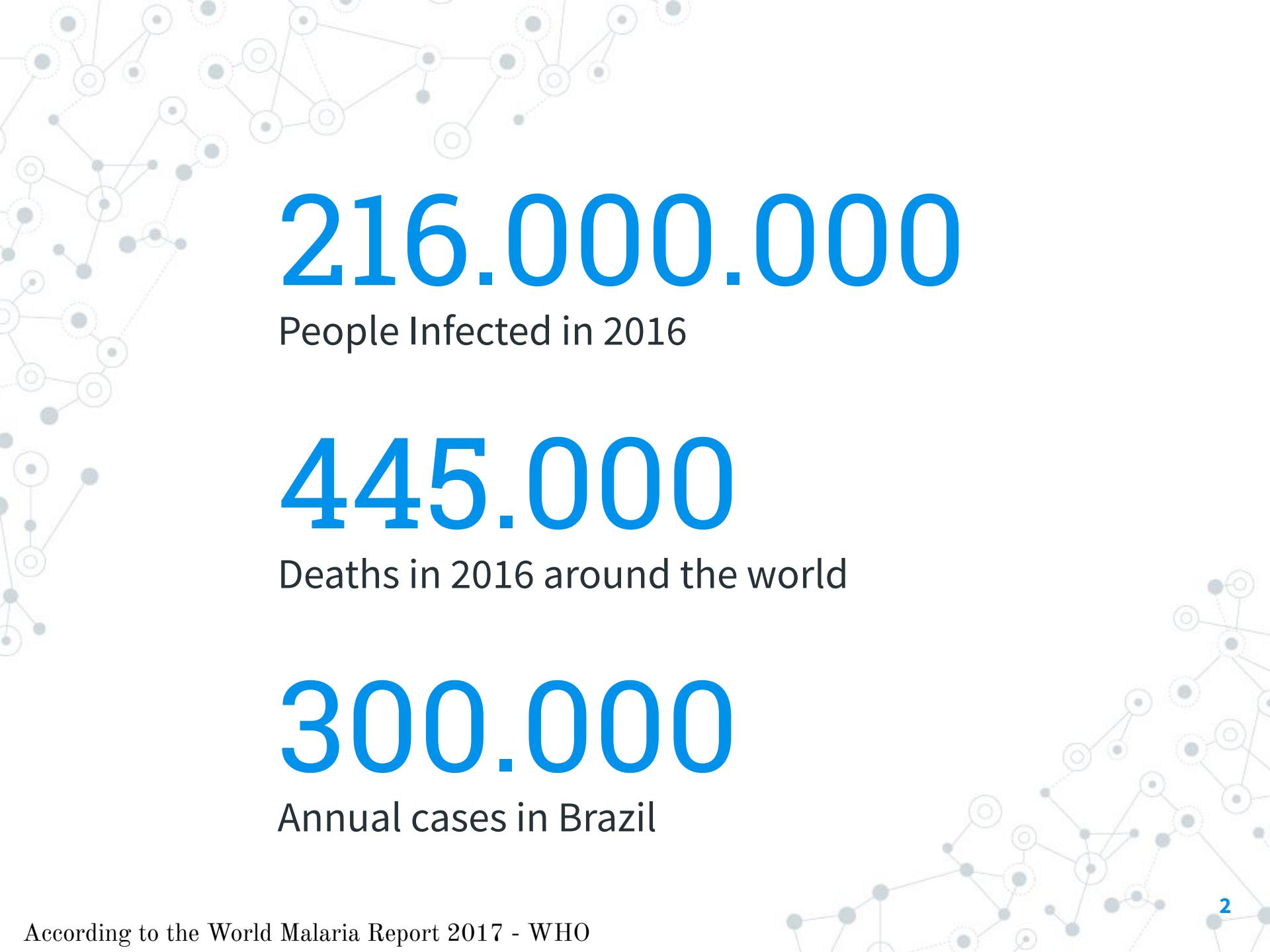


Comparative Analysis of Signaling Pathways Involved in Malaria Infection

Isabelle Franco Moscardini

Supervisor : Helder I. Nakaya

Computational Systems Biology Laboratory
(CSBL)



216.000.000

People Infected in 2016

445.000

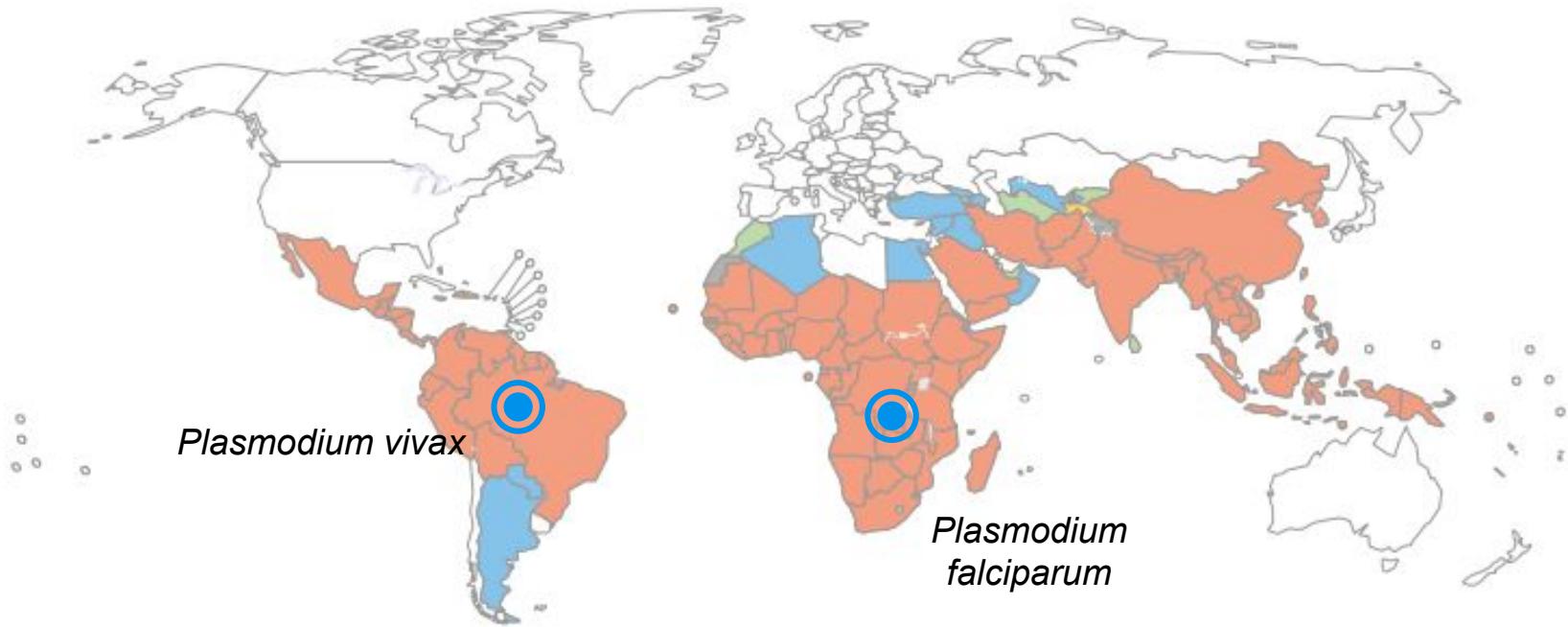
Deaths in 2016 around the world

300.000

Annual cases in Brazil

Malaria in the world

According to the World Malaria Report 2017 - WHO



■ ≥ 1 case

■ 0 cases em 2016

■ 0 cases (> 3 years)

■ "Malaria Free" Certified since 2000

■ Malaria Free

■ Not applicable

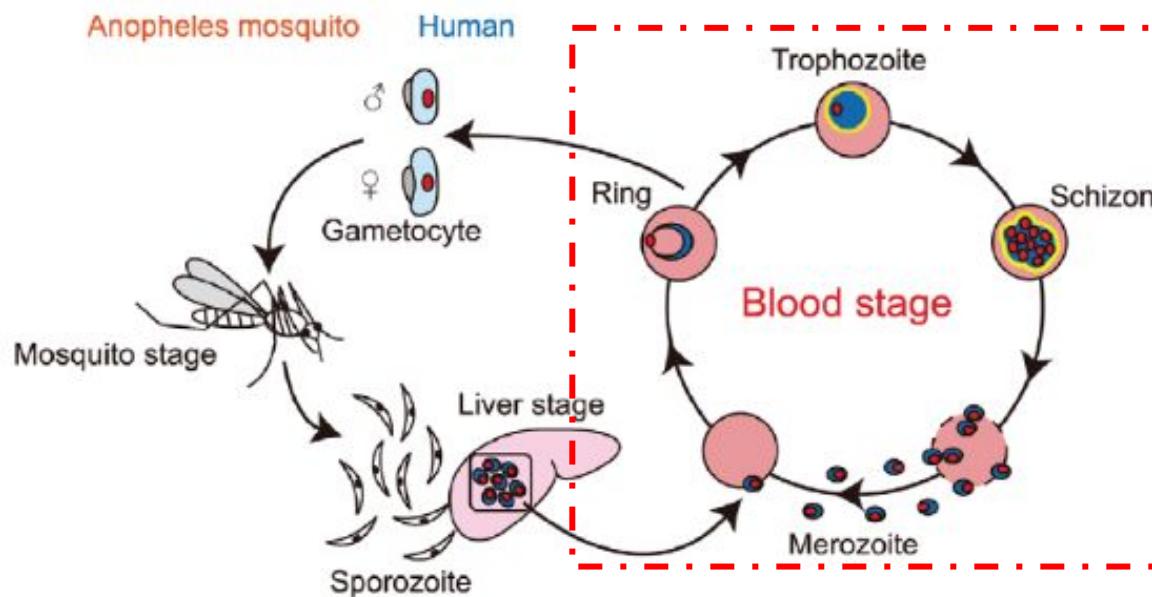
The Infection:

◆ Common symptoms: fever, chills and sweating, joint and muscle pain, headache, among others...

◆ ***Plasmodium falciparum*:** severe infections

◆ Anemia
◆ Hypoglycemia

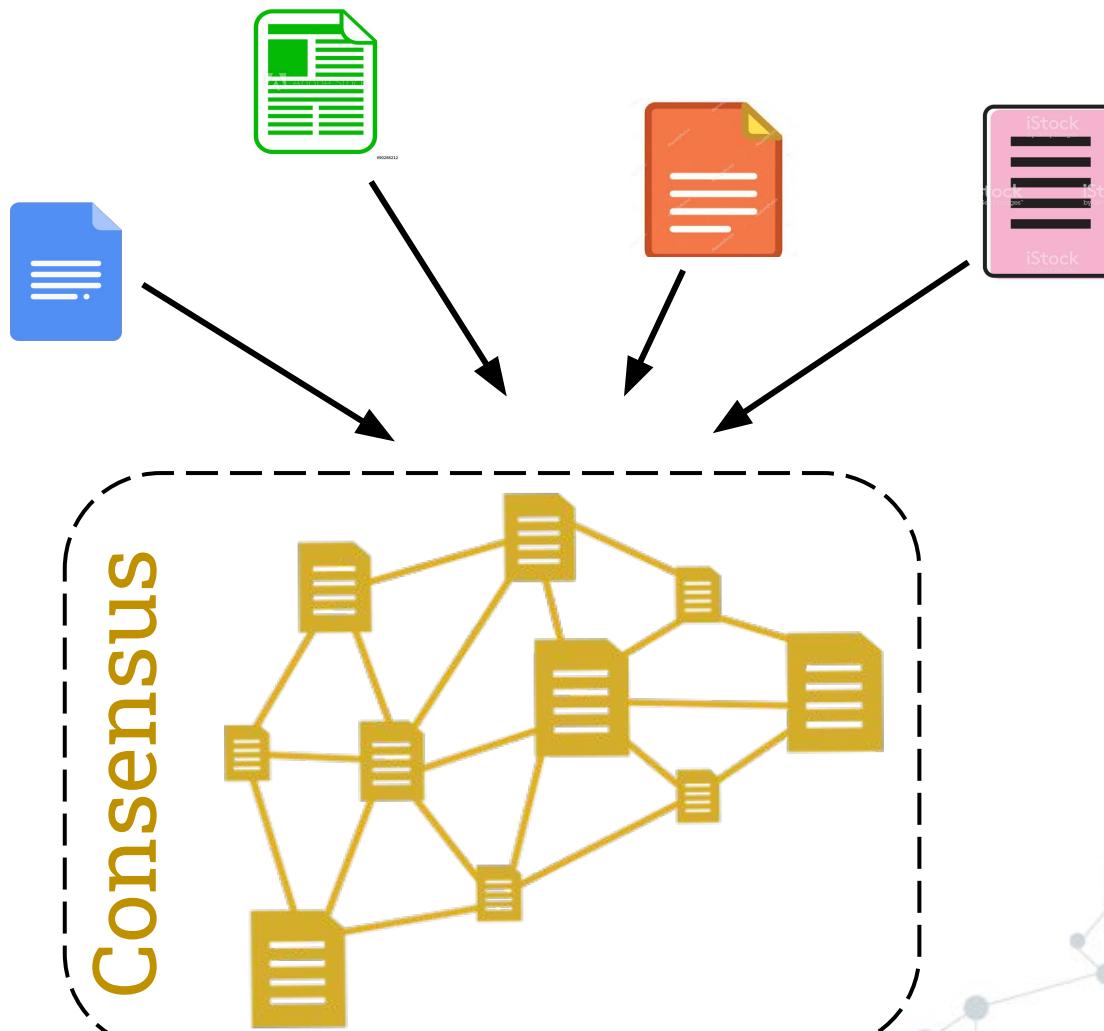
◆ Thrombocytopenia
◆ Metabolic Acidosis

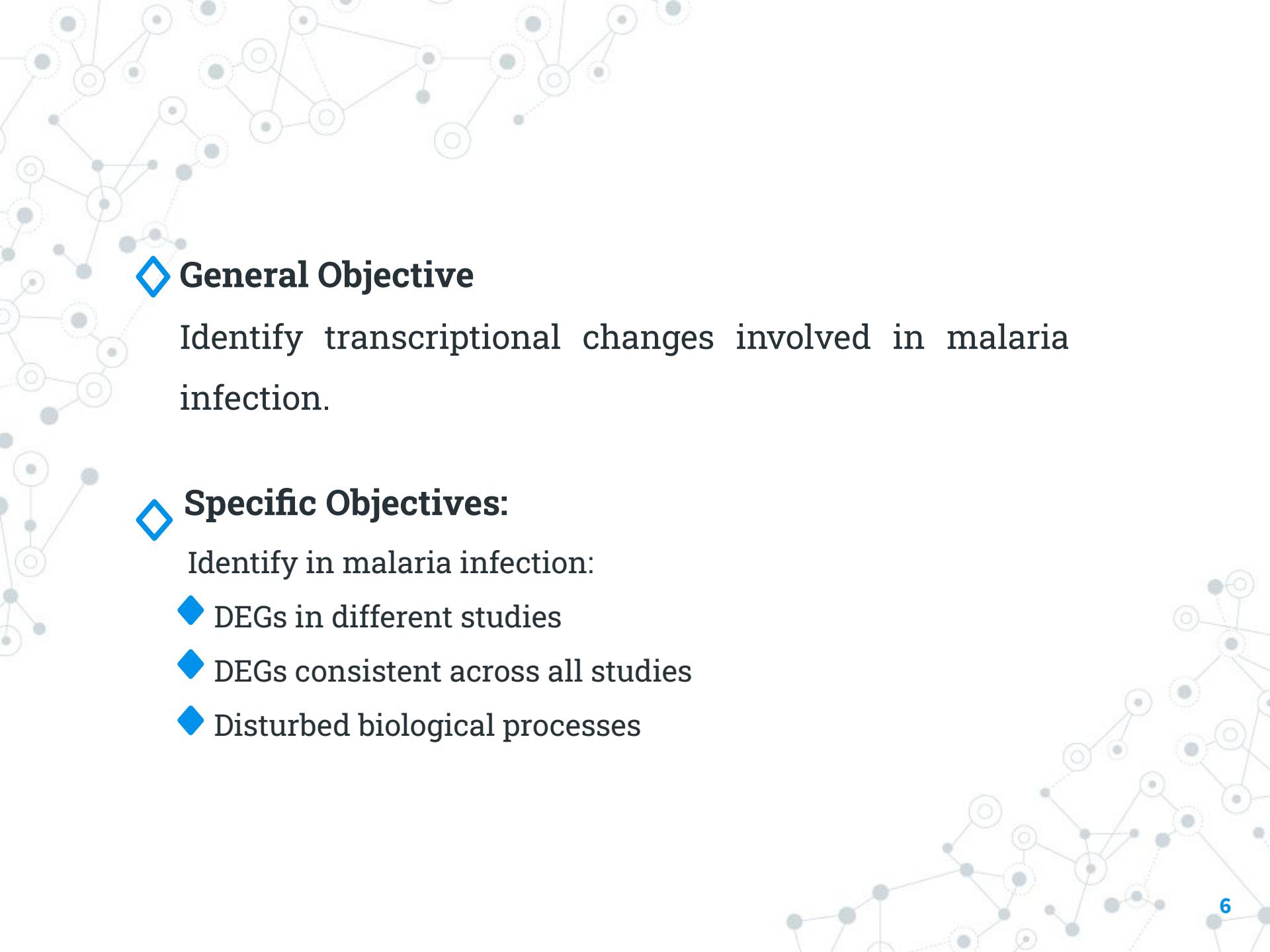


Symptoms

Transcriptomic Studies

microarrays



A faint, light-gray network diagram serves as the background for the entire slide. It consists of numerous small, semi-transparent circular nodes of varying sizes and shades of gray, connected by thin white lines representing edges. This pattern repeats across the entire slide area.

◆ General Objective

Identify transcriptional changes involved in malaria infection.

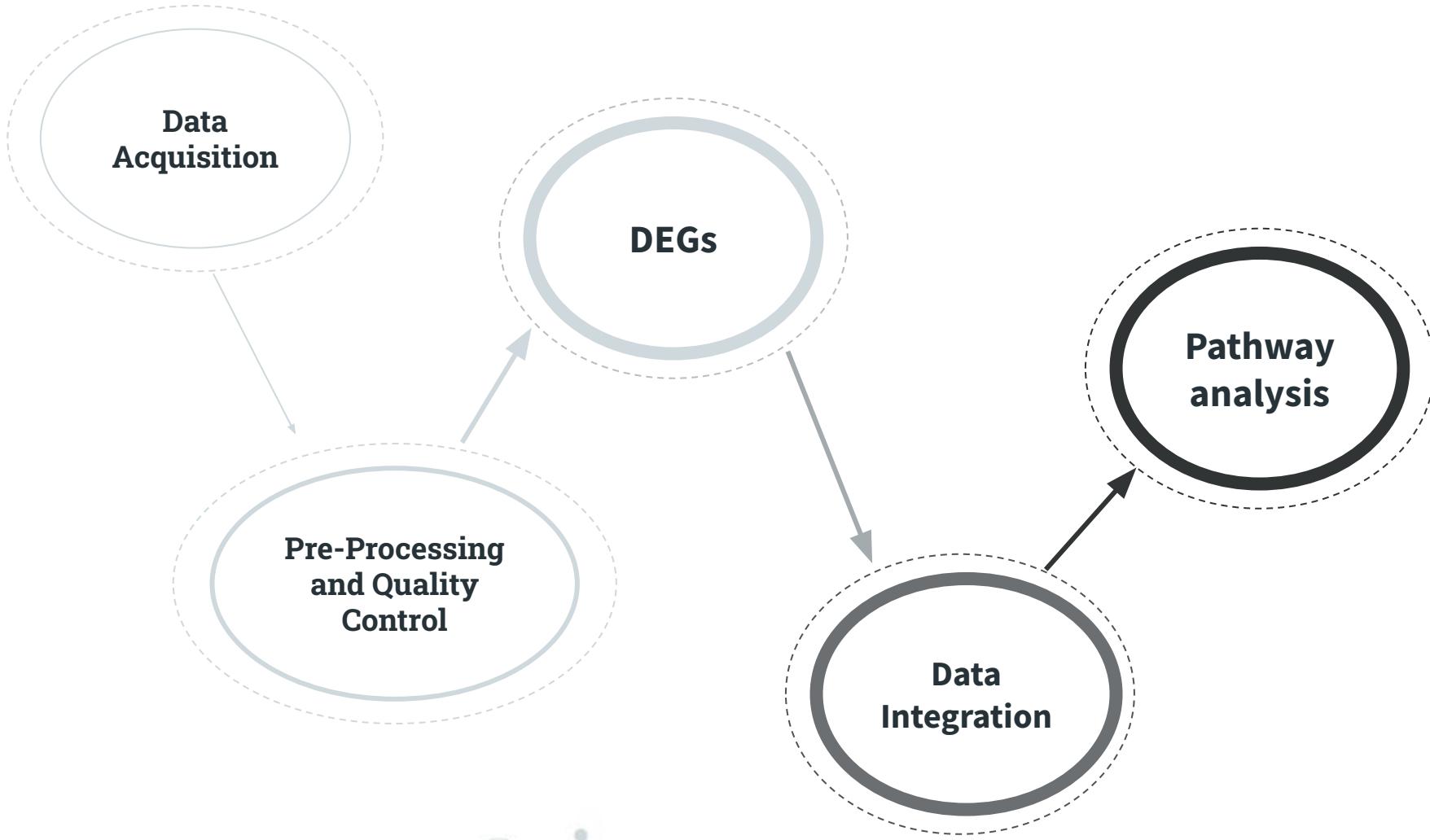
◆ Specific Objectives:

Identify in malaria infection:

- ◆ DEGs in different studies
- ◆ DEGs consistent across all studies
- ◆ Disturbed biological processes

Methods and Results

Process Steps



Selected studies:

From GEO Repository



Ockenhouse e
Vahey, 2006

PBMC

GSE5418

N control

22

N Infected

22 Experimental
15 Acute
12 Treated



Idaghdour Y
et al, 2012

Whole
Blood

GSE34404

62

93 Children



Popper S; 2016

Whole
Blood

GSE35858

8

9 Non Complicated
20 Complicated



Data acquisition

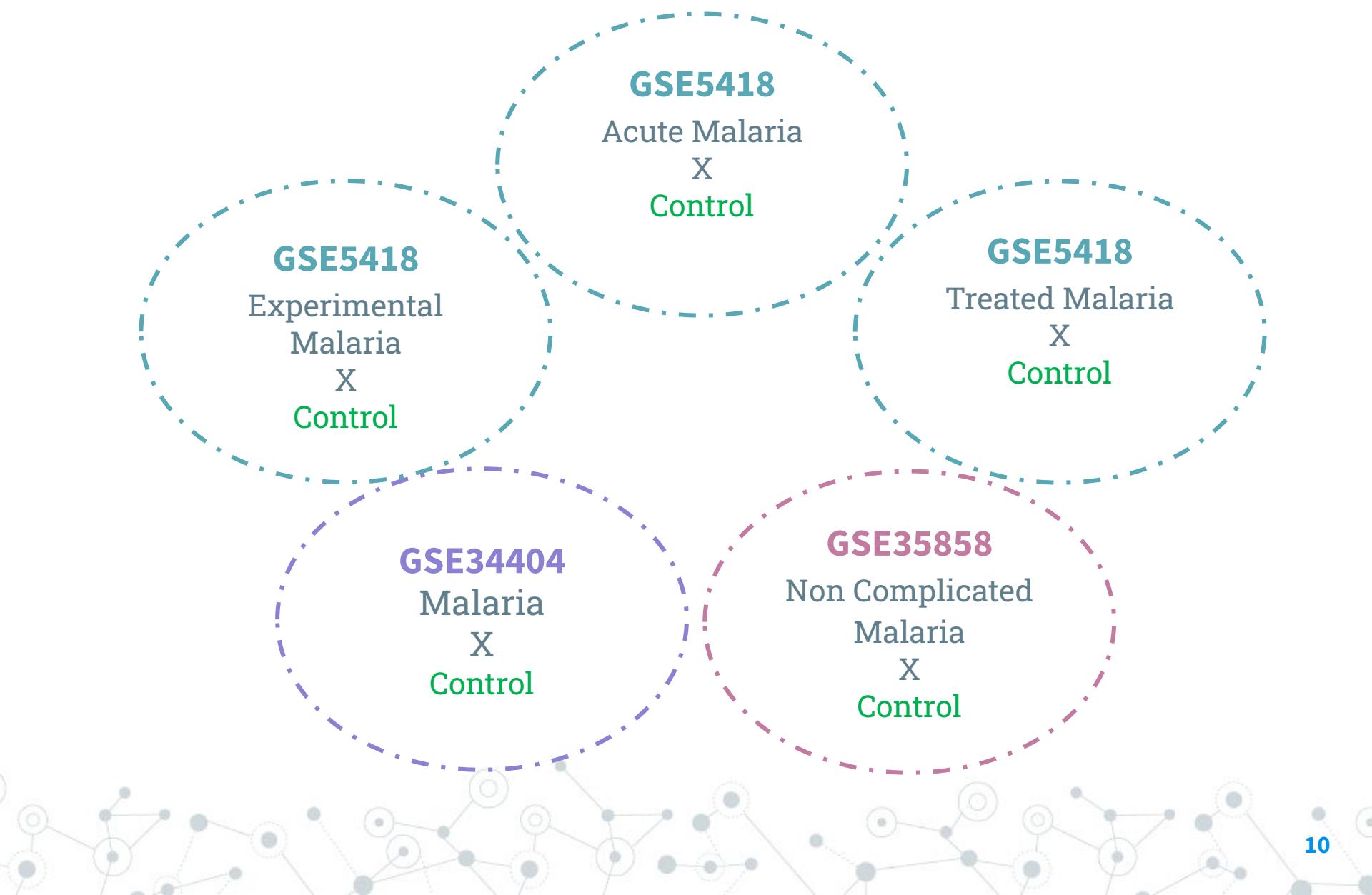
Pre-Processing and
Quality Control

Analysis -
DEGs

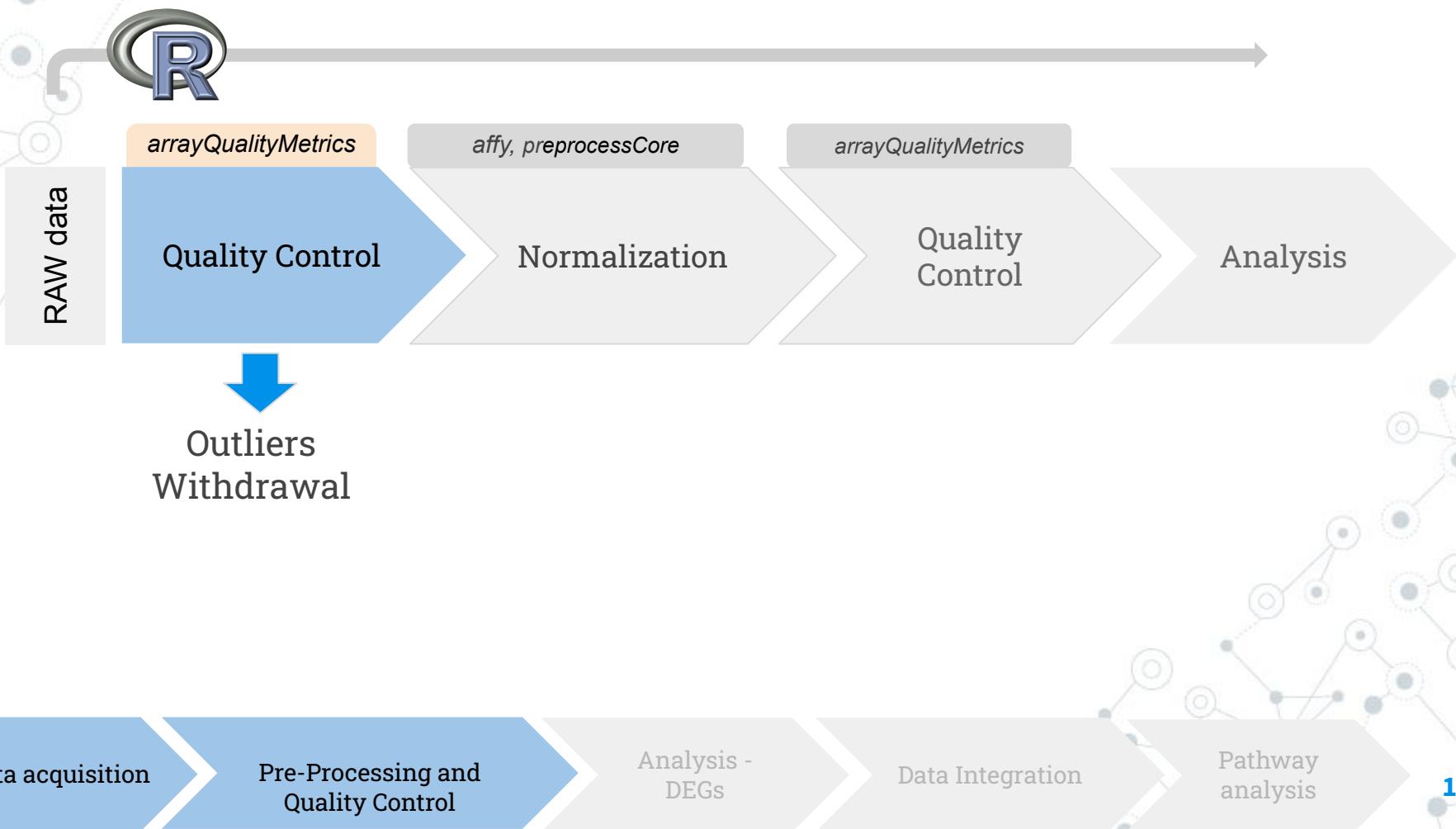
Data Integration

Pathway
analysis

Comparisons:



