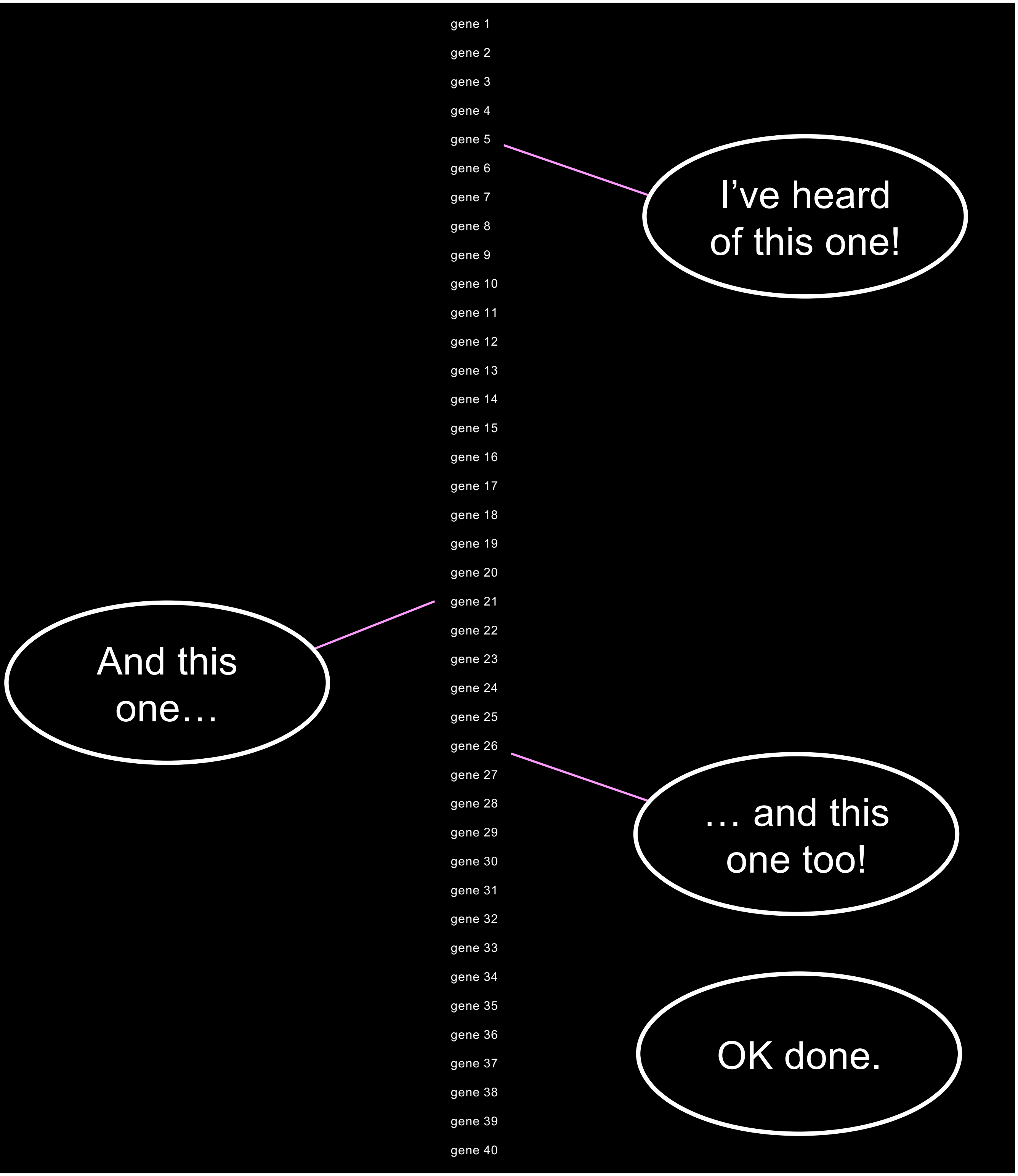
Interpreting your gene list

Steve W. Cole, Ph.D.