Pre-Processing and Quality Control:



Pre-Processing and Quality Control:

```
#--- Controle de qualidade dos dados brutos
# o controle de qualidade eh feito com o pacote arrayQualityMetrics
library(arrayQualityMetrics)

# mas para rodar o arrayQualityMetrics eh necessario criar um ExpressionSet, usando o pacote Biobase
library(Biobase)
eset <- ExpressionSet(assayData = as.matrix(expressaoGSE35858)) # criar ExpressionSet

arrayQualityMetrics(eset,outdir = 'Intermediate/Quality_Control/GSE35858/GSE35858_raw',do.logtransform = F,force = T)
# ir la na pasta e ver o arquivo index.html
outlier.raw <- c('GSM876686')

# tirar outlier da tabela de expressao
posicao_outlier <- grep(outlier.raw, colnames(expressaoGSE35858))
expressaoGSE35858 <- expressaoGSE35858[,-posicao_outlier]

#--- Normalizar os dados
library(preprocessCore)
Expressao_normalizada58 <- normalize.quantiles(as.matrix(expressaoGSE35858))
colnames(Expressao_normalizada58) <- colnames(expressaoGSE35858)

# visualizar os dados normalizados
ggplot(melt(Expressao_normalizada58), aes(x = value,colour = Var2)) + geom_density(show.legend = F) + theme_minimal()
boxplot(Expressao_normalizada58)
```

Data acquisition

Pre-Processing and Quality Control

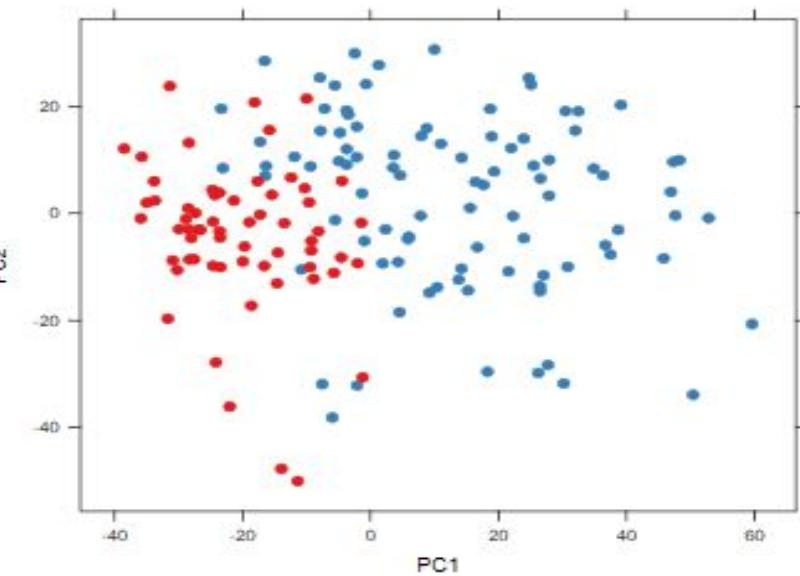
Analysis -
DEGs

Data Integration

Pathway
analysis

Pre-Processing and Quality Control:

GSE34404 Study



Principal Component Analysis

- ◊ The analysis shows the variability between the samples of each study
- ◊ Report generated by `arrayQualityMetrics`

Negatif Test
 Positive Test

Data acquisition

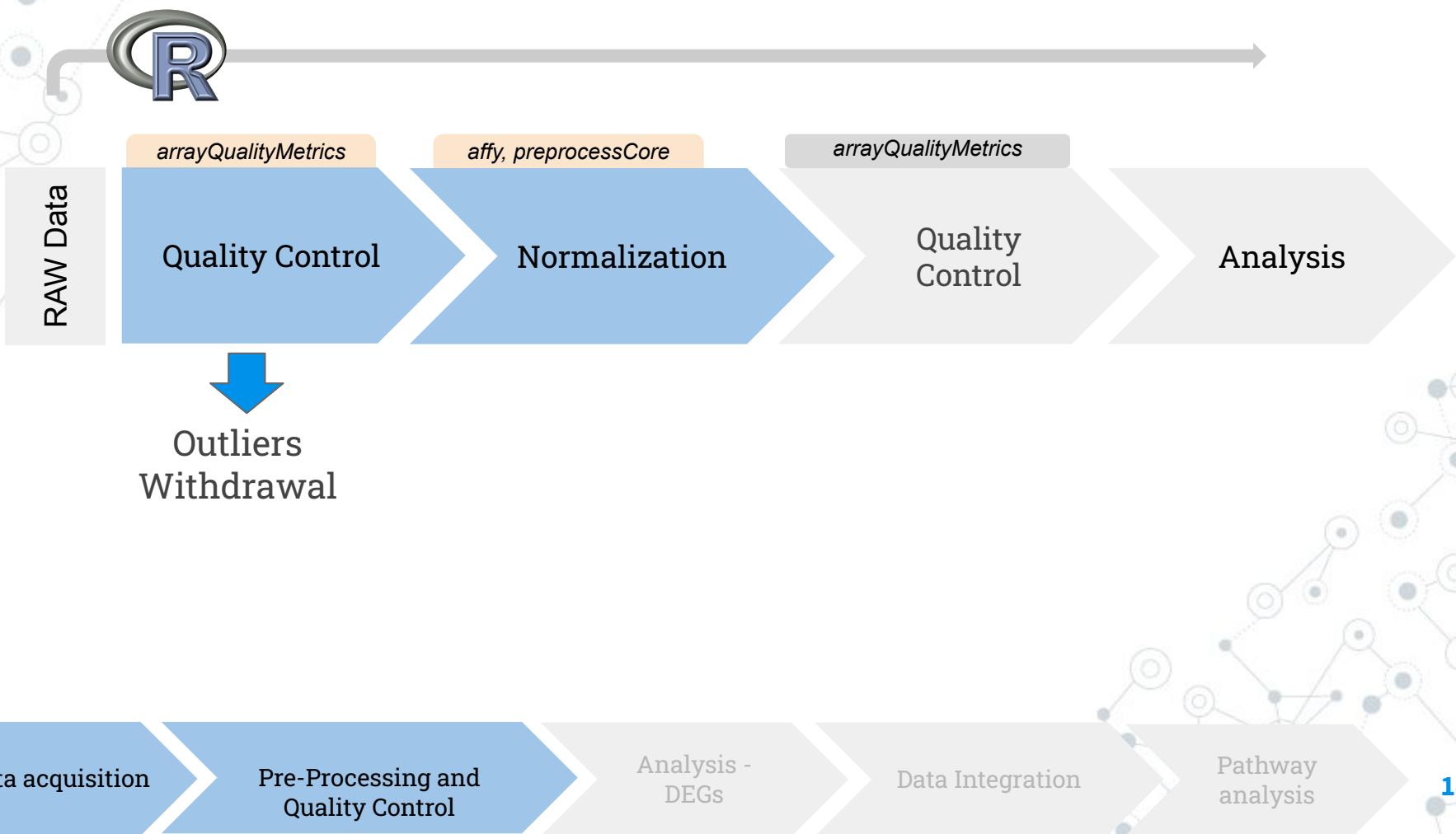
Pre-Processing and Quality Control

Analysis -
DEGs

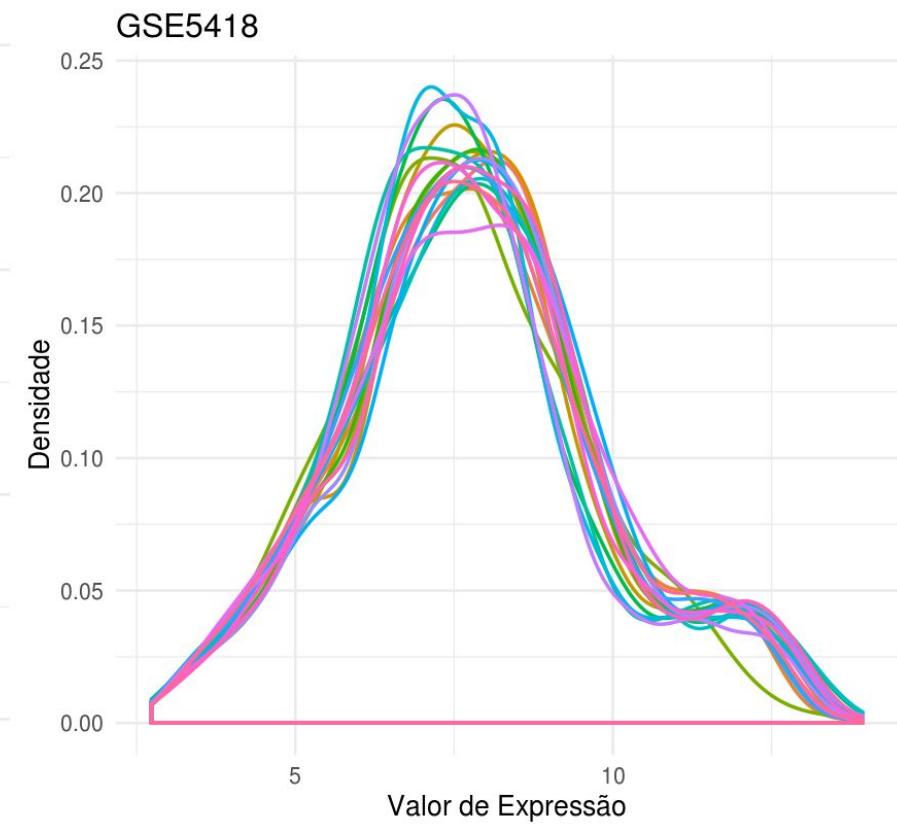
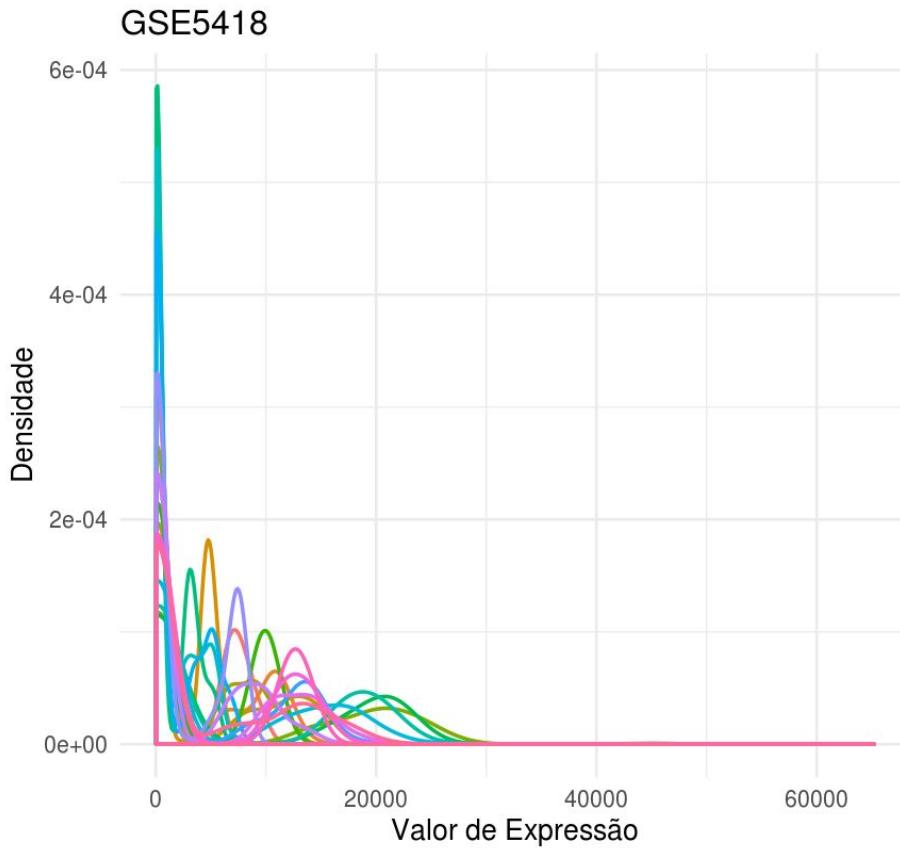
Data Integration

Pathway
analysis

Pre-Processing and Quality Control:



Pre-Processing and Quality Control:



Data acquisition

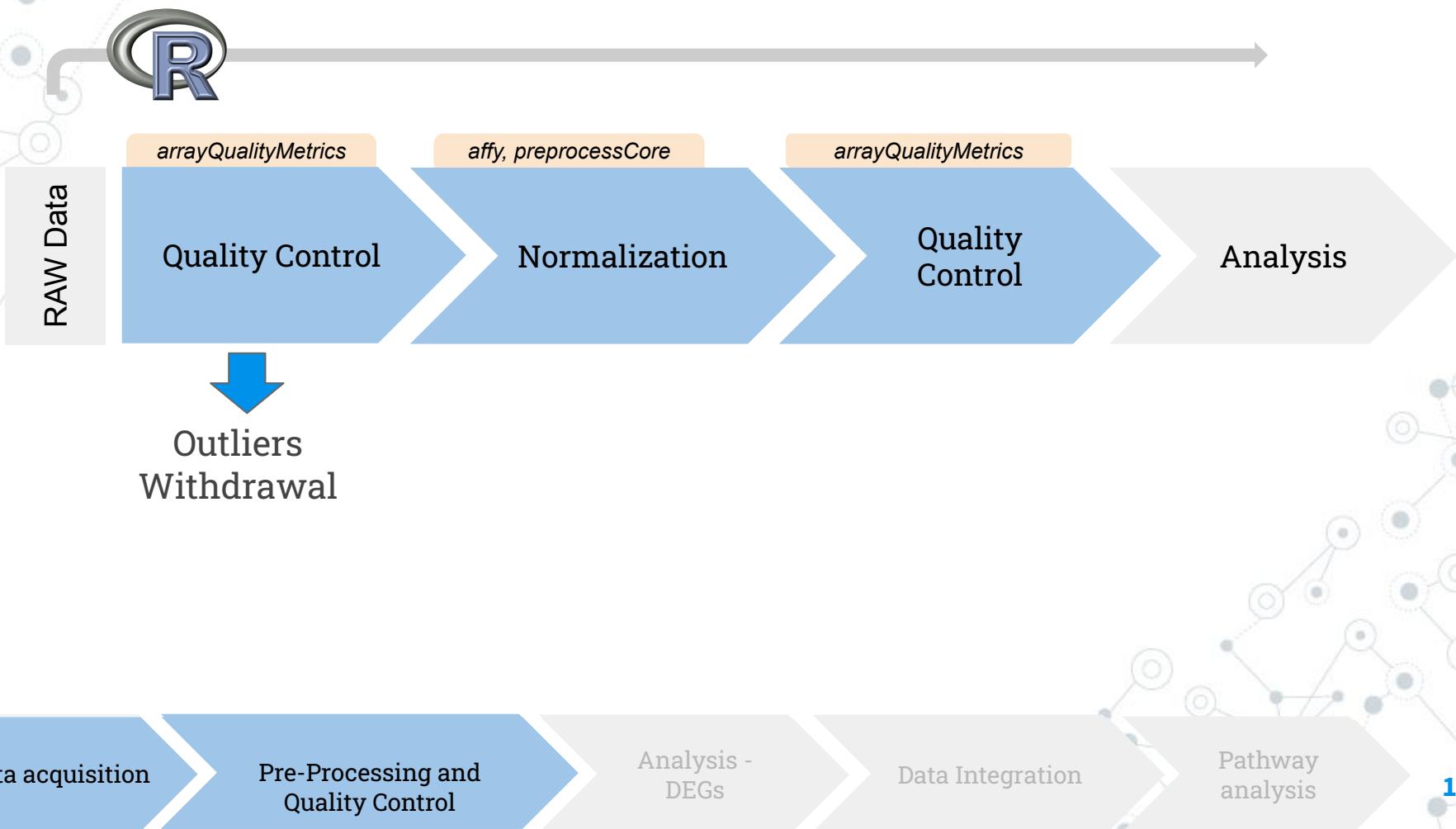
Pre-Processing and
Quality Control

Analysis -
DEGs

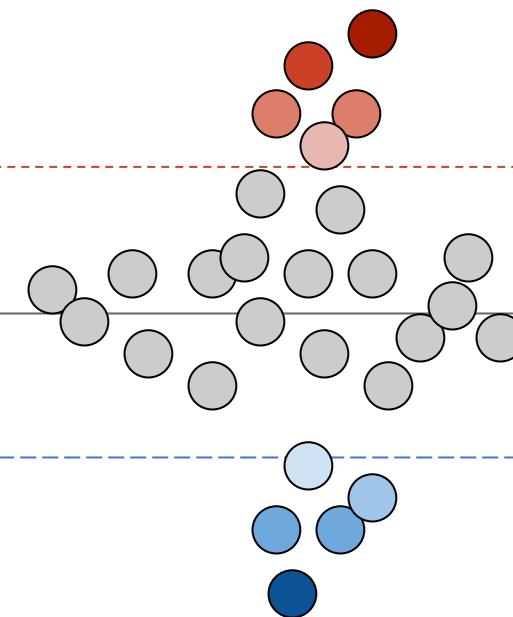
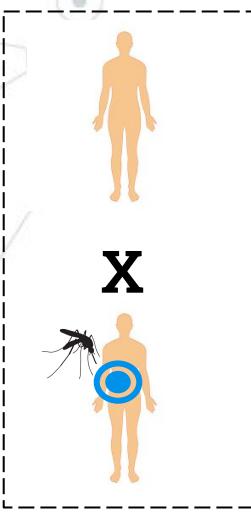
Data Integration

Pathway
analysis

Pre-Processing and Quality Control:



Analysis of Differentially Expressed Genes (DEGs)



Significant increase

Unaltered Genes

Significant Decrease

Data acquisition

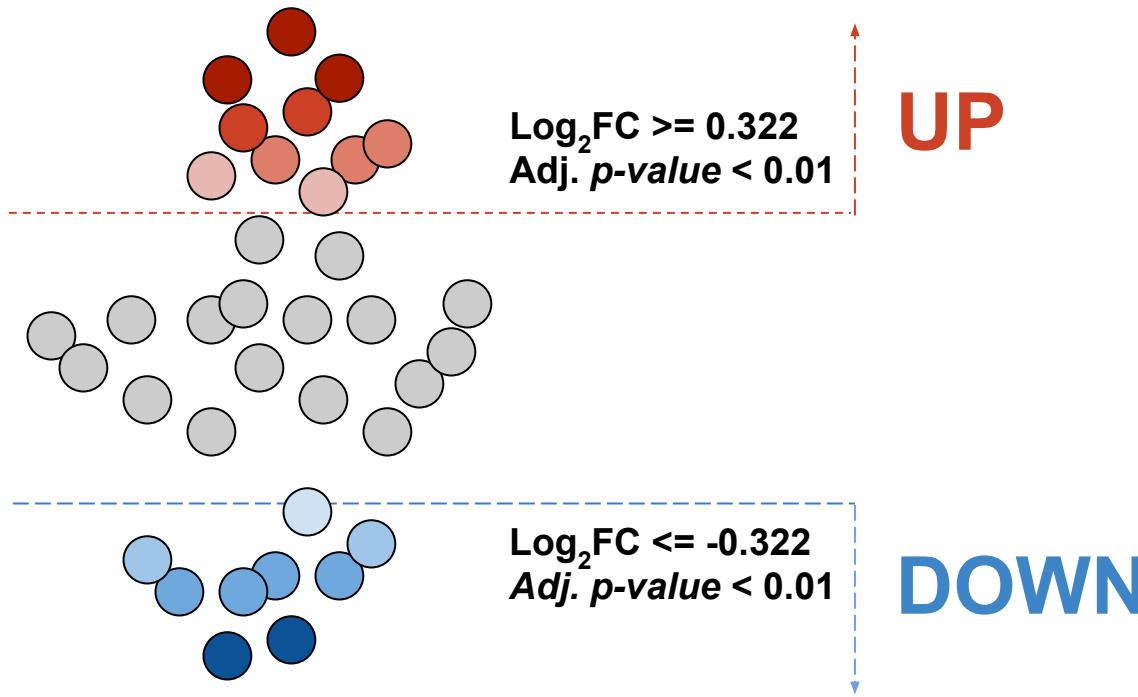
Pre-Processing and Quality Control

Analysis - DEGs

Data Integration

Pathway analysis

DEGs: Parameters



Data acquisition

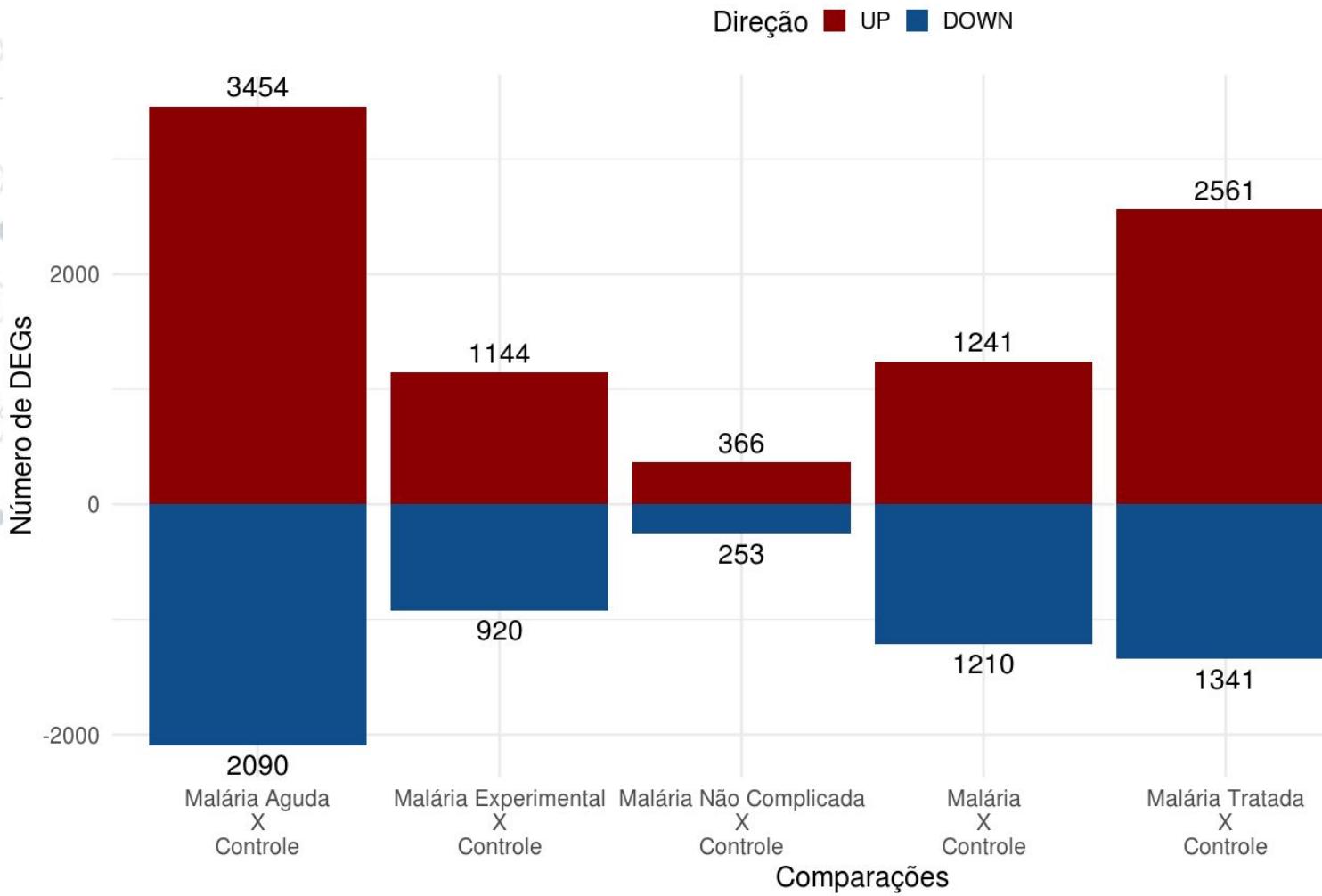
Pre-Processing and Quality Control

Analysis -
DEGs

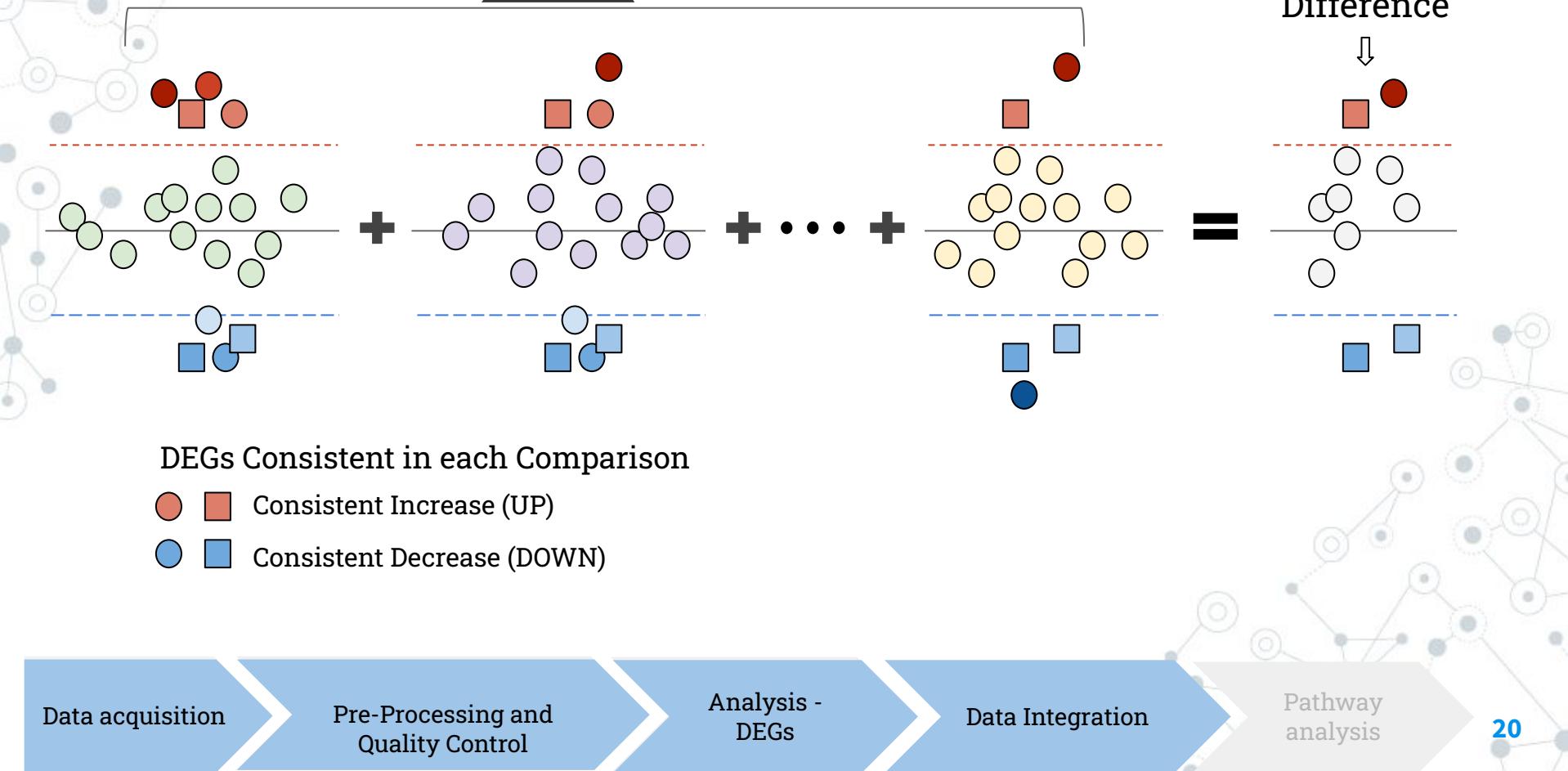
Data Integration

Pathway analysis

DEGs for each Comparison

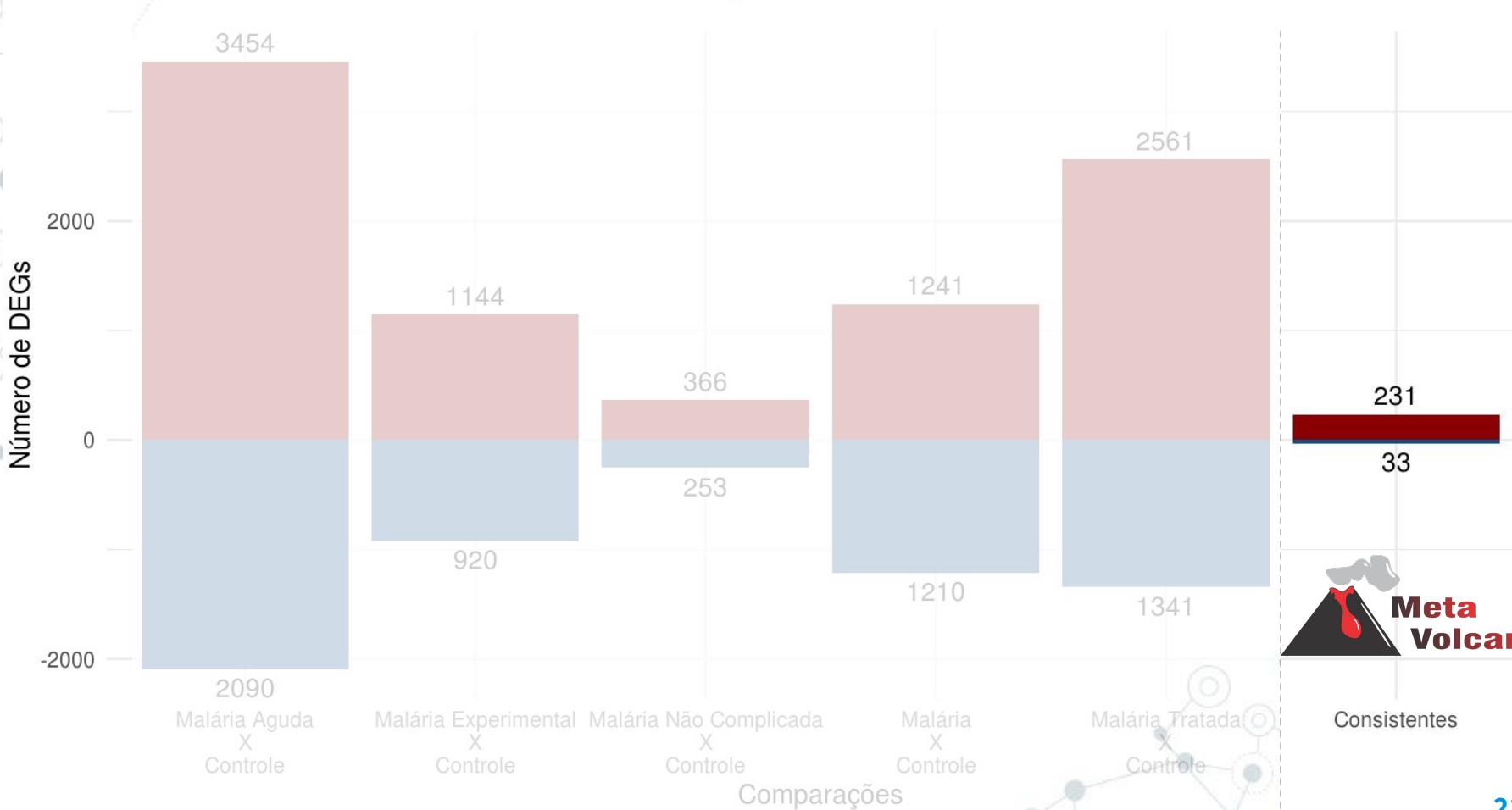


Data Integration

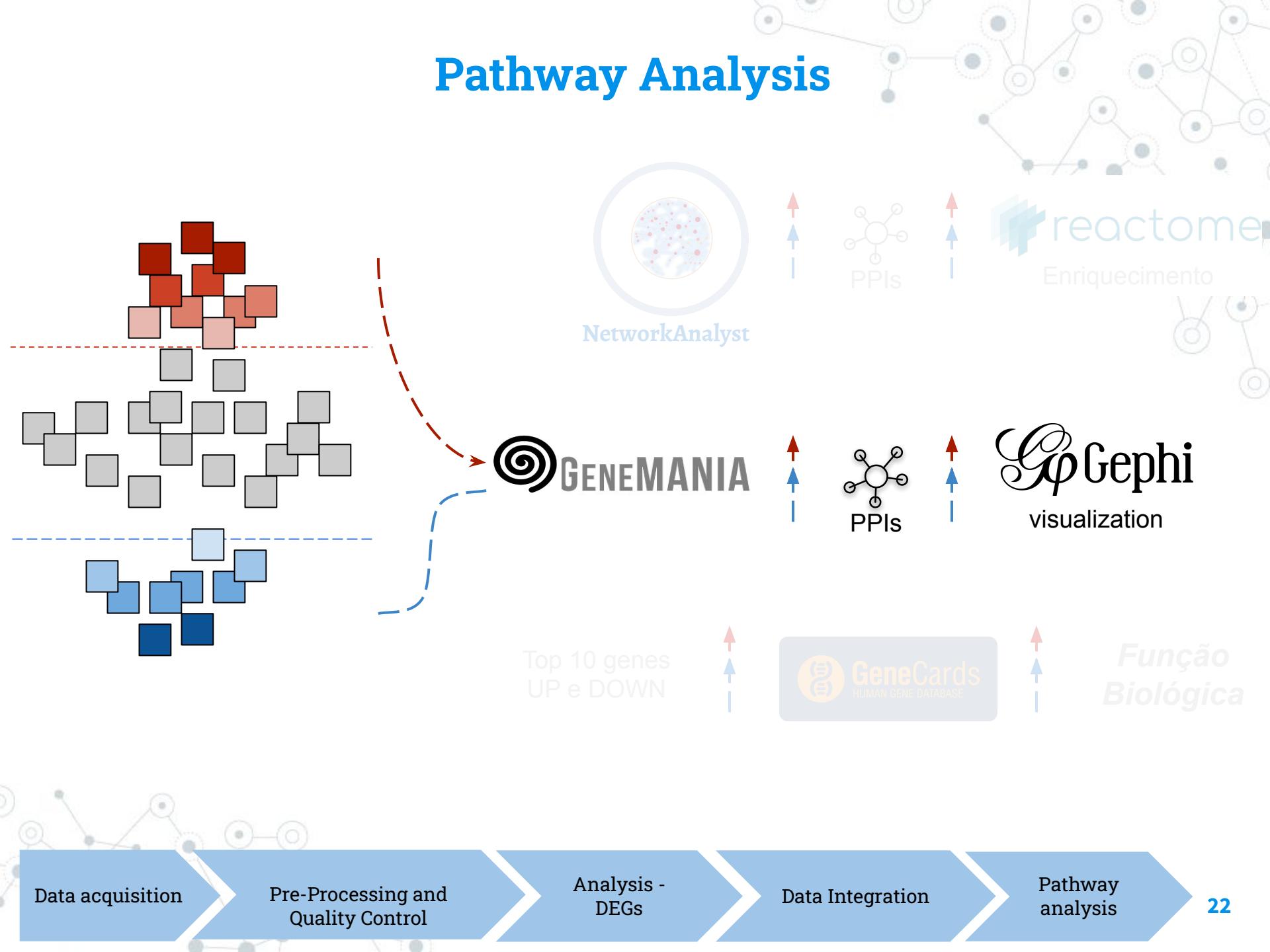


Consistent DEGs

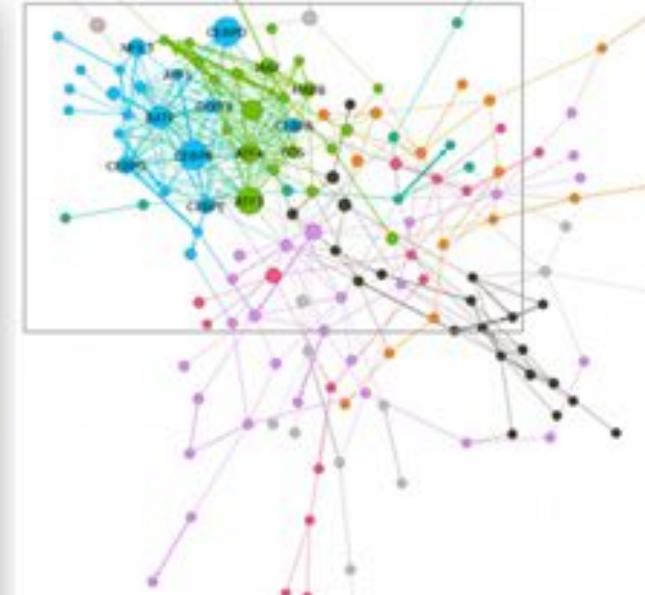
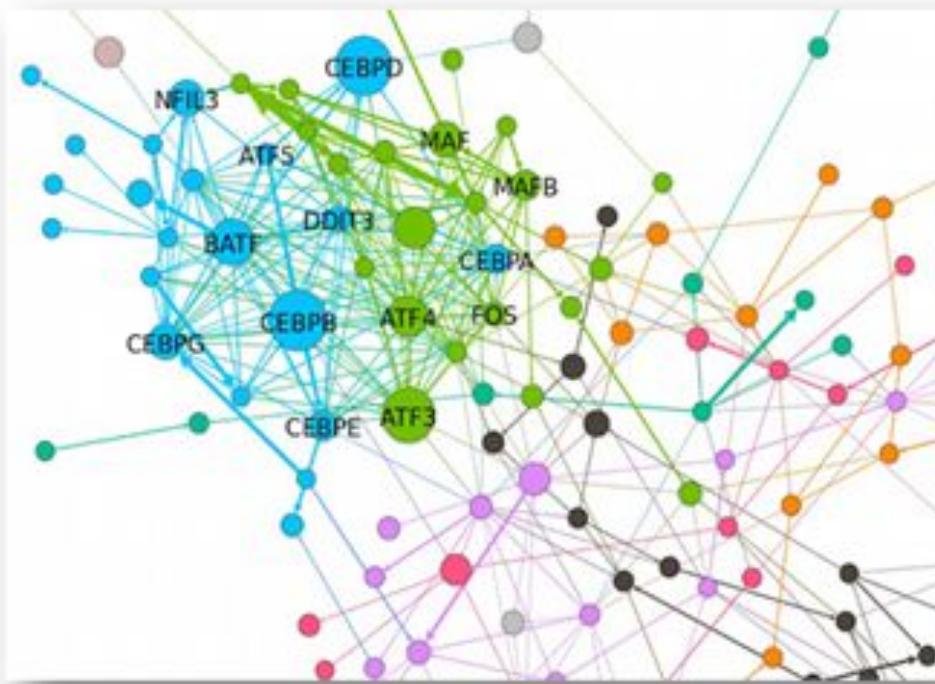
Direção ■ UP ■ DOWN



Pathway Analysis

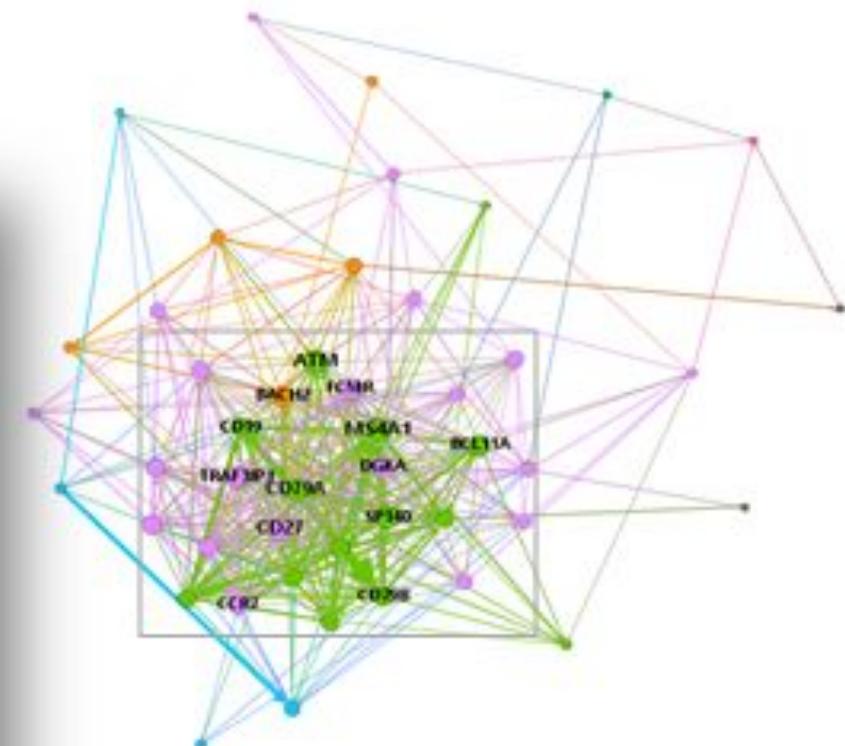
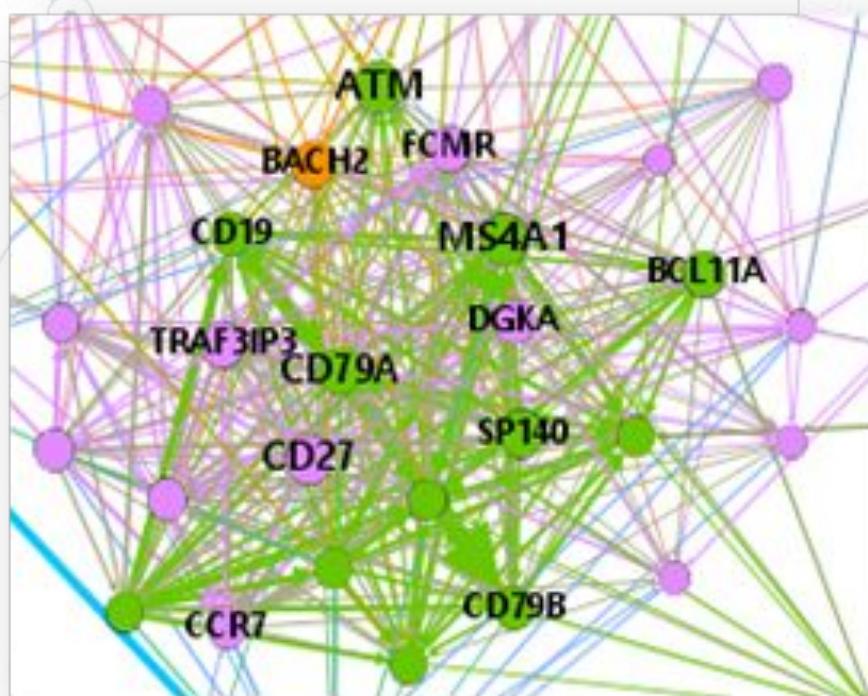


How do DEGs interact with each other?



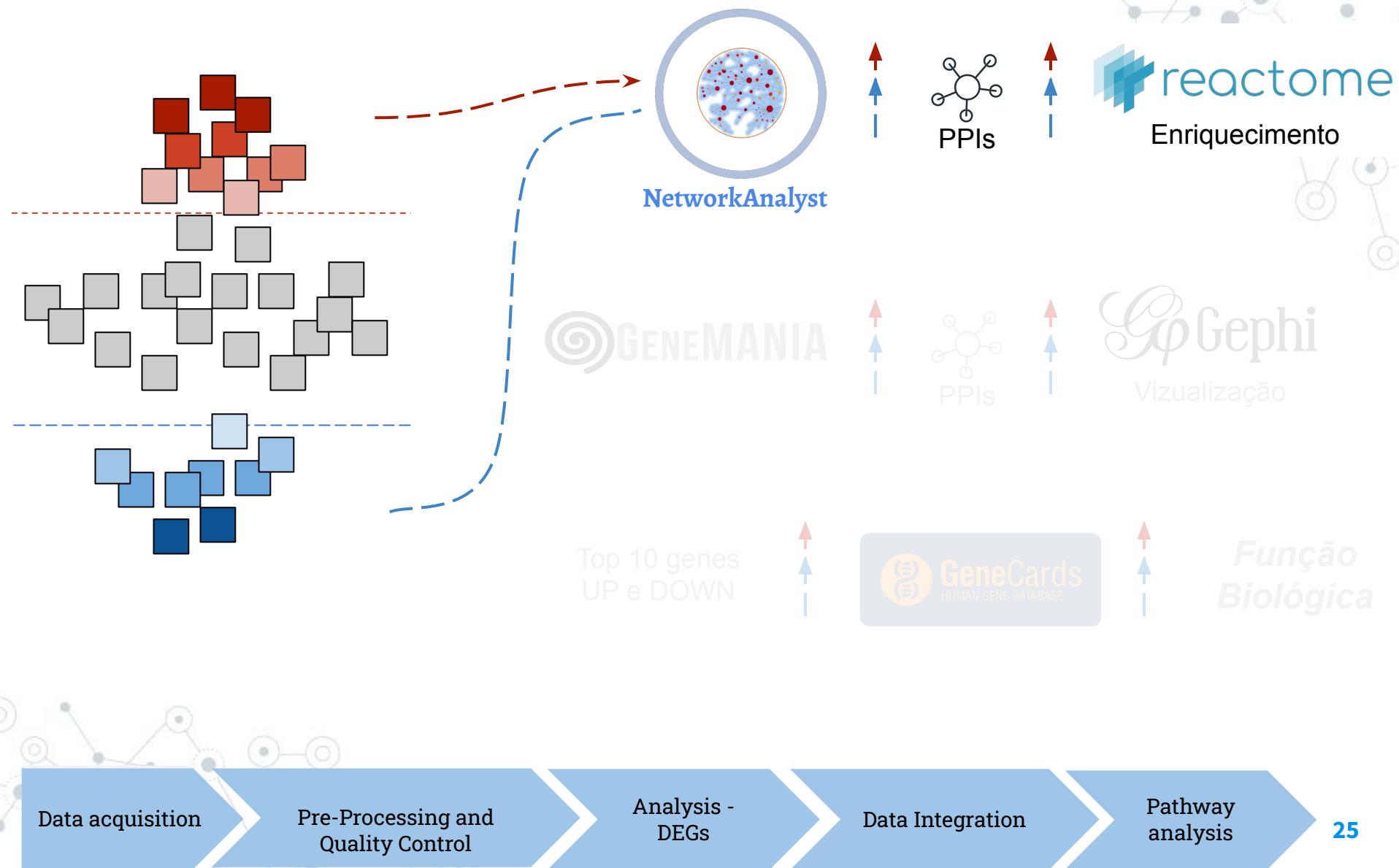
UP

How do DEGs interact with each other?