UCLA School of Medicine

Division of Hematology-Oncology



gene 1
gene 2
gene 3
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gene 26
gene 27
gene 28
gene 29
gene 30
gene 31
gene 32
gene 33
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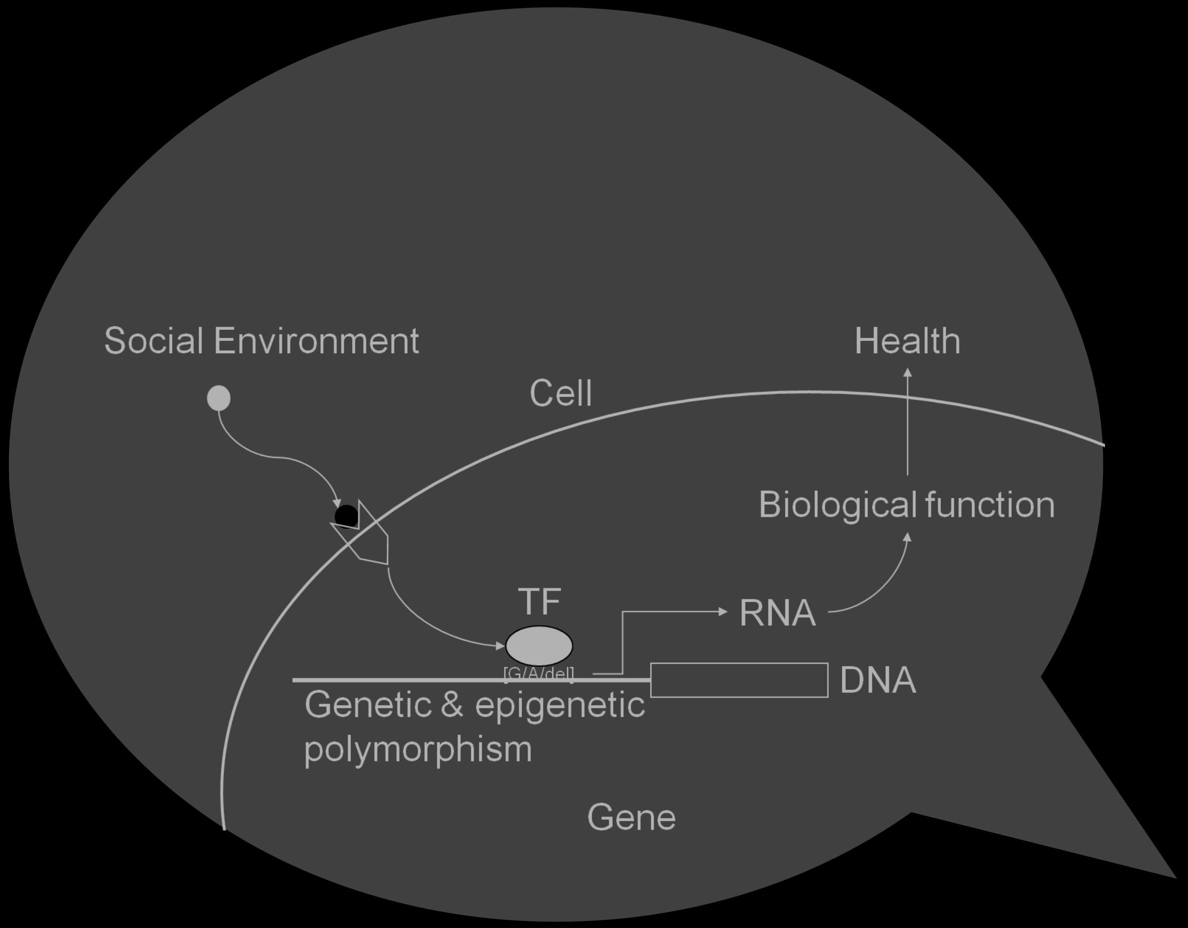
gene 35
gene 36
gene 37
gene 38
gene 39
gene 40

I’ve heard of this one!

And this one…

… and this one too!

OK done.



Social Environment

Cell

Health

Biological function

TF

RNA

[G/A/del]