DOWN

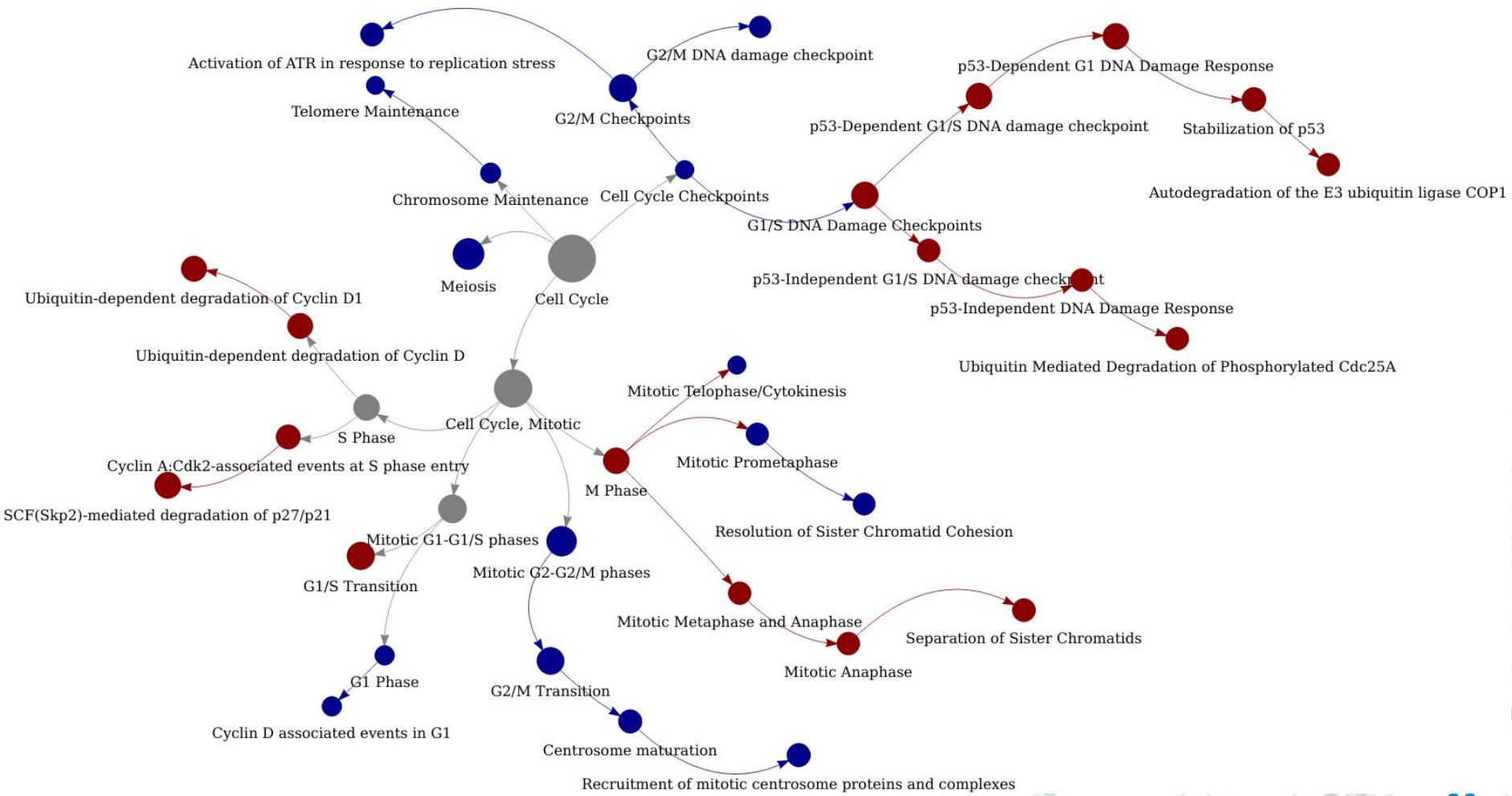
Pathway Analysis



Enrichment

- UP regulated
- DOWN regulated
- Both

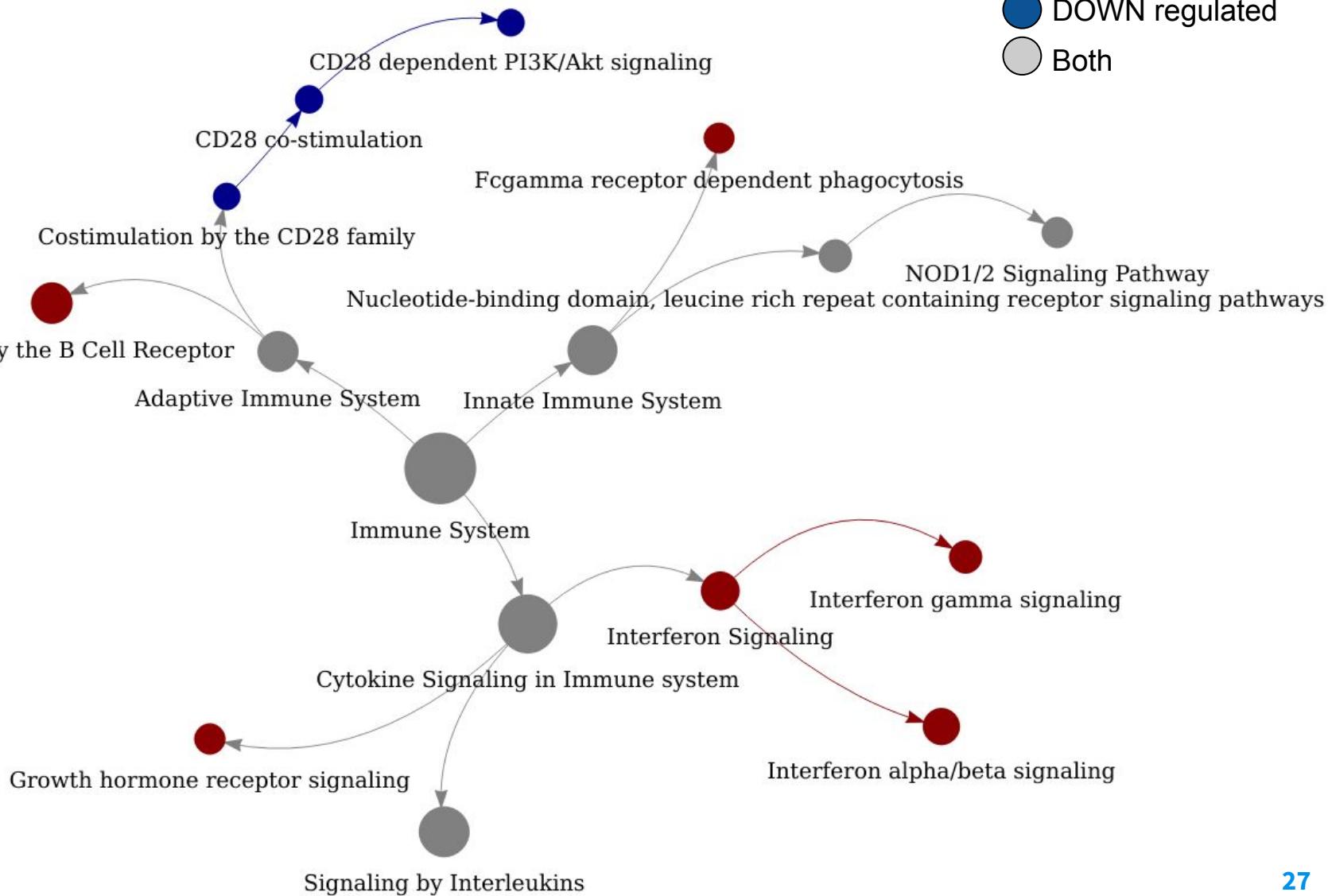
Integration of Enriched Pathways



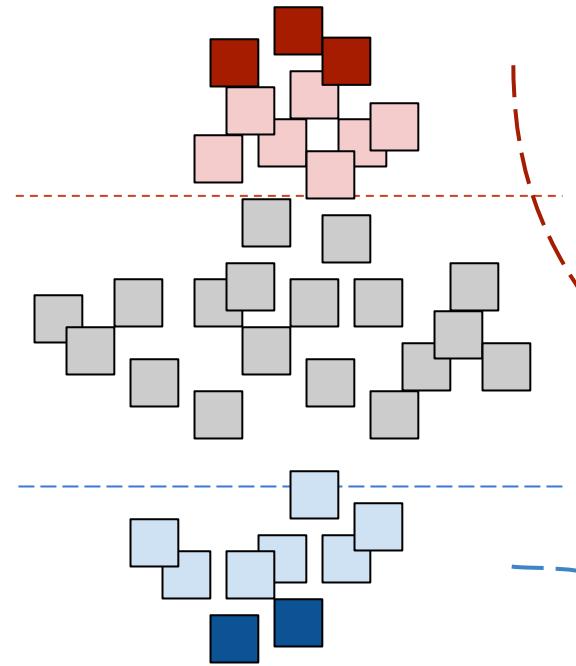
Integration of Enriched Pathways

Enrichment

- UP regulated
- DOWN regulated
- Both



Pathway Analysis



GENEMANIA

NetworkAnalyst

Top 10 genes
UP e DOWN



PPIs



PPIs



PPIs



PPIs

reactome
Enriquecimento

Gephi
Vizualização

**Biological
function**

Data acquisition

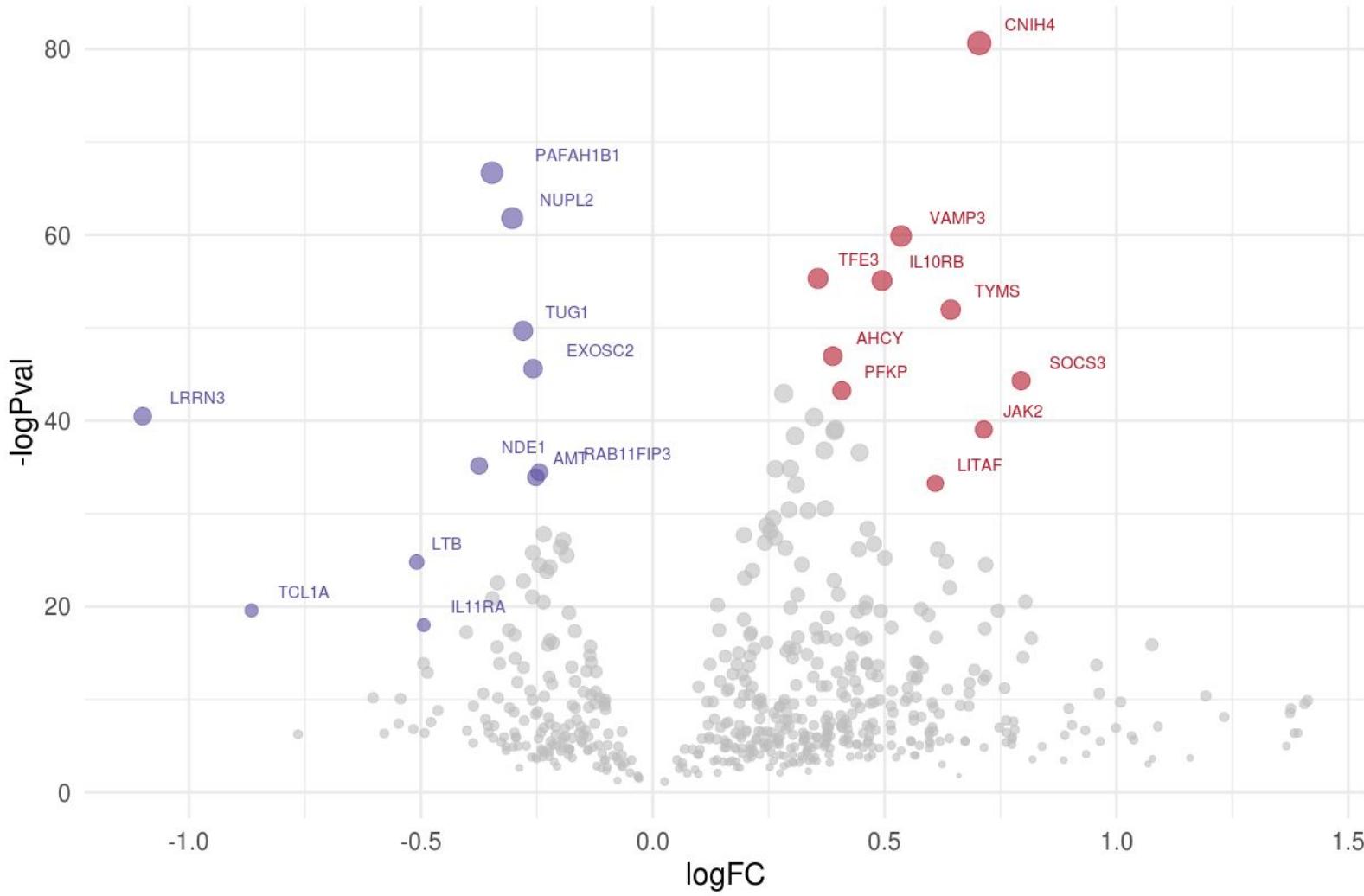
Pre-Processing and
Quality Control

Analysis -
DEGs

Data Integration

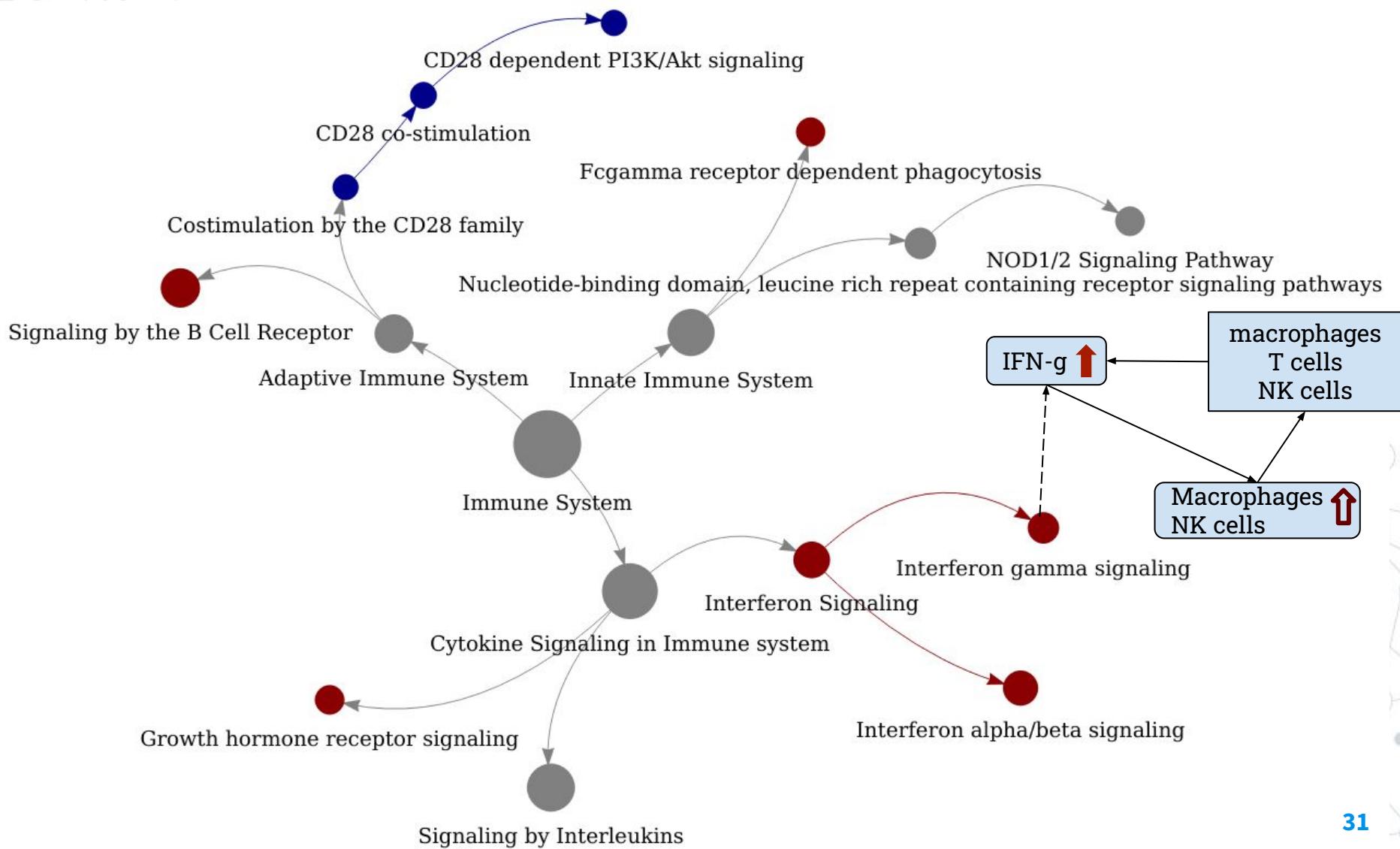
Pathway
analysis

Data Integration - Top 10 Genes

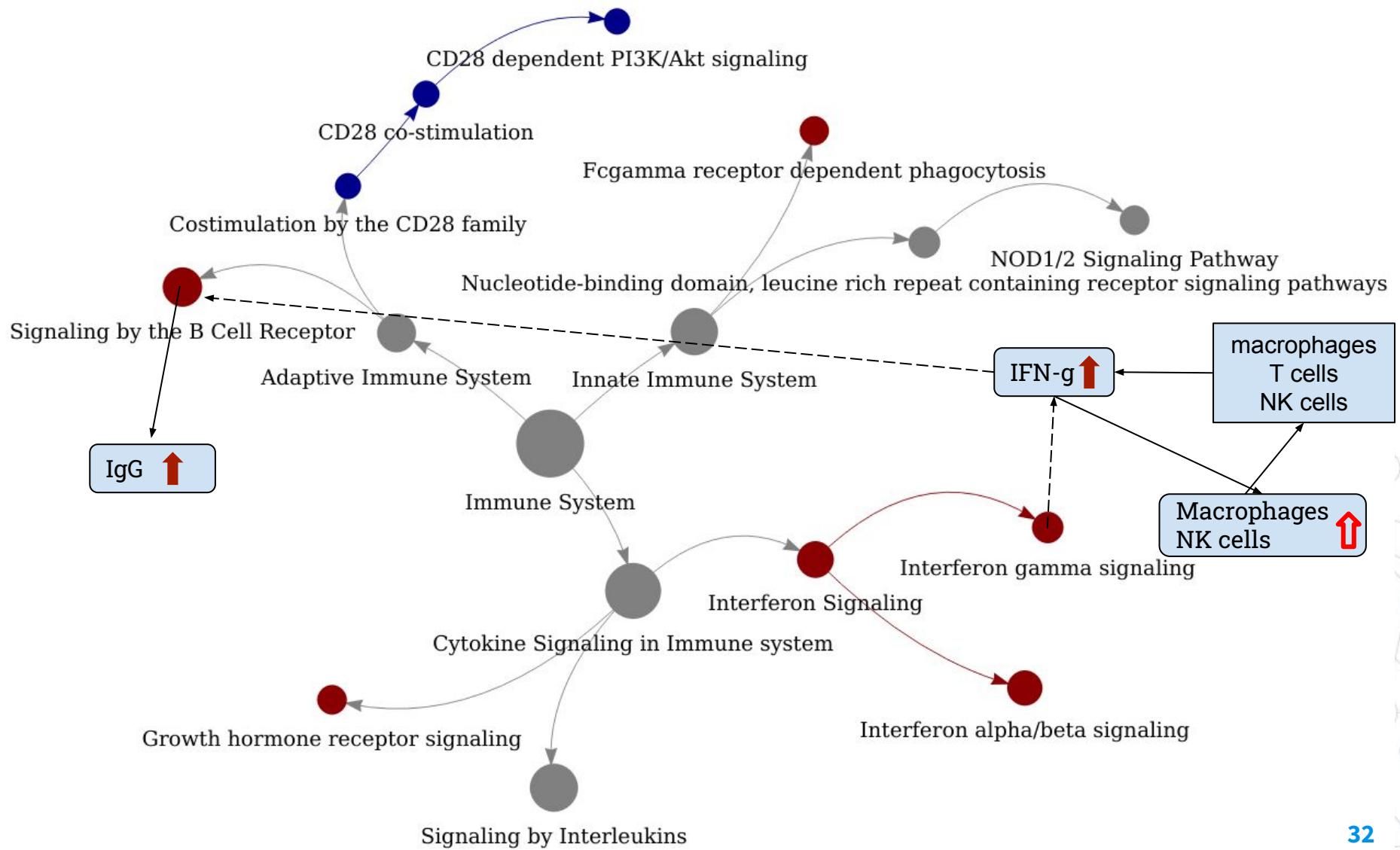


Discussion

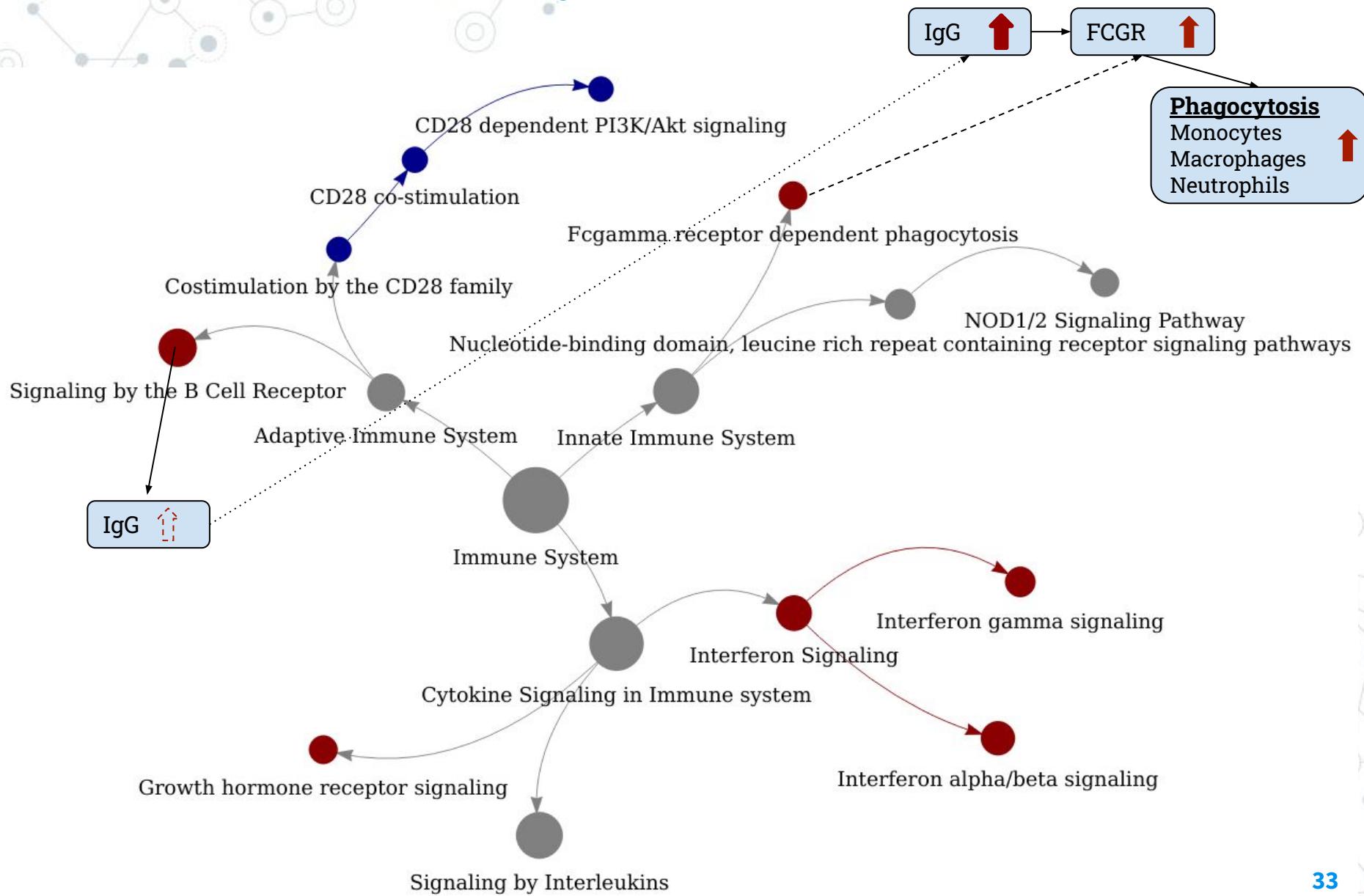
Structure of Enriched Pathways



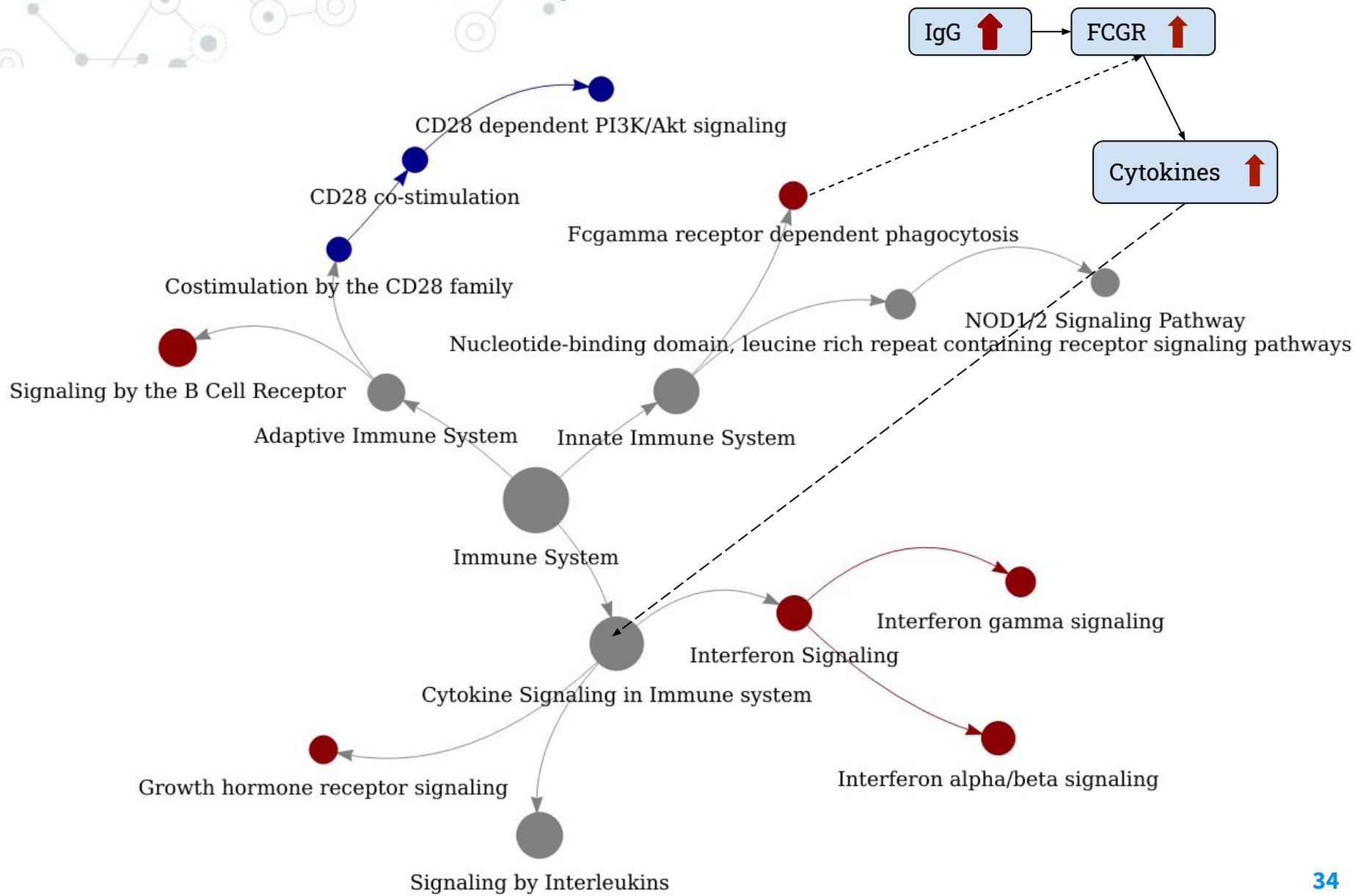
Structure of Enriched Pathways



Enriched Pathways

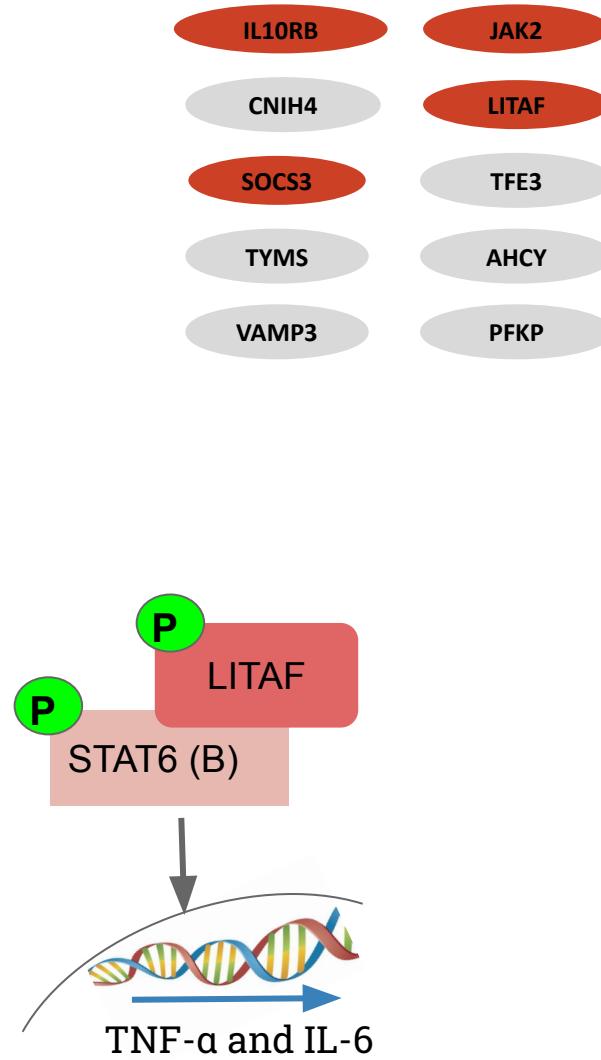
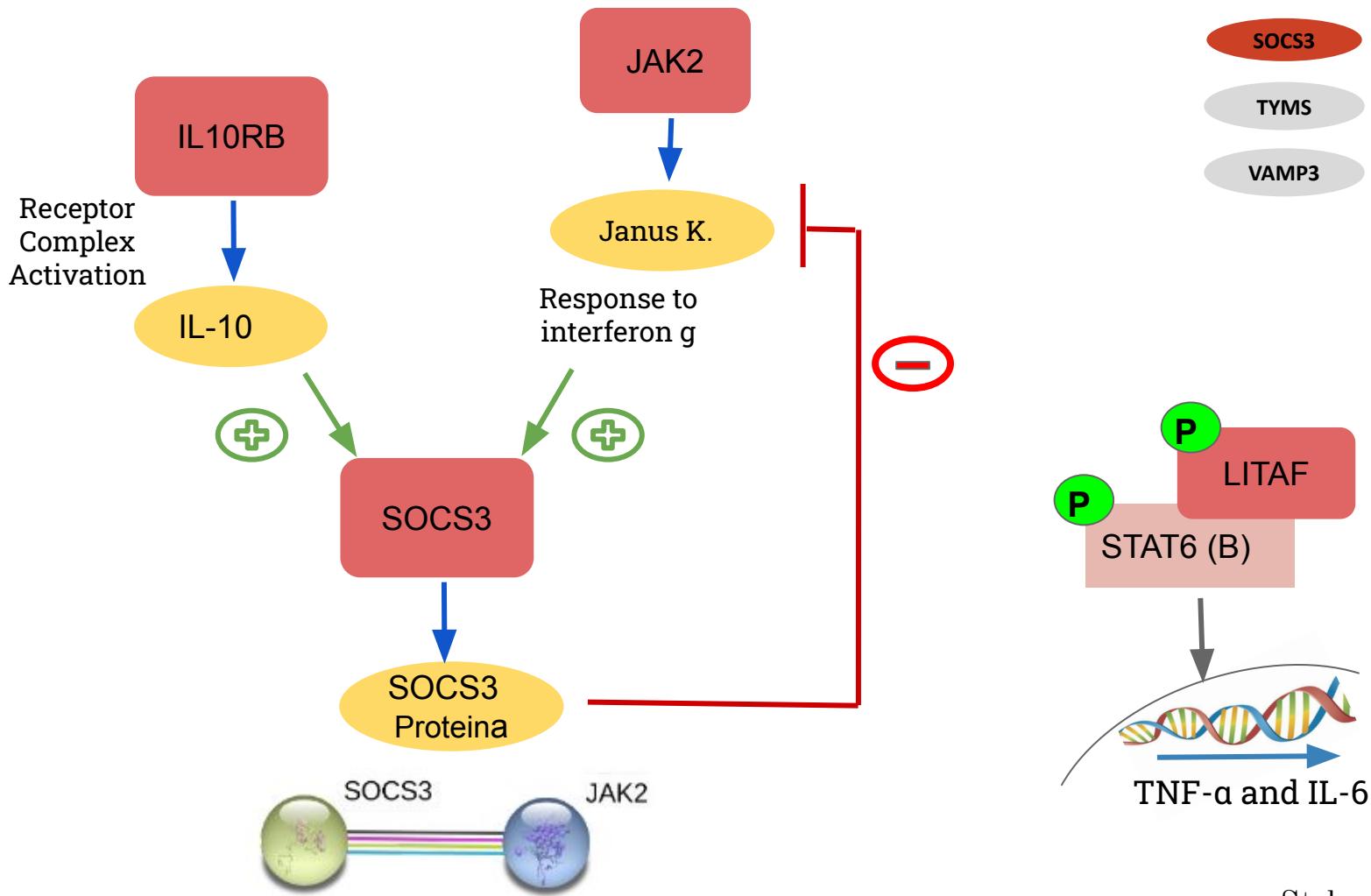


Enriched Pathways



Top 10 DEGs UP: Cytokine Inflammation

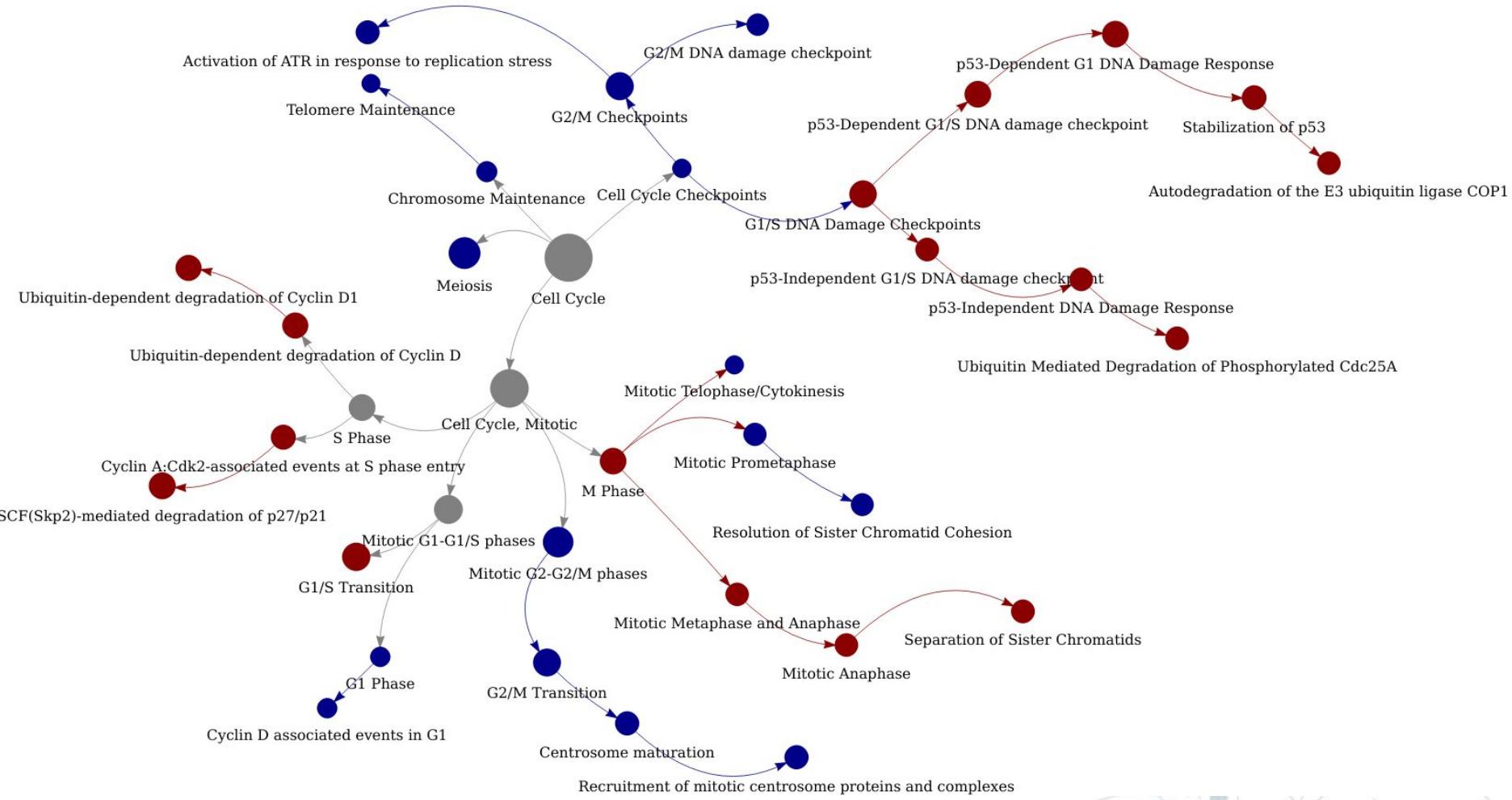
Genes UP



Stelzer et al; 2016

Enrichment

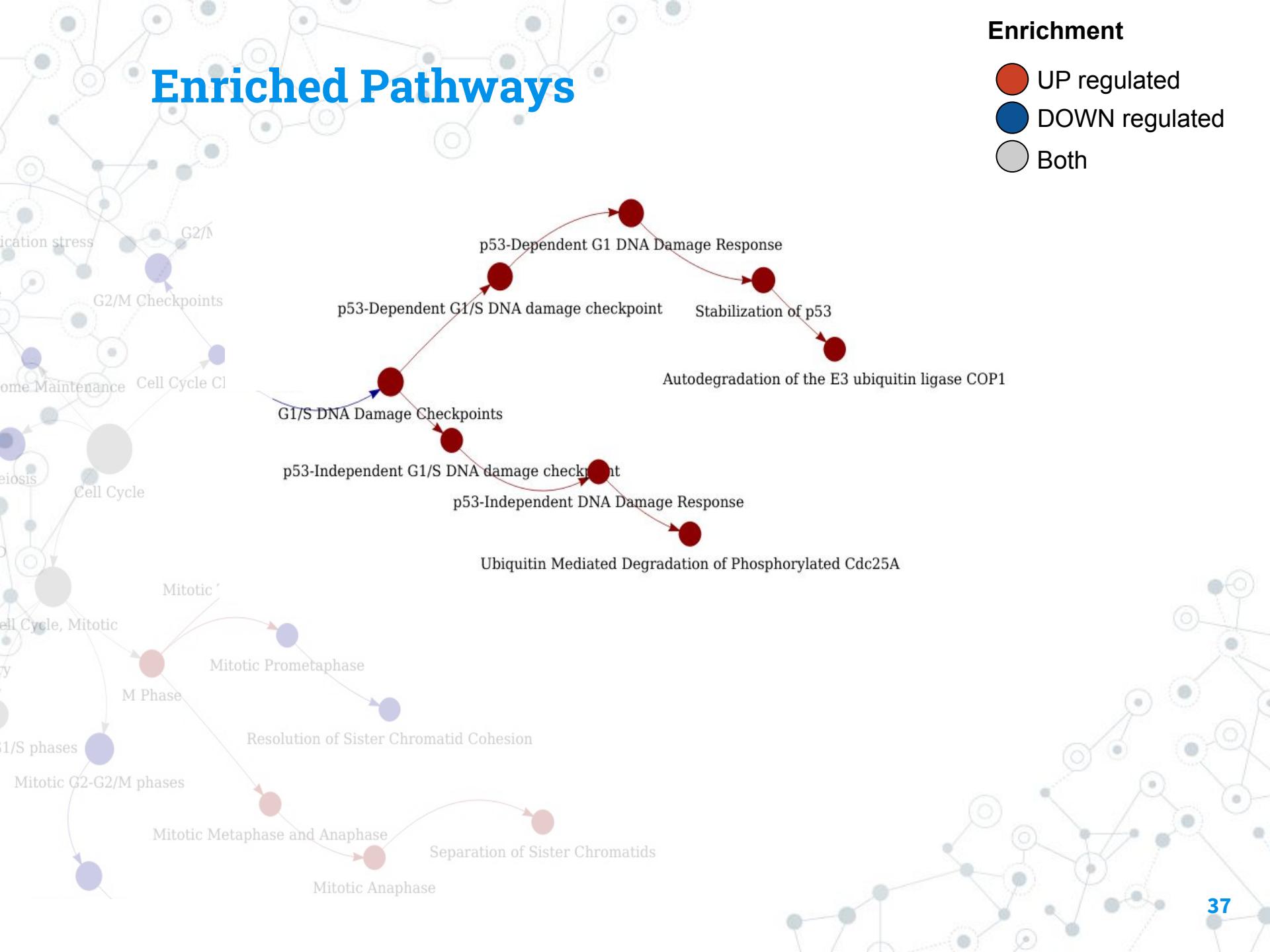
- UP regulated
- DOWN regulated
- Both



Enrichment

- UP regulated (Red)
- DOWN regulated (Blue)
- Both (Grey)

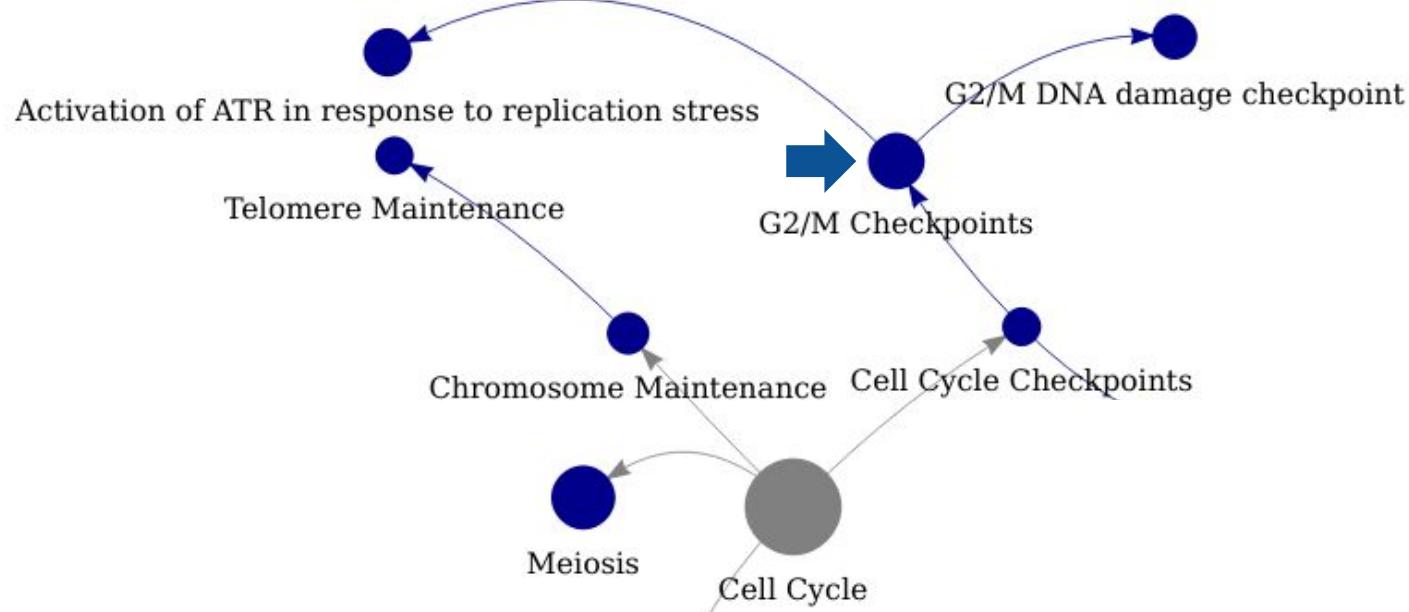
Enriched Pathways



Enrichment

- UP regulated (Red)
- DOWN regulated (Blue)
- Both (Grey)

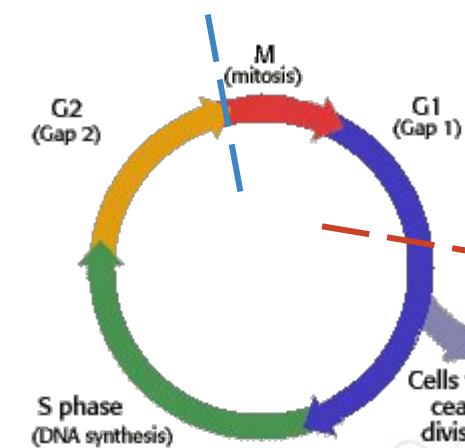
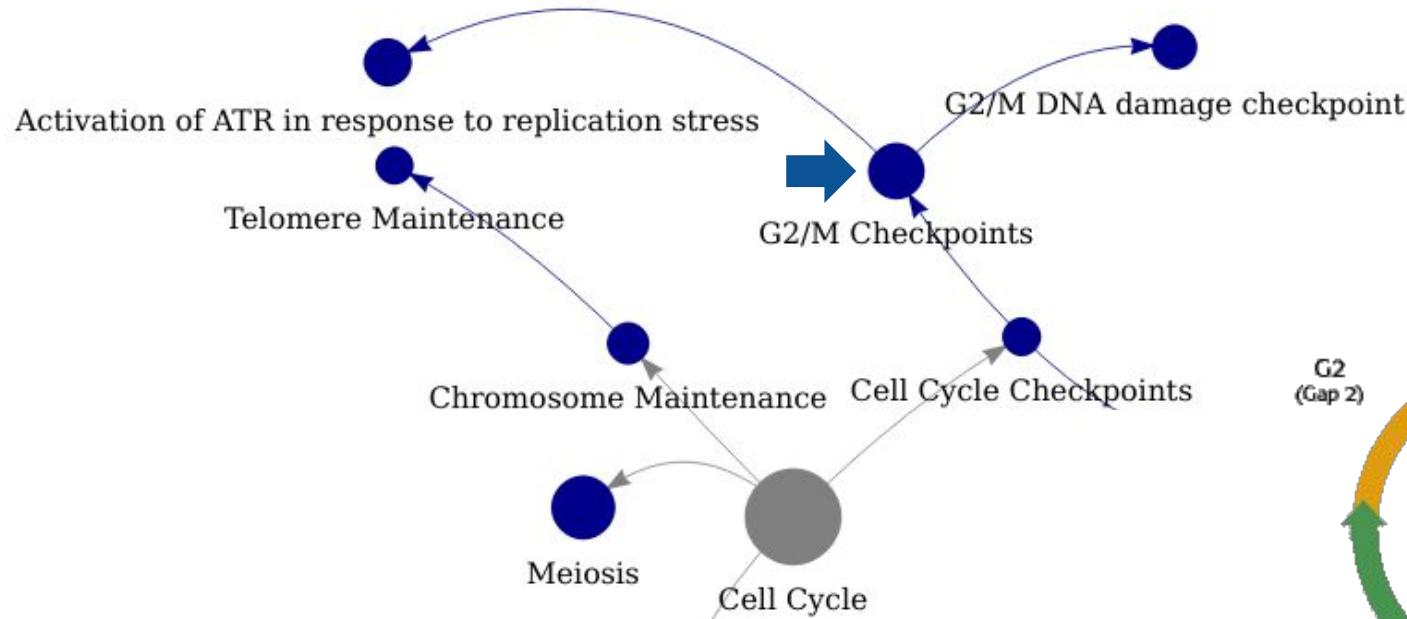
Enriched Pathways



Enrichment

- UP regulated (Red)
- DOWN regulated (Blue)
- Both (Grey)

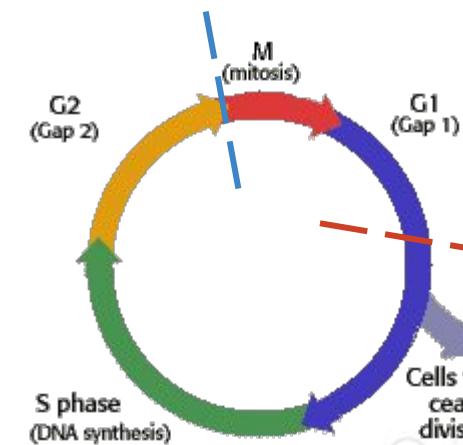
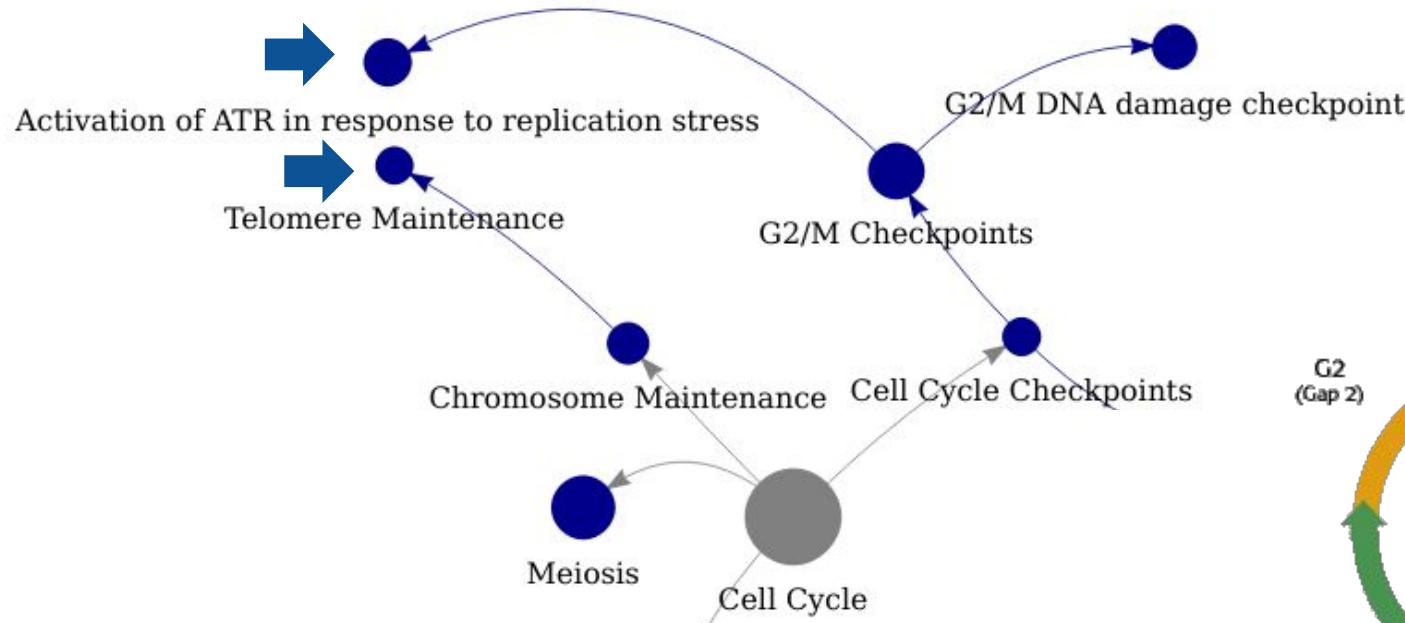
Enriched Pathways



Enrichment

- UP regulated
- DOWN regulated
- Both

Maintenance of telomeres

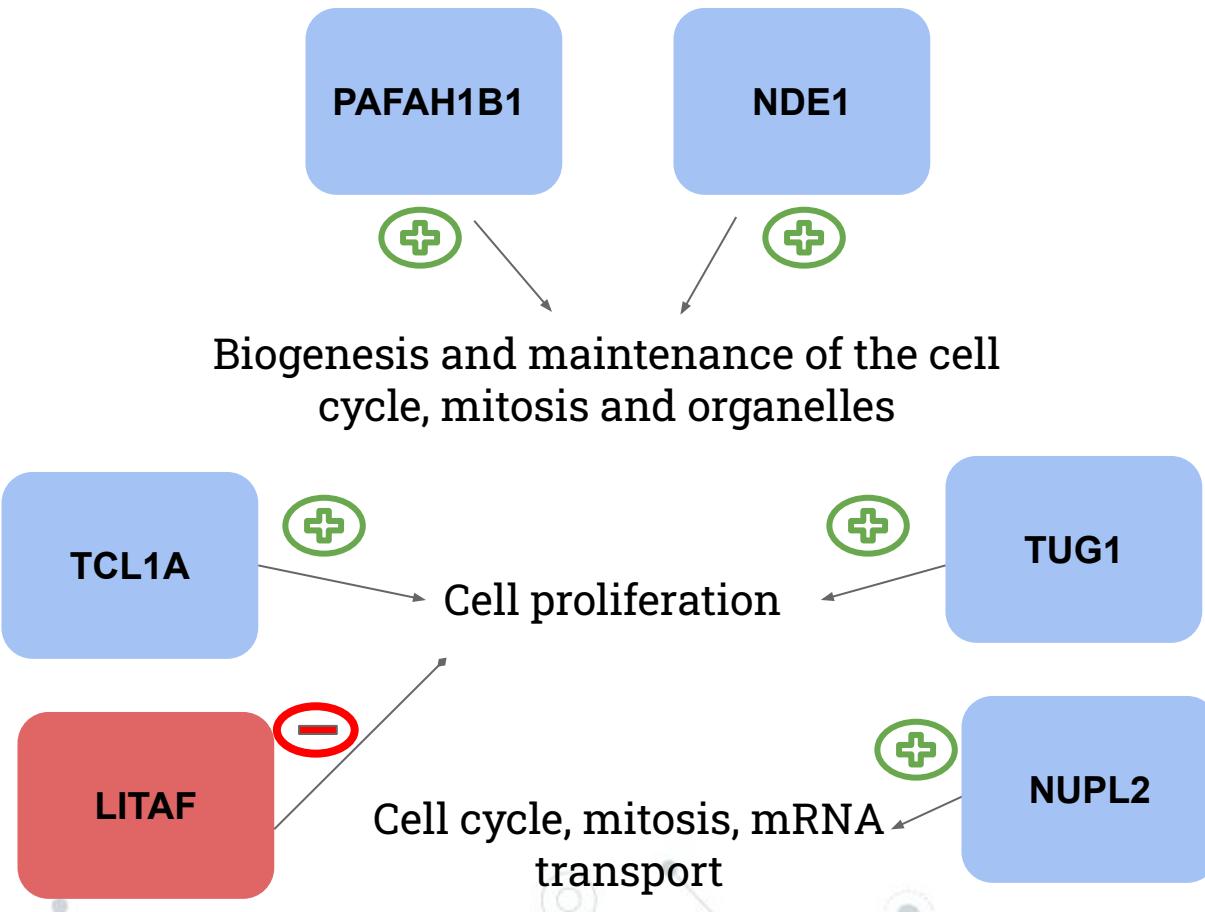


- Malaria infection may lead to telomeres decrease in peripheral blood cells
(Asghar et al, em 2017)

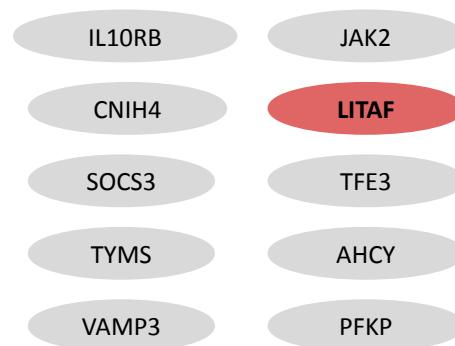
Immune system activation → Cellular stress and oxidative damage

Ilmonen and Kotrschal, 2008

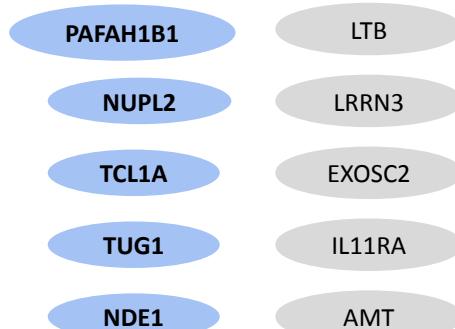
Top 10 DEGs DOWN: Regulation of the Cell Cycle



Genes UP

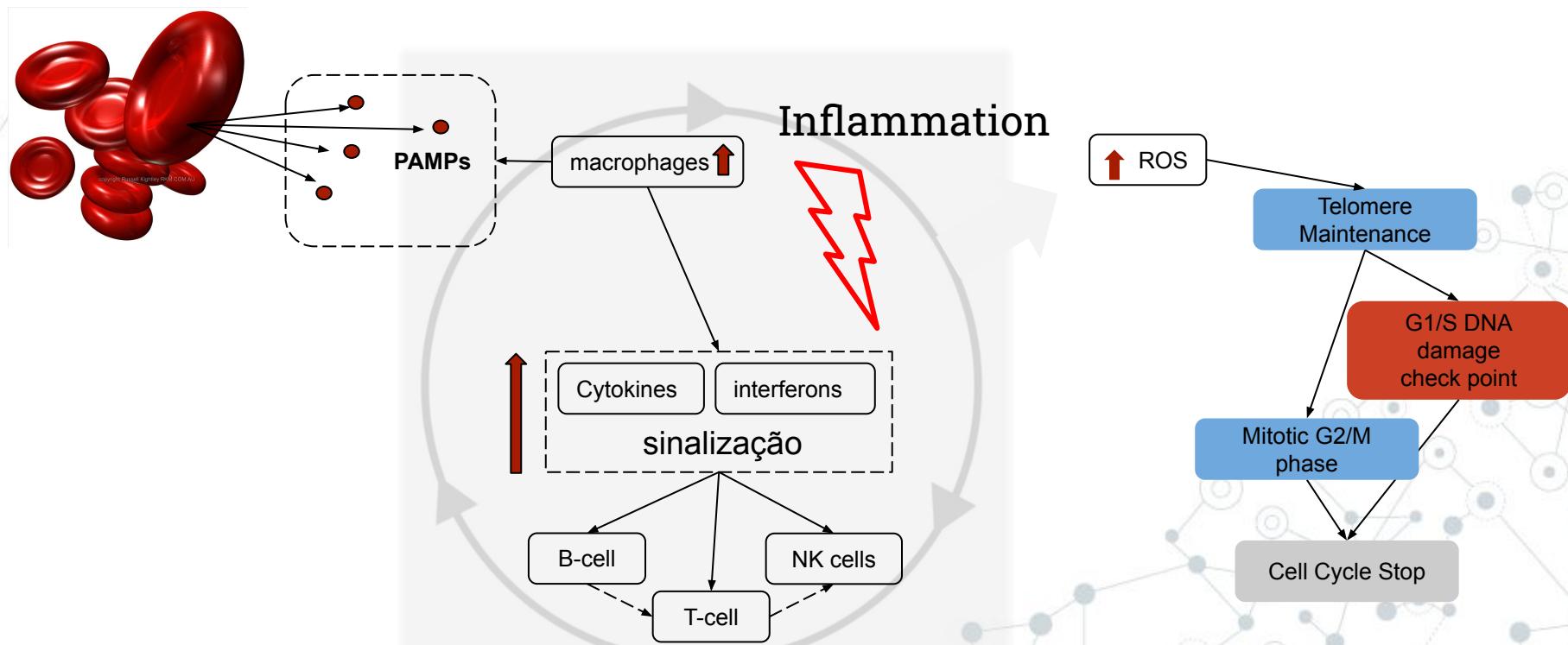


Genes DOWN



Conclusion

- ◆ Reliability of results: Literature
- ◆ Consistency: diverse studies and comparisons
- ◆ Consistency: essential processes involved in malaria infections



References

Asghar M, Yman V, Homann MV, Sondén K, Hammar U, Hasselquist D, Färnert A. **Cellular aging dynamics after acute malaria infection: A 12-month longitudinal study.** Aging Cell; 2018

David C et al. **Reactome: a database of reactions, pathways and biological processes.** Nucleic Acids Res. 2011

Hu WC. **Microarray analysis of PBMC after Plasmodium falciparum infection: Molecular insights into disease pathogenesis.** Asian Pacific Journal of Tropical Medicine. 2016; 9(4):313-323

Idaghdour Y et al. **Evidence for additive and interaction effects of host genotype and infection in malaria.** Proceedings of the National Academy of Sciences USA. 2012; 109(42):16786-93

Ilmonen P, Kotrschal A, Penn DJ. **Telomere attrition due to infection.** PLoS One. 2008; 14;3(5):e2143

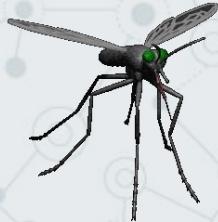
Ockenhouse CF et al. **Common and divergent immune response signaling pathways discovered in peripheral blood mononuclear cell gene expression patterns in presymptomatic and clinically apparent malaria.** Infection and Immunity. 2006; 74(10):5561-73

Schoenborn JR, Wilson CB **Regulation of interferon-gamma during innate and adaptive immune responses.** Adv Immunol. 2007

Stelzer G et al. **The GeneCards Suite: From Gene Data Mining to Disease Genome Sequence Analysis** Current Protocols in Bioinformatics. 2016; 54:1.30.1 - 1.30.33

World Health Organization. **World Malaria Report.** Geneva: WHO. 2017

Obrigada!



Backup Slides

NAs - RAW data

	GSM876651	GSM876652	GSM876653	GSM876654	GSM876655	GSM876656	GSM876657	GSM876658	GSM876659	GSM876660	GSM876661	GSM876662
493	1.042	0.898	0.649	0.807	1.625	0.719	0.508	1.283	1.132	1.451	0.675	-0.645
494	0.886	0.258	-0.028	-0.460	1.562	-0.070	1.091	1.397	1.262	1.830	0.180	-0.398
495	1.749	1.037	0.559	1.420	1.346	0.534	0.937	1.127	1.521	1.587	0.856	0.383
496	3.891	3.737	3.189	4.675	2.712	3.870	2.859	2.422	2.598	3.454	3.136	1.730
497	3.564	0.249	1.839	1.390	-0.072	0.663	0.180	0.399	1.510	NA	1.641	-1.621
498	NA	1.986	2.972	1.719	-1.558	4.323	2.018	0.885	-1.982	NA	1.370	0.474
499	2.242	0.708	2.495	1.810	-2.072	-0.347	0.109	0.352	0.188	0.754	-0.406	-2.116
500	1.461	-0.073	1.785	0.300	-0.335	0.094	1.261	-1.252	1.303	NA	0.808	-1.979
501	NA	0.658	2.700	0.876	1.434	0.591	1.487	-0.281	1.603	0.532	1.437	-1.312
502	0.113	0.411	0.589	-0.237	NA	-0.474	0.209	-0.660	1.995	-1.568	1.045	-3.242
503	-0.250	0.528	-2.312	0.577	0.513	-0.262	-0.946	-5.035	NA	-2.831	NA	NA
504	NA	NA	-0.674	1.289	NA	0.486	2.032	-0.711	NA	NA	-1.118	-1.979
505	-3.330	-3.512	-3.183	-2.027	-2.558	-2.664	-2.262	-3.301	-2.624	-1.680	-2.573	-2.016
506	-0.774	-0.706	-0.660	-0.789	-0.129	-1.231	0.211	-1.067	-0.631	-0.113	-0.851	-0.540
507	-1.064	-1.642	-0.792	-2.826	-1.554	-1.236	-2.225	-0.915	-1.421	-0.938	-1.447	-2.702
508	-0.864	-0.306	0.690	0.049	-0.711	0.149	-0.749	-0.658	-0.467	-0.875	-0.552	-1.225
509	-0.943	-1.214	-0.843	-0.379	-0.621	-0.754	-0.948	-0.517	-1.128	-0.487	-0.625	-1.685
510	1.406	-3.128	-3.029	-3.231	0.285	-2.333	-0.631	-0.922	-0.795	0.075	-3.257	-2.840
511	-2.887	-3.174	-2.029	-1.880	-1.694	-1.621	-2.028	-1.650	-0.970	-1.337	-2.063	-3.054
512	-0.486	0.664	0.641	-0.238	0.607	-0.402	-0.839	1.142	1.279	0.582	-0.193	-0.065
513	0.640	0.609	1.159	0.509	0.804	0.631	-0.324	0.903	1.005	0.762	0.838	0.493
514	-0.159	-0.192	0.001	-0.350	0.381	0.285	0.403	0.377	0.709	0.689	0.377	0.640
515	-0.556	0.730	1.731	-0.628	-0.246	0.740	-0.501	-0.190	0.350	-0.506	0.546	0.241
516	-1.085	-0.976	-0.079	-0.724	-1.130	0.119	-1.537	-1.414	-0.892	-0.153	-1.459	-1.384
517	-1.039	-0.984	-0.138	-1.109	-1.176	-0.978	-1.726	-1.334	-1.028	-0.633	-1.276	-1.717
518	-0.927	-0.138	-0.224	-1.125	-0.497	-0.586	-1.897	-0.536	-0.352	-0.934	-0.639	-0.740

NAs

Impute.knn function:

A function to impute missing expression data, using nearest neighbor averaging

The maximum percent missing data allowed in any row is 50% (default) . For any rows with more than rowmax% missing are imputed using the overall mean per sample.

Gene Symbol - Missing Information

	probe_id	gene_id	logFC	CI.L	CI.R	AveExpr	t	P.Value	adj.P.Val	B	comparison
26894	ILMN_1804217	LOC650850	4.8661140	4.2448545	5.4873734	10.122238	15.471374	2.370333e-33	1.865887e-29	65.092215587	malaria_vs_healthy
45959	ILMN_3294365	LOC646993	3.5283820	2.8514320	4.2053320	9.129901	10.295290	2.641878e-19	3.381533e-17	33.294710000	malaria_vs_healthy
25657	ILMN_1796316	MMP9	3.3441438	2.9521462	3.7361415	11.134341	16.850824	5.423414e-37	1.280766e-32	73.311906161	malaria_vs_healthy
25670	ILMN_1796409	C1QB	3.0558567	2.7534681	3.3582452	9.233368	19.961229	7.220945e-45	3.410525e-40	91.036122208	malaria_vs_healthy
15680	ILMN_1732962	KIAA1210	2.9098312	2.2250483	3.5946141	8.738364	8.393335	2.640767e-14	1.119624e-12	21.985272972	malaria_vs_healthy
14925	ILMN_1728183	DMRT2	2.8317300	2.1535069	3.5099530	8.363728	8.247056	6.212614e-14	2.457521e-12	21.146287281	malaria_vs_healthy
66	ILMN_1651429	SELM	2.5215001	1.9258803	3.1171199	9.069287	8.361988	3.173564e-14	1.326465e-12	21.805013838	malaria_vs_healthy
28362	ILMN_1813338	LAG3	2.4347621	2.1327334	2.7367907	9.987423	15.923113	1.492456e-34	2.349674e-30	67.805189500	malaria_vs_healthy
20391	ILMN_1762713	C19orf59	2.3707393	1.9802900	2.7611886	10.739464	11.993303	6.438762e-24	2.739722e-21	43.743086685	malaria_vs_healthy
18244	ILMN_1748915	S100A12	2.3483031	1.9925757	2.7040306	10.776452	13.039364	8.919491e-27	9.158184e-24	50.216735278	malaria_vs_healthy
10946	ILMN_1704870	PGYRP1	2.1234135	1.8120417	2.4347854	9.563119	13.470226	5.962565e-28	8.800560e-25	52.876703447	malaria_vs_healthy
26219	ILMN_1799848	ANKRD22	2.0722211	1.7436072	2.4008350	9.101122	12.455747	3.506008e-25	2.122978e-22	46.605966965	malaria_vs_healthy
33834	ILMN_2132599	ANKRD22	1.9565047	1.6538495	2.2591598	9.485889	12.768871	4.887196e-26	4.121914e-23	48.543976800	malaria_vs_healthy
13041	ILMN_1716815	CEACAM1	1.8648482	1.5240113	2.2056851	9.727447	10.807282	1.094541e-20	2.019386e-18	36.425918817	malaria_vs_healthy
24115	ILMN_1786303	LILRA3	1.8018248	1.5038964	2.0997531	9.739305	11.945942	8.673717e-24	3.471765e-21	43.449978900	malaria_vs_healthy
26427	ILMN_1801216	S100P	1.8017736	1.3580537	2.2454935	9.921169	8.020675	2.309296e-13	8.067335e-12	19.859291456	malaria_vs_healthy
46163	ILMN_3299604	LOC732229	1.7964020	1.2453150	2.3474900	7.964110	6.438764	1.405014e-09	2.480315e-08	11.344350000	malaria_vs_healthy
23983	ILMN_1785345	GPR84	1.7924033	1.4613042	2.1235023	8.337539	10.692947	2.232870e-20	3.739740e-18	35.724666144	malaria_vs_healthy
41961	ILMN_3237878	LOC100133875	1.7799640	1.4769920	2.0829350	9.708006	11.604570	7.418348e-23	2.340002e-20	41.338650000	malaria_vs_healthy
5126	ILMN_1674574	VNN1	1.7651800	1.4698773	2.0604828	8.708235	11.807044	2.077810e-23	7.607521e-21	42.590595895	malaria_vs_healthy
11265	ILMN_1706635	ELANE	1.7275720	1.2891556	2.1659884	9.164033	7.783394	9.004380e-13	2.838632e-11	18.526259302	malaria_vs_healthy
21896	ILMN_1772131	IL1R2	1.7203653	1.2634819	2.1772487	10.200535	7.437637	6.342364e-12	1.699128e-10	16.615658801	malaria_vs_healthy
38130	ILMN_2371724	CEACAM1	1.7191392	1.3950988	2.0431796	8.950694	10.479282	8.437745e-20	1.218725e-17	34.417147618	malaria_vs_healthy
2988	ILMN_1664330	CEACAM1	1.6815711	1.3461125	2.0170298	8.428744	9.901383	3.004361e-18	3.146319e-16	30.904341134	malaria_vs_healthy
28194	ILMN_1812281	ARG1	1.6800643	1.3524039	2.0077247	8.339133	10.127951	7.437424e-19	8.786150e-17	32.276957812	malaria_vs_healthy

Showing 1 to 29 of 47,231 entries, 11 total columns

Biomart

	probe_id	gene_id	logFC	CLL	CLR	AveExpr	t	P_Value	adj.P.Val	B	comparison
26894	ILMN_1804217	LOC650850	4.8661140	4.2448545	5.4873734	10.122238	15.471374	2.370333e-33	1.865887e-29	65.092215587	malaria_vs_healthy
45959	ILMN_3294365	LOC646993	3.5283820	2.8514320	4.205320	9.129901	10.295290	2.641878e-19	3.381533e-17	33.294710000	malaria_vs_healthy
25657	ILMN_1796316	MMP9	3.3441438	2.9521462	3.7361415	11.134341	16.850824	5.423414e-37	1.280766e-32	73.311906161	malaria_vs_healthy
25670	ILMN_1796409	C1Q8	3.0558567	2.7534681	3.3582452	9.233368	19.961229	7.220945e-45	3.410525e-40	91.036122208	malaria_vs_healthy
15680	ILMN_1732962	KIAA1210	2.9098312	2.2250483	3.5946141	8.738364	8.393335	2.640767e-14	1.119624e-12	21.985272972	malaria_vs_healthy
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66	ILMN_1651429	SELM	2.5215001	1.9258803	3.1171199	9.069287	8.361988	3.173544e-14	1.326465e-12	21.805013838	malaria_vs_healthy
28362	ILMN_1813338	LAG3	2.4347621	2.1327334	2.7367907	9.987423	15.923113	1.492456e-34	2.349674e-30	67.805189500	malaria_vs_healthy
20391	ILMN_1762713	C19orf59	2.3707393	1.9802900	2.7611886	10.739464	11.993303	6.438762e-24	2.739722e-21	43.743086685	malaria_vs_healthy
18244	ILMN_1748915	S100A12	2.3483031	1.9925757	2.7040306	10.776452	13.039364	8.919491e-27	9.158184e-24	50.216735278	malaria_vs_healthy
10946	ILMN_174870	PGYRP1	2.1234135	1.8120417	2.4347854	9.563119	13.470226	5.962565e-28	8.8005560e-25	52.876703447	malaria_vs_healthy
26219	ILMN_1799848	ANKRD22	2.0722211	1.7436072	2.4008350	9.101122	12.455747	3.506008e-25	2.122978e-22	46.605966965	malaria_vs_healthy
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13041	ILMN_1716815	CEACAM1	1.8648482	1.5240113	2.2056851	9.727447	10.807282	1.094541e-20	2.019386e-18	36.425918817	malaria_vs_healthy
24115	ILMN_1786303	LIRRA3	1.8018248	1.5038964	2.0997531	9.739305	11.945942	8.673717e-24	3.471765e-21	43.449978900	malaria_vs_healthy
26427	ILMN_1801216	S100P	1.8017736	1.3580537	2.2454935	9.921169	8.020675	2.309296e-13	8.067335e-12	19.859291456	malaria_vs_healthy
46163	ILMN_3299604	LOC732229	1.7964020	1.2453150	2.3474900	7.964110	6.438764	1.405014e-09	2.480315e-08	11.344350000	malaria_vs_healthy
23983	ILMN_1785345	GPR84	1.7924033	1.4613042	2.1235023	8.337539	10.692947	2.232870e-20	3.739740e-18	35.724666144	malaria_vs_healthy
41961	ILMN_3237878	LOC100133875	1.7799640	1.4769920	2.0829350	9.708006	11.604570	7.418348e-23	2.340002e-20	41.338650000	malaria_vs_healthy
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11265	ILMN_1706635	ELANE	1.7275720	1.2891556	2.1659884	9.164033	7.783394	9.004380e-13	2.838632e-11	18.526259302	malaria_vs_healthy
21896	ILMN_1772131	IL1R2	1.7203653	1.2634819	2.1772487	10.200535	7.437637	6.342364e-12	1.699128e-10	16.615658801	malaria_vs_healthy
38130	ILMN_2371724	CEACAM1	1.7191392	1.3950988	2.0431796	8.950694	10.479282	8.437745e-20	2.128725e-17	34.417147618	malaria_vs_healthy
2988	ILMN_1664330	CEACAM1	1.6815711	1.3461125	2.0170298	8.428744	9.901383	3.004361e-18	3.146319e-16	30.904341134	malaria_vs_healthy
28194	ILMN_1812281	ARG1	1.680643	1.3524039	2.0077247	8.339133	10.127951	7.437424e-19	8.786150e-17	32.276957812	malaria_vs_healthy

Showing 1 to 29 of 47,231 entries, 11 total columns

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13	200624_s_at		ENSG00000280987
14	200626_s_at		ENSG00000280987
24	200689_x_at		ENSG00000283041
27	200032_s_at		ENSG00000237550
35	200823_x_at		ENSG00000230202
106	200034_s_at		ENSG00000230383
115	200012_x_at		ENSG00000239470
141	200084_at		ENSG00000259137
143	200741_s_at		ENSG00000234287
159	1255_g_at		ENSG00000287363
171	200800_s_at		ENSG00000285565
188	200819_s_at		ENSG00000268798
203	200858_s_at		ENSG00000240376
214	200819_s_at		ENSG00000233762
235	200903_s_at		ENSG00000272945
245	200733_s_at		ENSG00000285976
246	200732_s_at		ENSG00000285976
247	200730_s_at		ENSG00000285976
248	200731_s_at		ENSG00000285976
251	200032_s_at		ENSG00000273673
253	200091_s_at		ENSG00000185641
263	200055_at		ENSG00000285338
290	200012_x_at		ENSG00000244021
310	200020_at		ENSG00000225057
317	200041_s_at		ENSG00000254899
331	200817_x_at		ENSG00000239246
348	200689_x_at		ENSG00000255508
353	200038_s_at		ENSG00000212664



Tools

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Search results

Items: 1 to 20 of 2617

[Polyamine synthesis effects capsule expression in *Streptococcus pneumoniae* TIGR4](#)

1. (Submitter supplied) Purpose: We recently reported that isogenic deletion of lysine decarboxylase (*ΔcadA/SP_0916*), an enzyme that catalyzes the biosynthesis of polyamine cadaverine in *Streptococcus pneumoniae* TIGR4 results in loss of capsular polysaccharide (CPS), which constitutes a novel mechanism of regulation of CPS. Here, we conducted RNA-Seq to elucidate molecular mechanisms of CPS regulation in polyamine synthesis impaired pneumococci. more...
Organism: *Streptococcus pneumoniae* TIGR4
Type: Expression profiling by high throughput sequencing
Platform: GPL26601 6 Samples
Download data: XLSX
Series Accession: GSE130511 ID: 200130511
[PubMed](#) [Full text in PMC](#) [Similar studies](#) [SRA Run Selector](#)

[Expression analysis of wild-type *Streptococcus pneumoniae* PN4595-T23 and Vp1 deletion mutant](#)

2. (Submitter supplied) Investigation of differentially regulated genes in deletion of Vp1 compared to the wild-type. VP1 is a signaling peptide. Its characterization is described in Cuevas et al 2019 ADD TITLE AND REF
Organism: *Streptococcus pneumoniae*
Type: Expression profiling by array
Platform: GPL24257 6 Samples
Download data: CSV, PAIR
Series Accession: GSE137991 ID: 200137991
[Analyze with GEO2R](#)

[Transcriptomic comparison of ST556 WT and rr11 mutants of *Streptococcus pneumoniae* ST556 under different condition](#)

3. (Submitter supplied) The transcriptome of *Streptococcus pneumoniae* ST556 WT and rr11 mutants under different growth conditions. The rr11 mutant is a non-virulent derivative of ST556. The rr11 mutation is located in the *rrl* gene, which encodes a regulatory protein involved in the regulation of virulence genes. The rr11 mutation has been shown to affect the expression of several virulence genes, including *cpxA*, *cpxB*, and *cpxC*. The transcriptome analysis will help to understand the molecular mechanisms underlying the virulence of *Streptococcus pneumoniae* ST556 and the role of the rr11 mutation in this process.

Top Organisms [Tree]

- Streptococcus pneumoniae* (2000)
- Mus musculus* (622)
- Homo sapiens* (242)
- Streptococcus mitis* (31)
- Streptococcus oralis* (19)

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Streptococcus pneumoniae (2617) [GEO DataSets](#)

Data retrieval

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MDP - Molecular Degree Perturbation

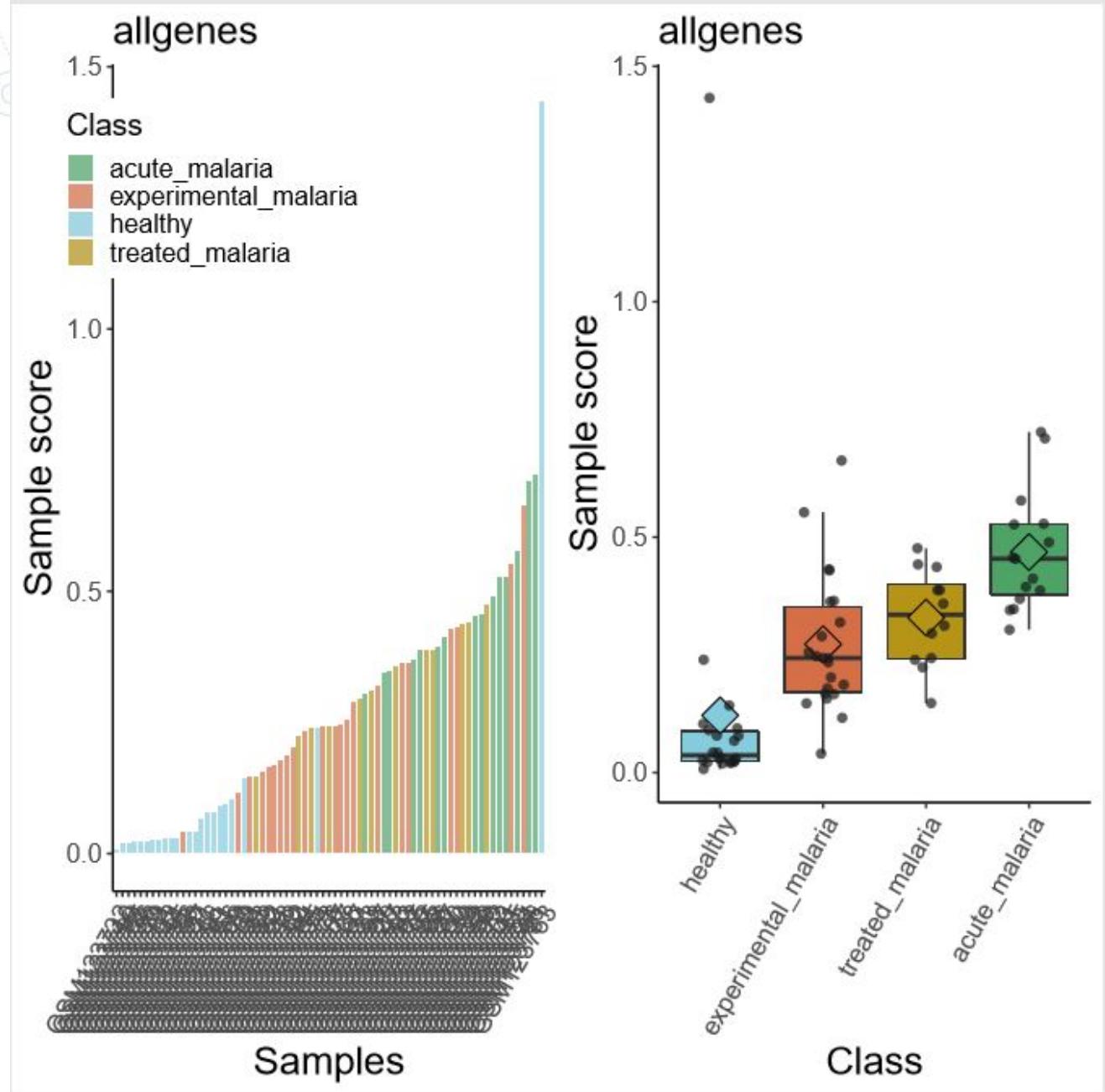
Based on the Molecular Distance to Health (Pankla et al. 2009)

- Quantifies the heterogeneity of samples between at least two classes (control and test)
- Assigns a score to all samples based on how perturbed they are compared to the controls
- Calculate the z-score using the modified z-score (using median absolute deviation)
- Look at genes that are most perturbed in the test versus control classes



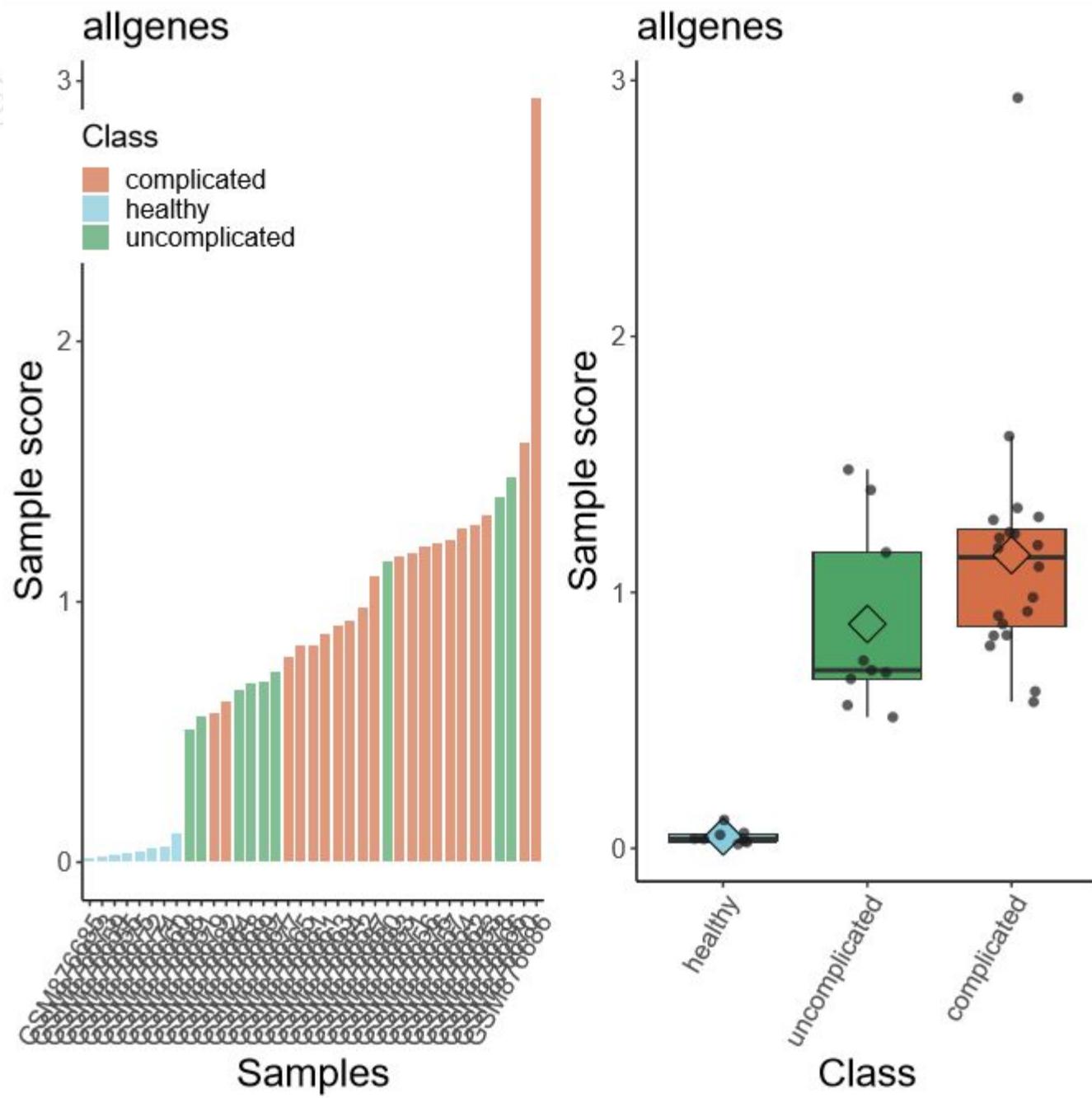
MDP

GSE5418



MDP

GSE35858



Metavolcano

MetaVolcanoR was designed to identify the genes whose expression is consistently perturbed across several studies



Data retrieval

Quality Control

DEG Analysis

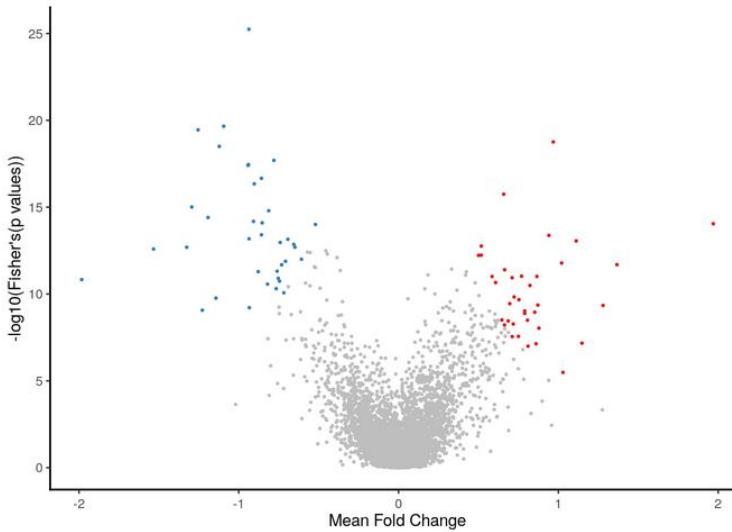
Enrichment analysis

Network Analysis

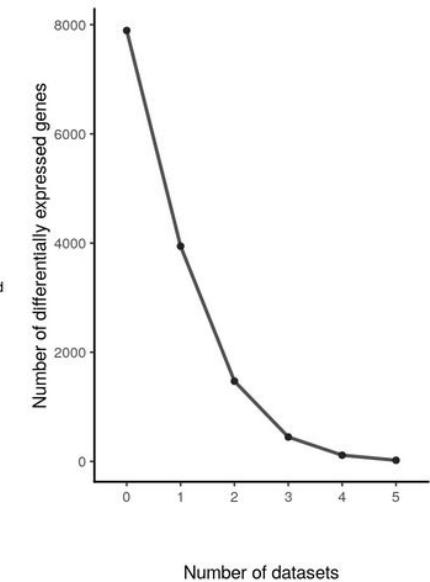
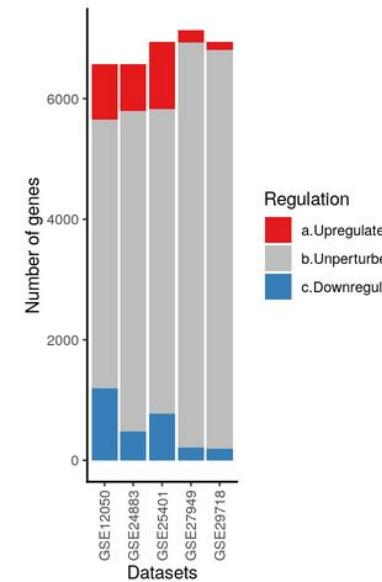
Metavolcano

Vote-counting approach:

identifies DEGs for each study based on the user-defined p-value and fold change thresholds. It plots the inverse cumulative distribution of the consistently DEG.



The combining approach:



Vote-counting approach

The combining approach:

Summarizes the fold change of a gene in different studies by the mean or median depending on the user preference.

In addition, the combining MetaVolcano summarizes the gene differential expression p-values using the Fisher method.

Metavolcano

	Gene.symbol	dircon	randomSummary	randomP	dircon_abs	score	score_abs
19	AAMP	-4	-0.0474121425	1.507076e-01	4	-7.145370e-03	7.145370e-03
20	AANAT	1	0.0018142860	9.936159e-01	1	1.802703e-03	1.802703e-03
21	AAR2	3	0.1276943350	1.933081e-05	3	2.468434e-06	2.468434e-06
22	AARS	-5	-0.0660071763	6.524859e-02	5	-4.306875e-03	4.306875e-03
23	AARS2	-2	-0.1403095079	1.337806e-01	2	-1.877069e-02	1.877069e-02
24	AARSD1	-4	-0.0837186081	9.428402e-03	4	-7.893327e-04	7.893327e-04
25	AASDHPPPT	0	-0.0261321686	8.621641e-01	0	-2.253022e-02	2.253022e-02
26	AASS	-1	-0.1869732000	3.622885e-01	1	-6.773825e-02	6.773825e-02
27	AATF	4	0.3798790428	7.410910e-04	4	2.815249e-04	2.815249e-04
28	AATK	2	0.0886646651	2.414610e-01	2	2.140906e-02	2.140906e-02
29	ABAT	-2	-0.0943143945	2.792970e-01	2	-2.634173e-02	2.634173e-02
30	ABCA1	3	0.3588877686	1.653723e-01	3	5.935008e-02	5.935008e-02
31	ABCA12	-1	-0.2975107000	1.509267e-01	1	-4.490231e-02	4.490231e-02
32	ABCA2	-1	-0.0195311348	6.089388e-01	1	-1.189326e-02	1.189326e-02
33	ABCA3	0	-0.0559415725	4.373000e-01	0	-2.446325e-02	2.446325e-02
34	ABCA4	-2	-0.0735158169	3.966174e-02	2	-2.915766e-03	2.915766e-03
35	ABCA5	-4	-0.3160655972	4.753785e-06	4	-1.502508e-06	1.502508e-06
36	ABCA7	0	-0.0372252342	6.609471e-01	0	-2.460391e-02	2.460391e-02
37	ABCA9	1	0.2648482000	4.751535e-01	1	1.258436e-01	1.258436e-01
38	ABCBl	-1	-0.0773343317	4.979509e-01	1	-3.850870e-02	3.850870e-02
39	ABCBl0	1	0.0243765700	7.606158e-01	1	1.854120e-02	1.854120e-02
40	ABCBl4	-2	-0.1040954964	4.343398e-03	2	-4.521281e-04	4.521281e-04
41	ABCBl5	1	0.1742286000	5.028398e-01	1	8.760907e-02	8.760907e-02
42	ABCBl6	0	-0.1282208498	4.381454e-01	0	-5.617937e-02	5.617937e-02
43	ABCBl7	-1	-0.0721623317	6.279468e-01	1	-4.531410e-02	4.531410e-02
44	ABCBl8	3	0.1139920123	2.143373e-02	3	2.443274e-03	2.443274e-03
45	ABCBl9	-3	-0.0345608554	2.912088e-01	3	-1.006442e-02	1.006442e-02
46	ABCC1	3	0.0802657065	2.365826e-02	3	1.898947e-03	1.898947e-03

The vote-counting MetaVolcano visualizes genes based on the number of studies where genes were identified as DE and the gene FC sign consistency.

If a gene was differentially expressed in five studies, from which three of them it was downregulated, this gene will get a sign consistency score of $2 + (-3) = -1$.

Reactome

The Reactome pathway map for *Homo sapiens* displays a complex network of biological processes. The central hub is Signal Transduction, which branches into various pathways such as Immune System, Metabolism, and Disease. Other major clusters include the Neuronal System, Hemostasis, and Cell Cycle. The map also shows connections to external systems like the Circadian Clock and Developmental Biology. A sidebar on the left provides an Event Hierarchy, and a search bar at the top allows users to find specific terms.

Data retrieval

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DEG Analysis

Enrichment analysis

Network Analysis

Reactome

reactome 3.6 70 Pathways for: Homo sapiens

Analysis: Tour: Layout:

Event Hierarchy: Autophagy, Cell Cycle, Cell Cycle Checkpoints, G1/S DNA Damage Checkpoints, p53-Dependent G1/S DNA damage c, p53-Dependent G1 DNA Damage, Stabilization of p53, ATM phosphorylates TP53 at, CHEK2 phosphorylates TP53, ATM phosphorylates MDM2, Phosphorylation of MDM4 by, Phosphorylation of MDM4 by, MDM2 forms homo- or hetero, MDM2 ubiquitinates phospho, MDM2 binds TP53, MDM2 ubiquitinates TP53, Ubiquitinated TP53 transloca, Autodegradation of the E3 ut, Transcriptional activation of p53, Inactivation of Cyclin E:Cdk2 co, Inactivation of Cyclin A:Cdk2 co, p53-Independent G1/S DNA damage, G2/M Checkpoints, Mitotic Spindle Checkpoint

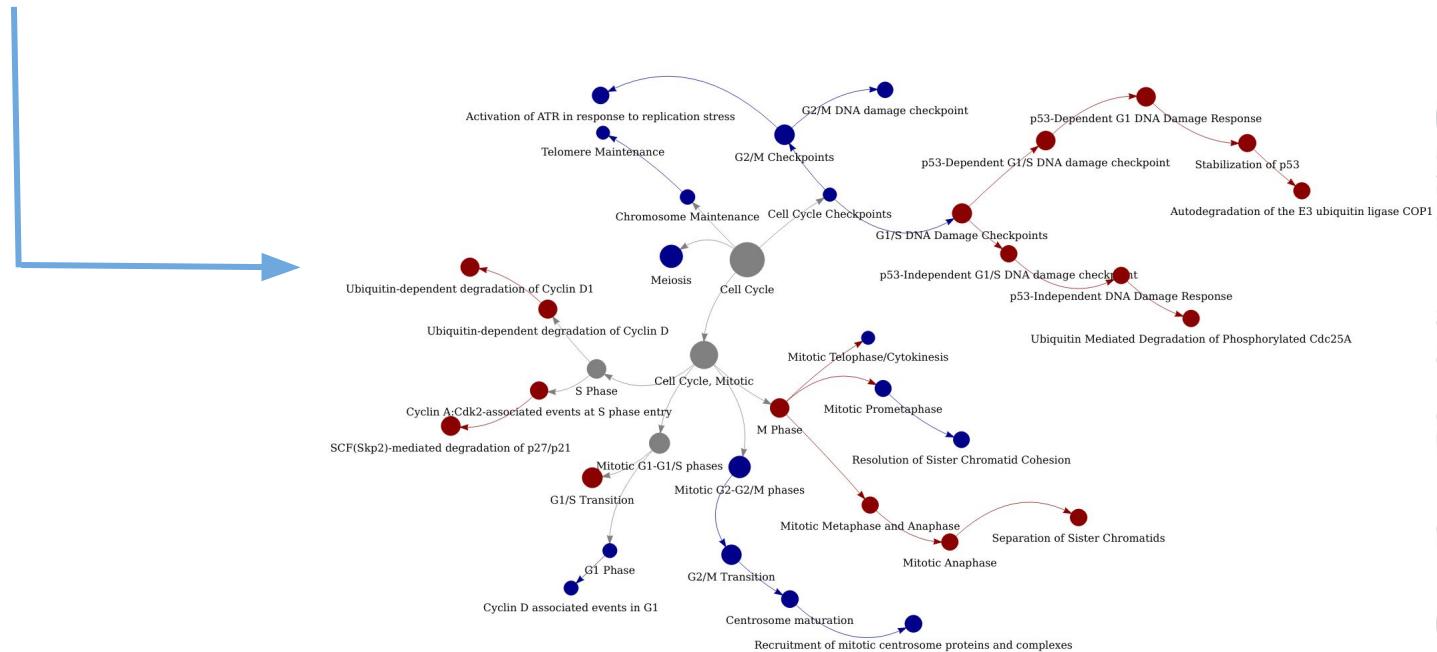
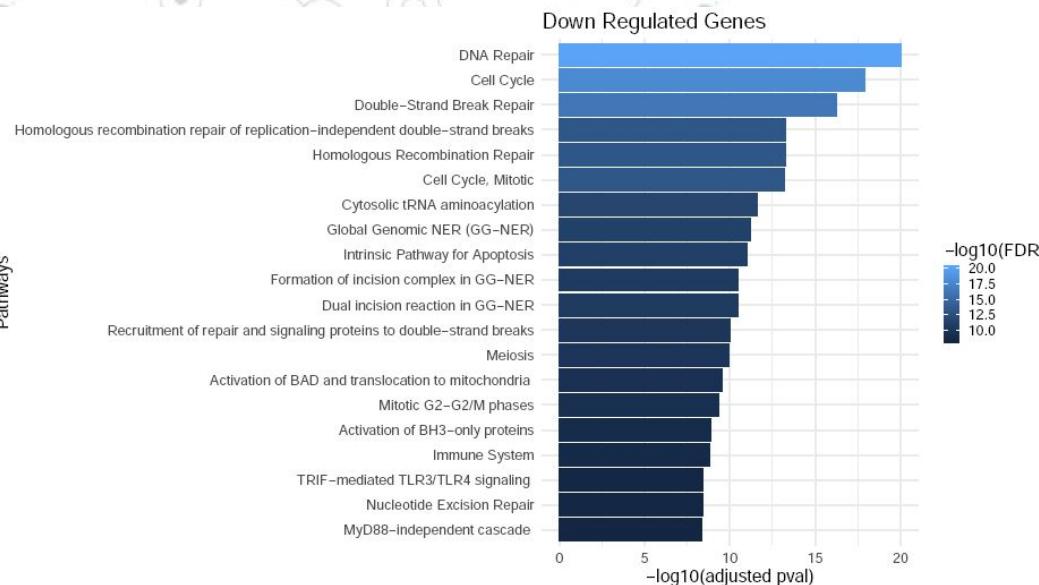
Search for a term, e.g. pten ...

Cell Cycle Checkpoints

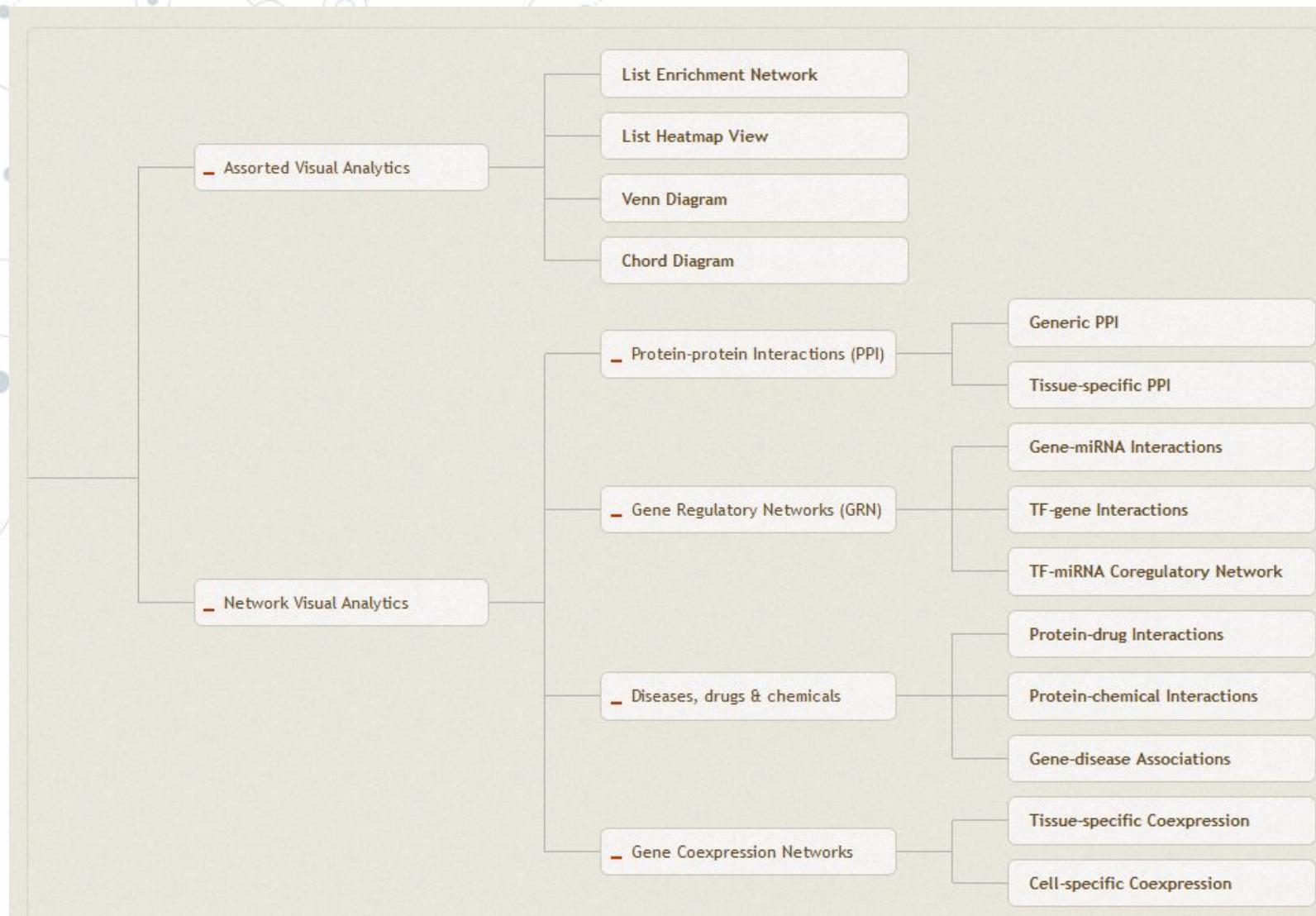
The Reactome pathway map displays a complex network of biological processes. Key clusters include the Cell Cycle (highlighted with a blue border), Cell Cycle Checkpoints, DNA Replication, Chromatin organization, Metabolism of RNA, Signal Transduction, Metabolism, Gene expression (Transcription), Disease, and various cellular functions like Digestion and absorption, Circadian Clock, Developmental Biology, Immune System, Neuronal System, Hemostasis, and Cell-Cell communication. Numerous arrows indicate interactions between these pathways, such as the influence of the Cell Cycle on DNA Replication and the role of Signal Transduction in regulating Gene expression.

Reactome

Pathways



Network Analyst



Data retrieval

Quality Control

DEG Analysis

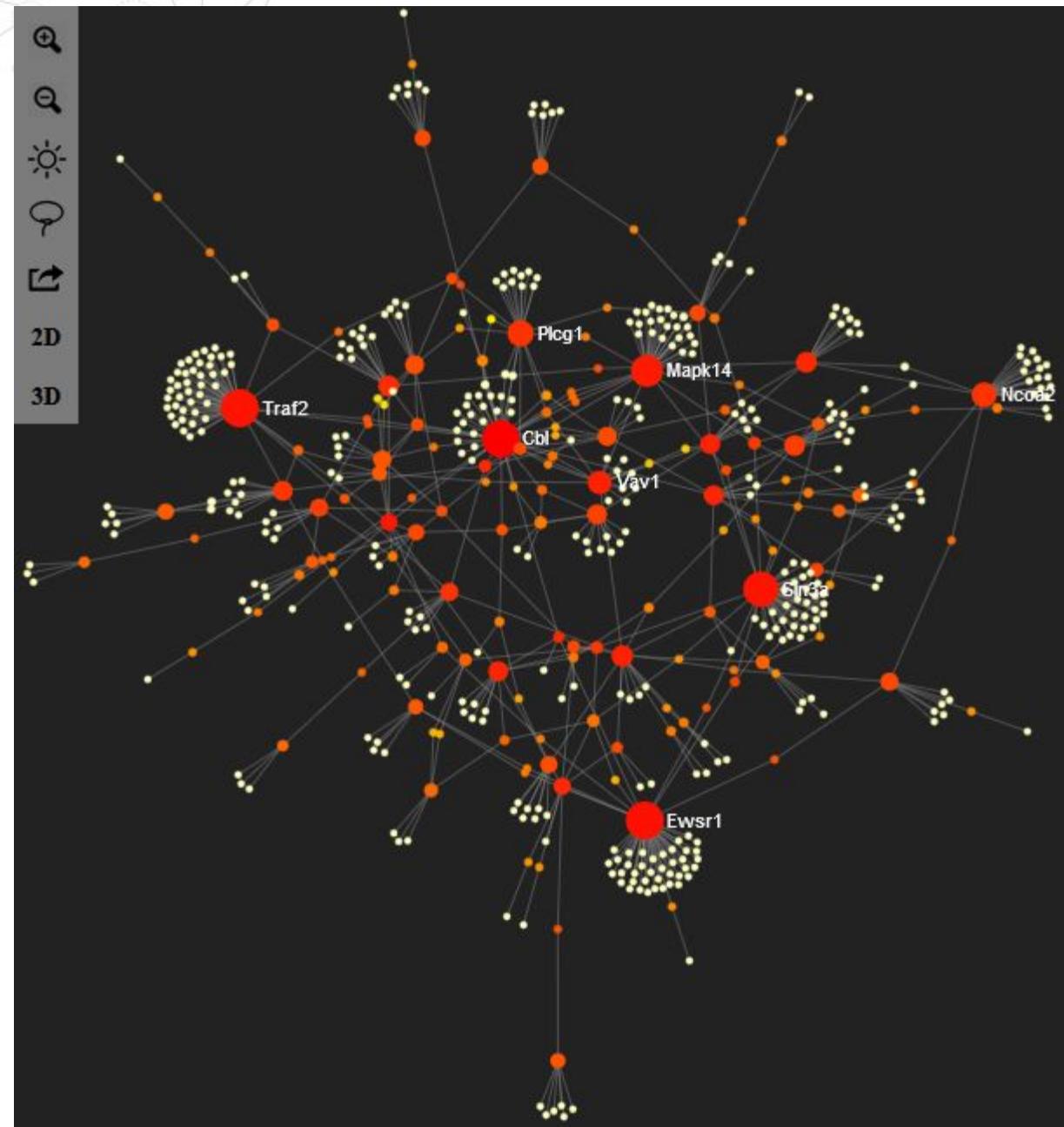
Enrichment analysis

Network Analysis

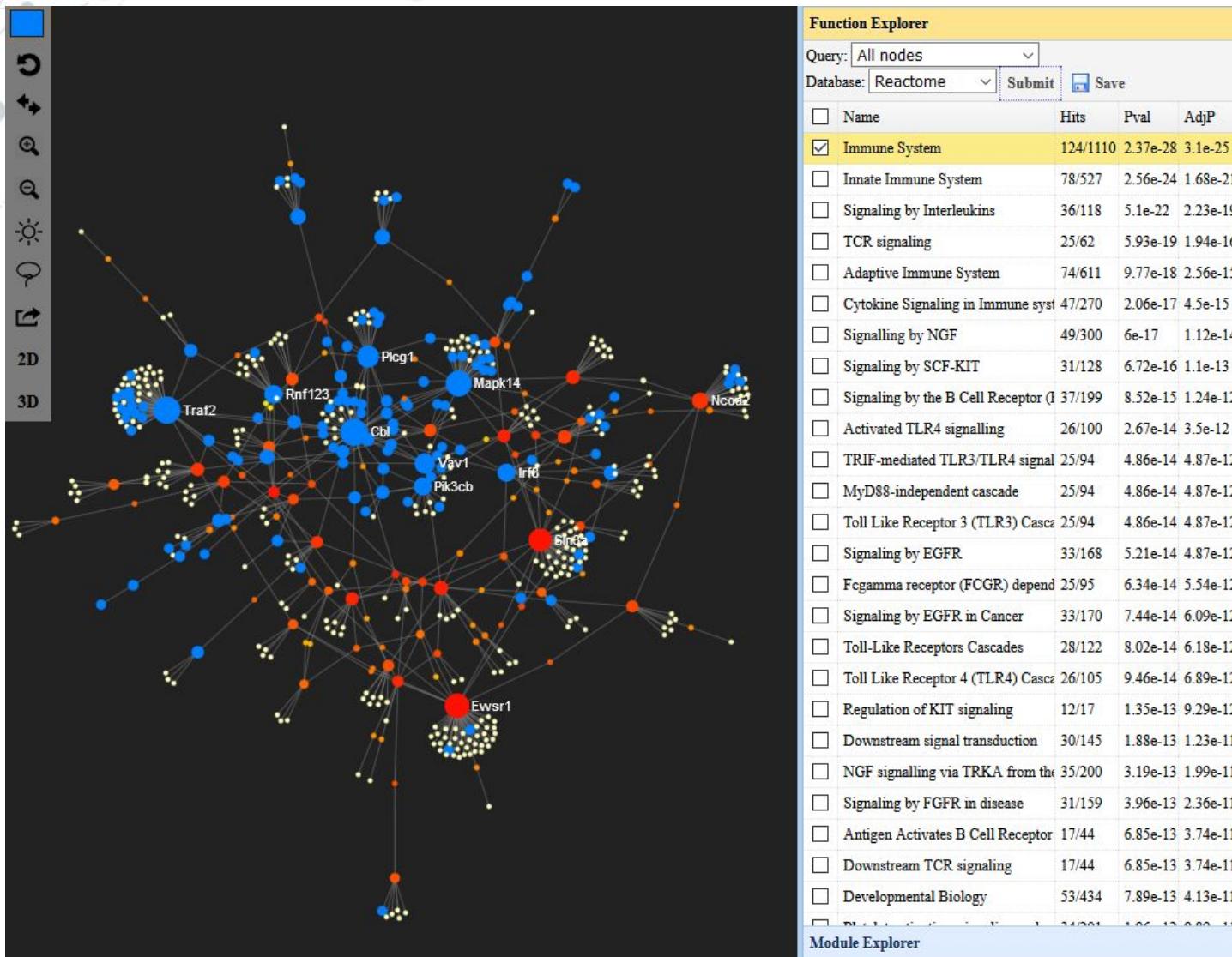
Network Analyst

Pneumococcus data
day 01, comparison I_NS X NI_NS
DEGs UP: $\log FC \geq 0.5$ & $FDR < 0.001$
331 genes

PPi Interactions



Network Analyst



Gephi

Arquivo Área de Trabalho Exibir Ferramentas Janela Ajuda

Visão geral

Laboratório de dados

Visualização

Área de Trabalho 1 X

Aparência X

Nós Arestas |



Único Partition Ranking

#c0c0c0

Aplicar

Distribuição X

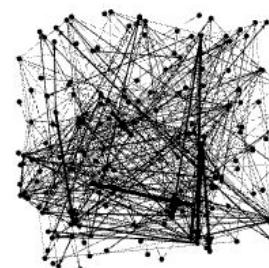
--- Escolha uma distribuição

Executar

<Nenhuma Propriedade>

Grafo X

Arrastando (Configurar)



Filtros

Estatísticas X

Configurações

Visão Geral da Rede

Grau médio

Executar

Grau ponderado médio

Executar

Diâmetro da rede

Executar

Densidade do grafo

Executar

HITS

Executar

Modularidade

Executar

PageRank

Executar

Componentes conectados

Executar

Visão geral dos nós

Coeficiente de clustering médio

Executar

Centralidade de autovetor

Executar

Visão geral das arestas

Comprimento médio de caminho

Executar

Dinâmico

Número de nós

Executar

Número de arestas

Executar

Grau

Executar

Coeficiente de clustering

Executar

Configuração pré-definida... Restaurar



Data retrieval

Quality Control

DEG Analysis

Enrichment analysis

Network Analysis

Gephi

Visão geral Laboratório de dados Visualização

Área de Trabalho 1

Aparência X

Nós Arestas | A

Único Ranking

--Escolha um atributo

Distribuição X

--- Escolha uma distribuição

Executar

<Nenhuma Propriedade>

Configuração pré-definida... Restaurar

Grafo X

Arrastando (Configurar)

Filtros Estatísticas X

Configurações

Visão Geral da Rede

- Grau médio Executar
- Grau ponderado médio Executar
- Diâmetro da rede Executar
- Densidade do grafo Executar
- HITS Executar
- Modularidade 0,568 Executar
- PageRank Executar
- Componentes conectados Executar

Visão geral dos nós

- Coeficiente de clustering médio Executar
- Centralidade de autovetor Executar

Visão geral das arestas

- Comprimento médio de caminho Executar

Dinâmico

- Número de nós Executar
- Número de arestas Executar
- Grau Executar
- Coeficiente de clustering Executar

Arial Negrito, 32

Gephi

Arquivo Área de Trabalho Exibir Ferramentas Janela Ajuda

Visão geral Laboratório de dados Visualização

Área de Trabalho 1



Configurações de visualização X

Configuração pré-definida

Padrão com arestas curvas

Nós

- Largura da borda: 1.0
- Cor da borda: custom [0,0,0]
- opacidade: 100.0
- Per-Node Opacity:
- Rótulos de nó

 - Mostrar rótulos:
 - Fonte: Arial 10 Simples
 - Tamanho proporcional:
 - Cor: original
 - Limitar rótulos:
 - Número máximo de carac: 30
 - Tamanho do contorno: 0.0
 - Cor do contorno: custom [255,255,2...
 - Opacidade do contorno: 80.0
 - Caixa:
 - Cor da caixa: parent
 - Opacidade da caixa: 100.0

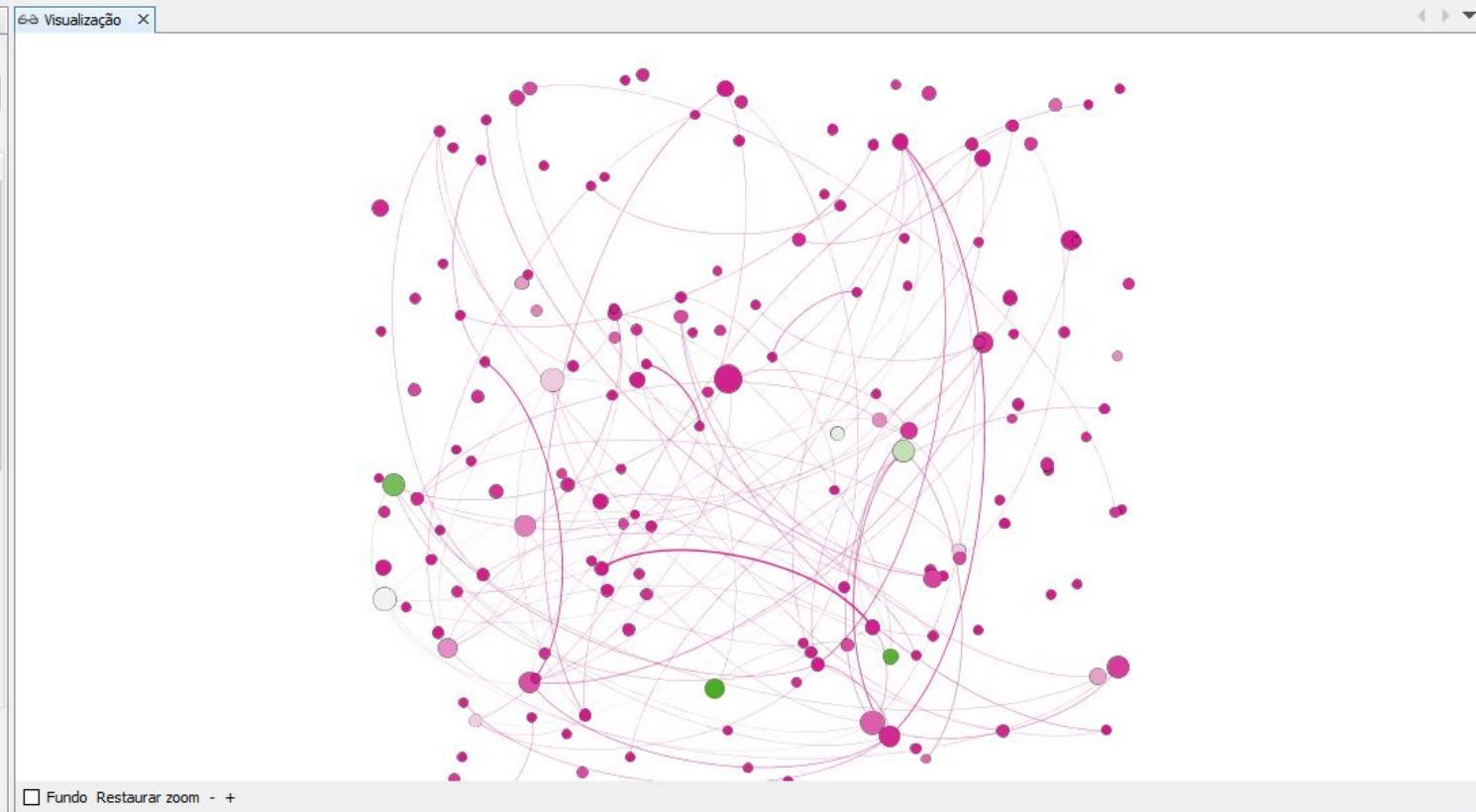
- Arestas

 - Mostrar arestas:
 - Espessura: 1.0
 - Reescalar peso:
 - Min. rescaled weight: 0.1

Relação de previsão: 100%

Atualizar

Exportação: SVG/PDF/PNG



MDP - Molecular Degree Perturbation

First: the baseline is established, for each gene the average expression level and standard deviation of the uninfected control group is calculated.

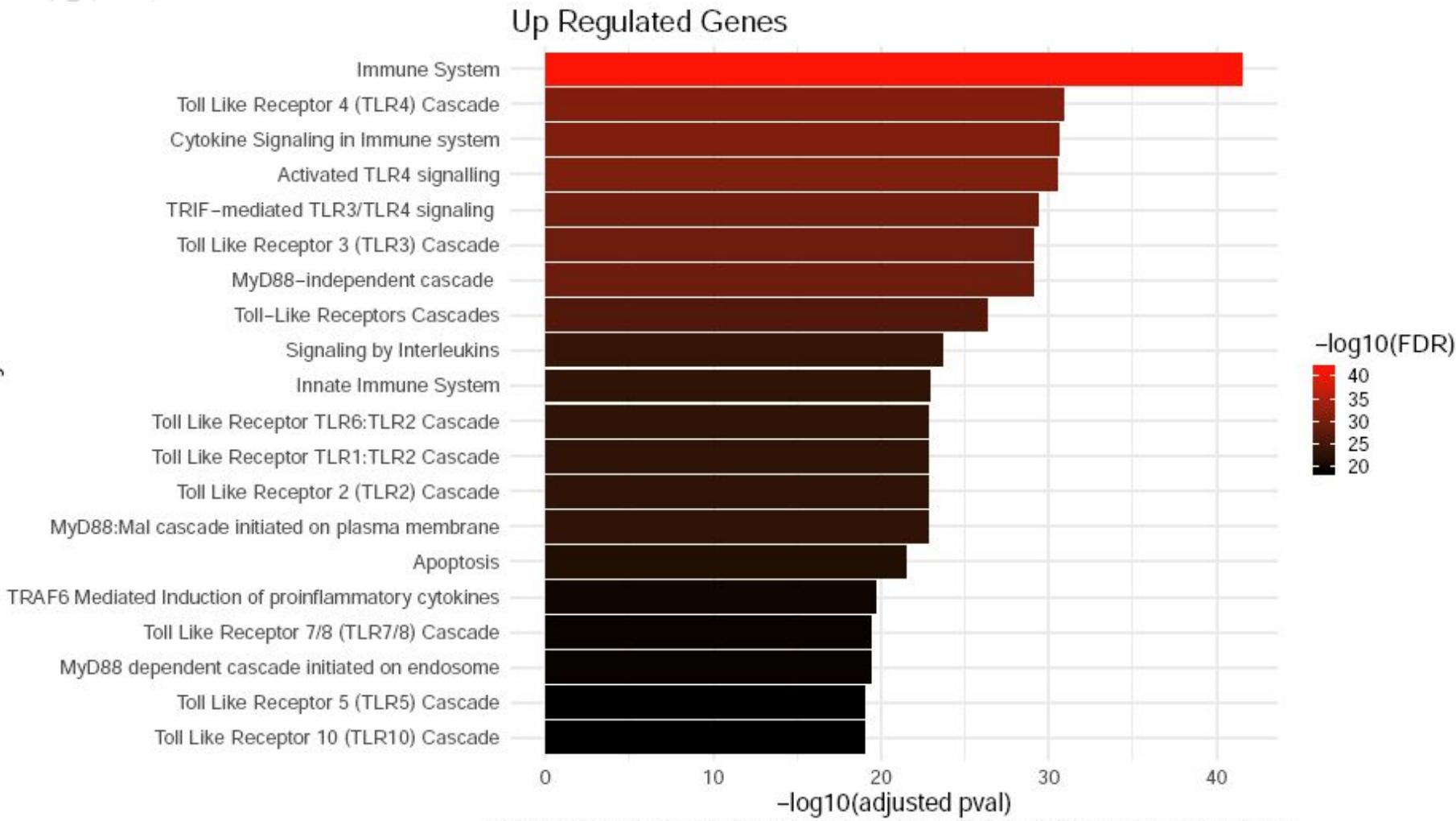
Step 2: the 'distance' of an individual gene from the baseline is calculated: the difference in raw expression level from the baseline average of a gene is determined for a given sample, and then the number of standard deviations from baseline levels that the difference in expression represents is calculated.

Step 3: filters are applied, qualifying genes must differ from the average baseline expression by at least 200 and 2 standard deviations.

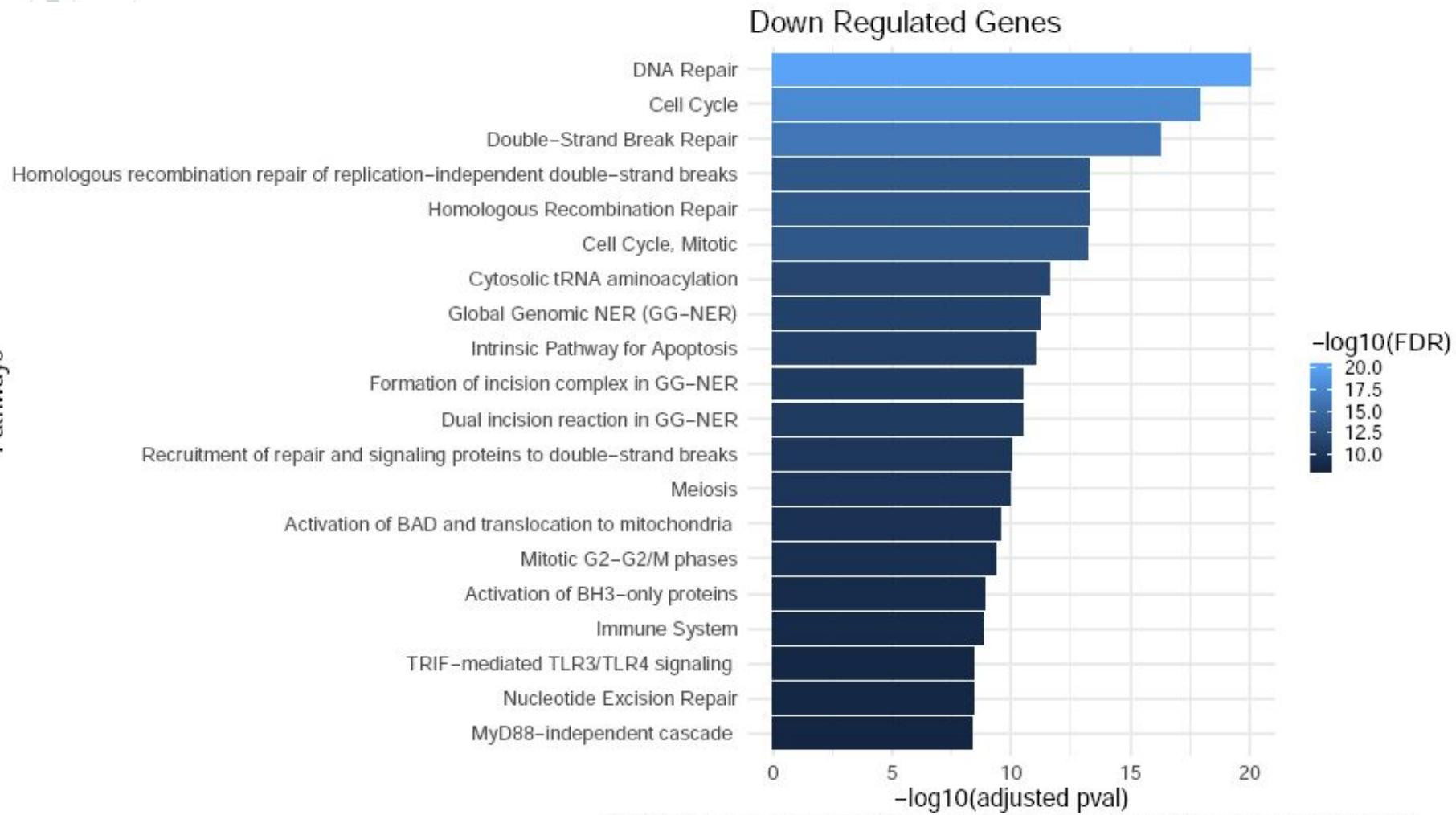
Step 4: a global distance from baseline is calculated. The number of standard deviations for all qualifying genes is added to yield a single value, the global distance of the sample from the baseline.

Step 5: We settle a sample perturbation threshold, $sMDP > 2 SD sMDP(\text{control})$

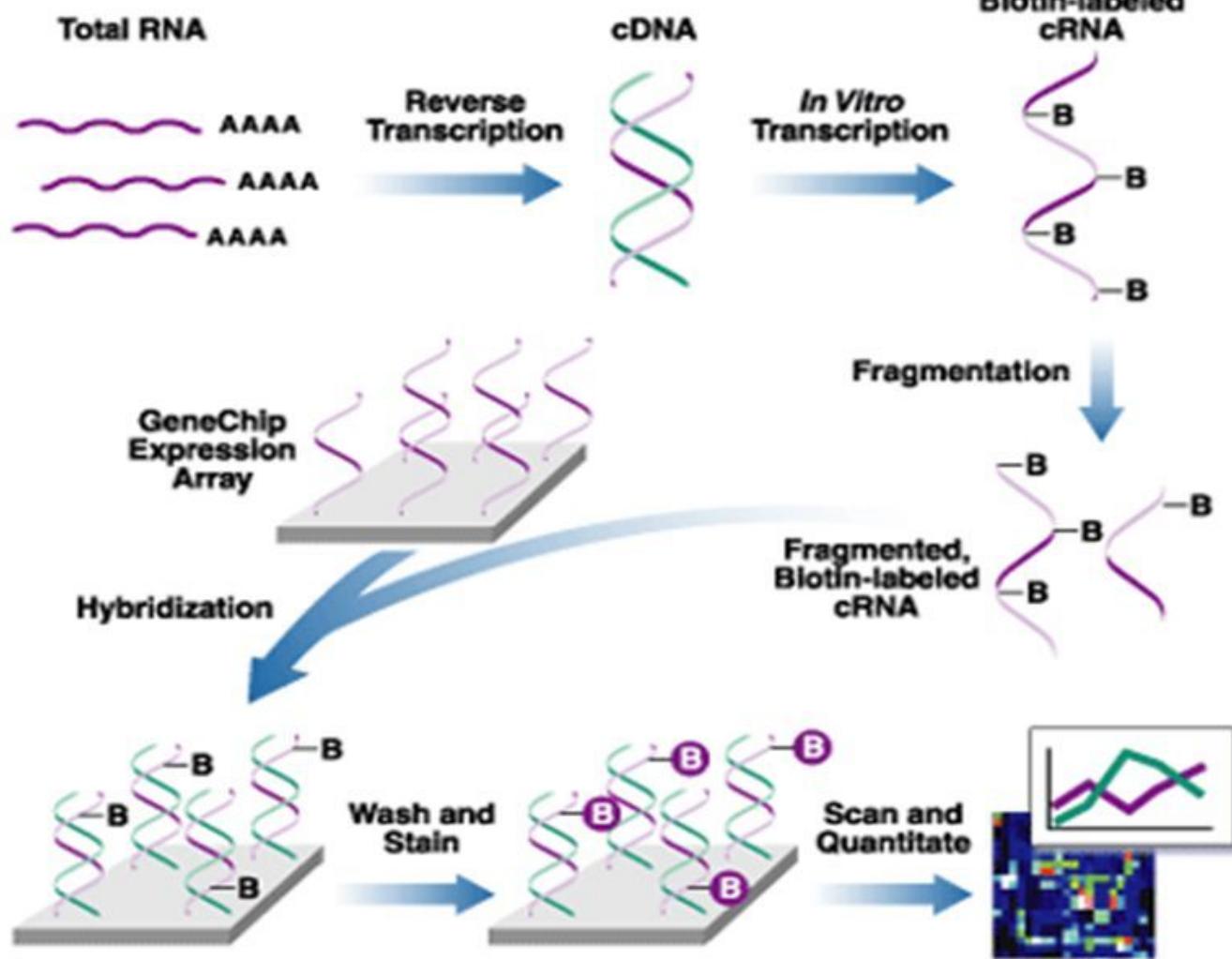
4.5. Enriquecimento de Vias - Genes UP



4.5. Enriquecimiento de Vias - Genes DOWN



A técnica Microarray



Tecnologia Affymetrix - Ryan MM et al; 2004

Estudos escolhidos

GSE35858

Vietnã

8 indivíduos
controle



9 indivíduos com malária
não complicada

20 indivíduos com malária
complicada

Desenho do estudo inadequado

Whole
Blood

GSE34404
Oeste Africano

62 indivíduos
controle



93 crianças infectadas
com malária

Whole
Blood

GSE5418
USA

22 Indivíduos
Controle



22 Indivíduos Infectados
Experimentalmente

PBMC

Camarões

15 indivíduos com
malária aguda

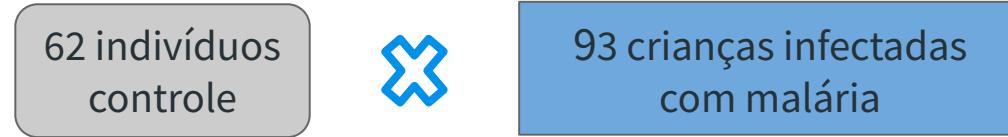
12 indivíduos
após tratamento

Estudos escolhidos

GSE35858
Vietnã



GSE34404
Oeste Africano



GSE5418
USA



Camarões

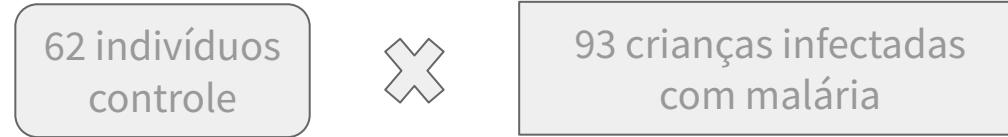


Estudos escolhidos

GSE35858
Vietnã



GSE34404
Oeste Africano



GSE5418
USA

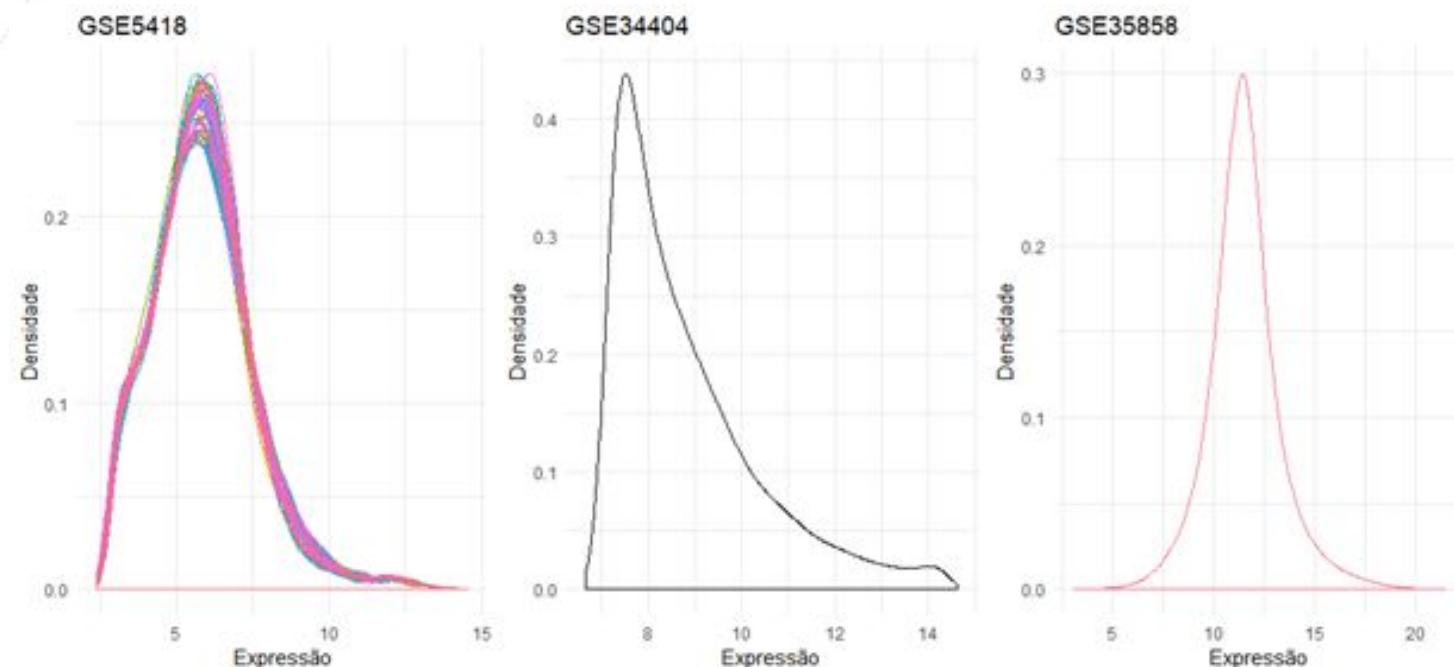


PBMC

Camarões



Pré Processamento e controle de qualidade



Aquisição dos dados

Pré Processamento
Controle de Qualidade

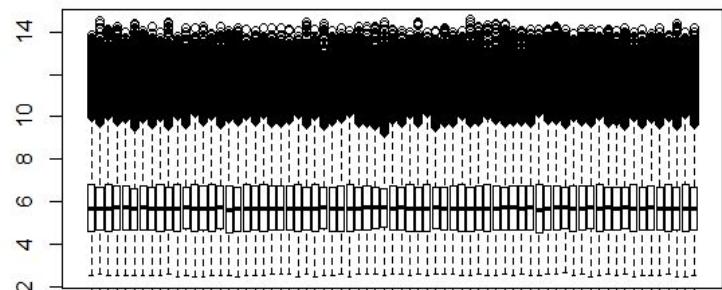
Análise -
DEGs

Integração dos
Estudos

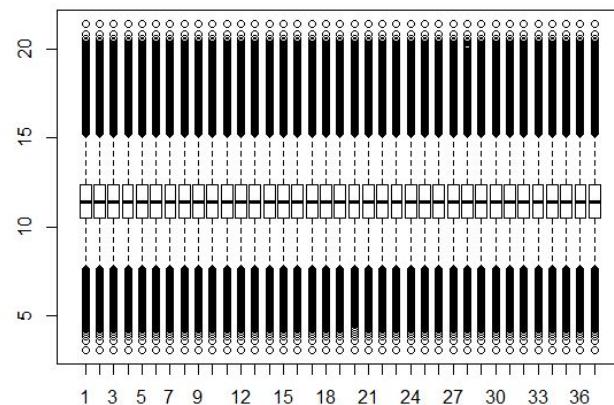
Análises de
Vias

Boxplots

Estudo GSE5418



Estudo GSE35858



Estudo GSE34404