DNA

Genetic & epigenetic polymorphism

Gene

gene 1

gene 2

gene 3

gene 4

gene 5

gene 6

gene 7

gene 8

gene 9

gene 10

gene 11

gene 12

gene 13

gene 14

gene 15

gene 16

gene 17

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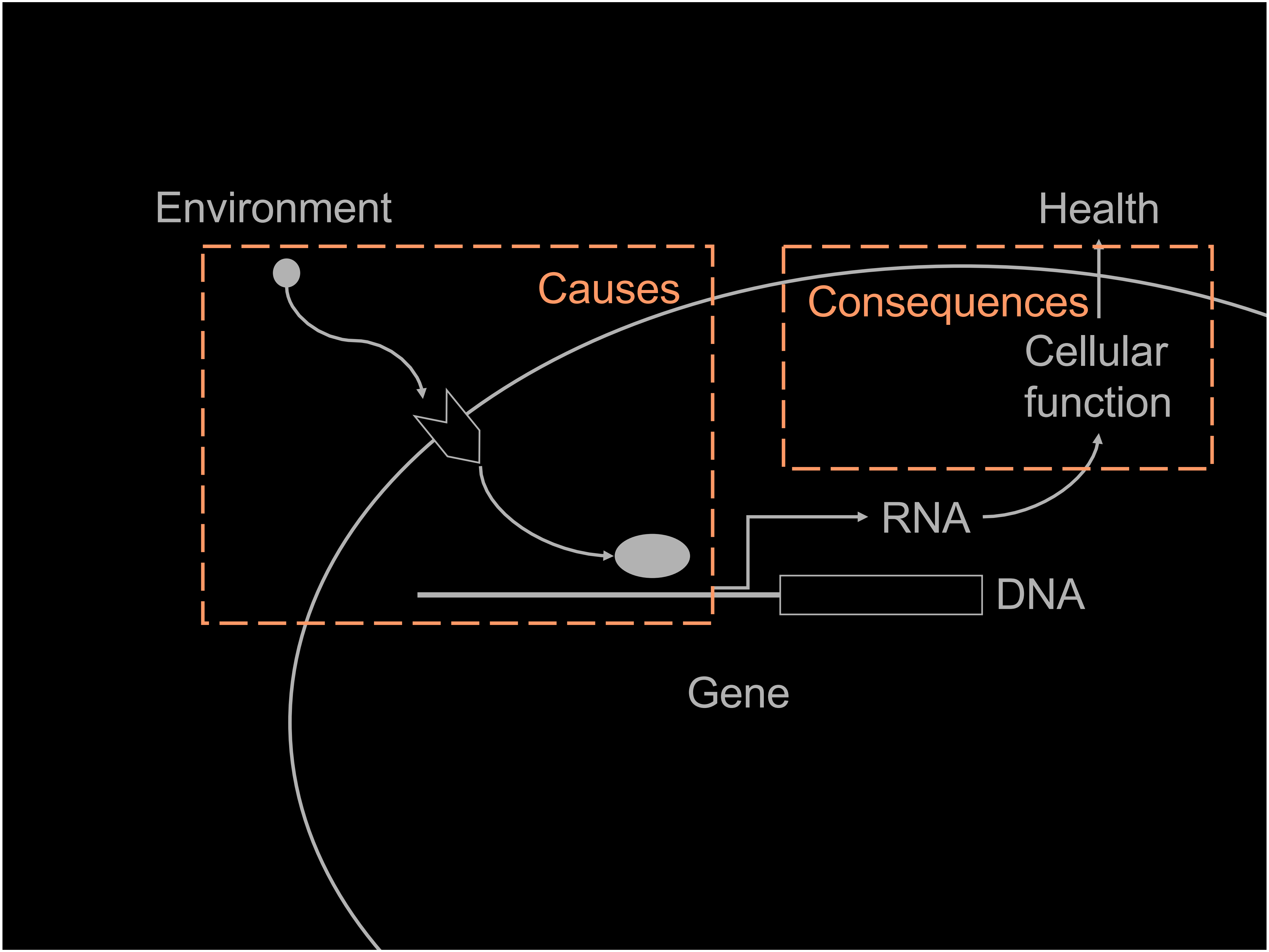
Environment
Health
Causes
Consequences
Cellular function
RNA
DNA
Gene

Interpreting results within an unbiased
“expert annotation” reference space

gene 1
gene 2
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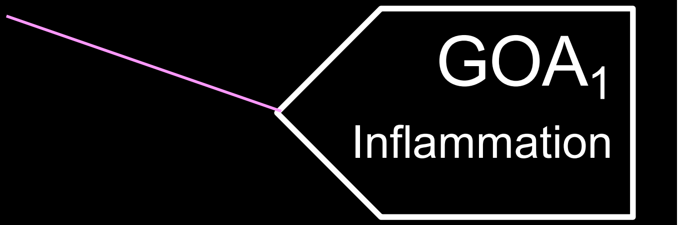


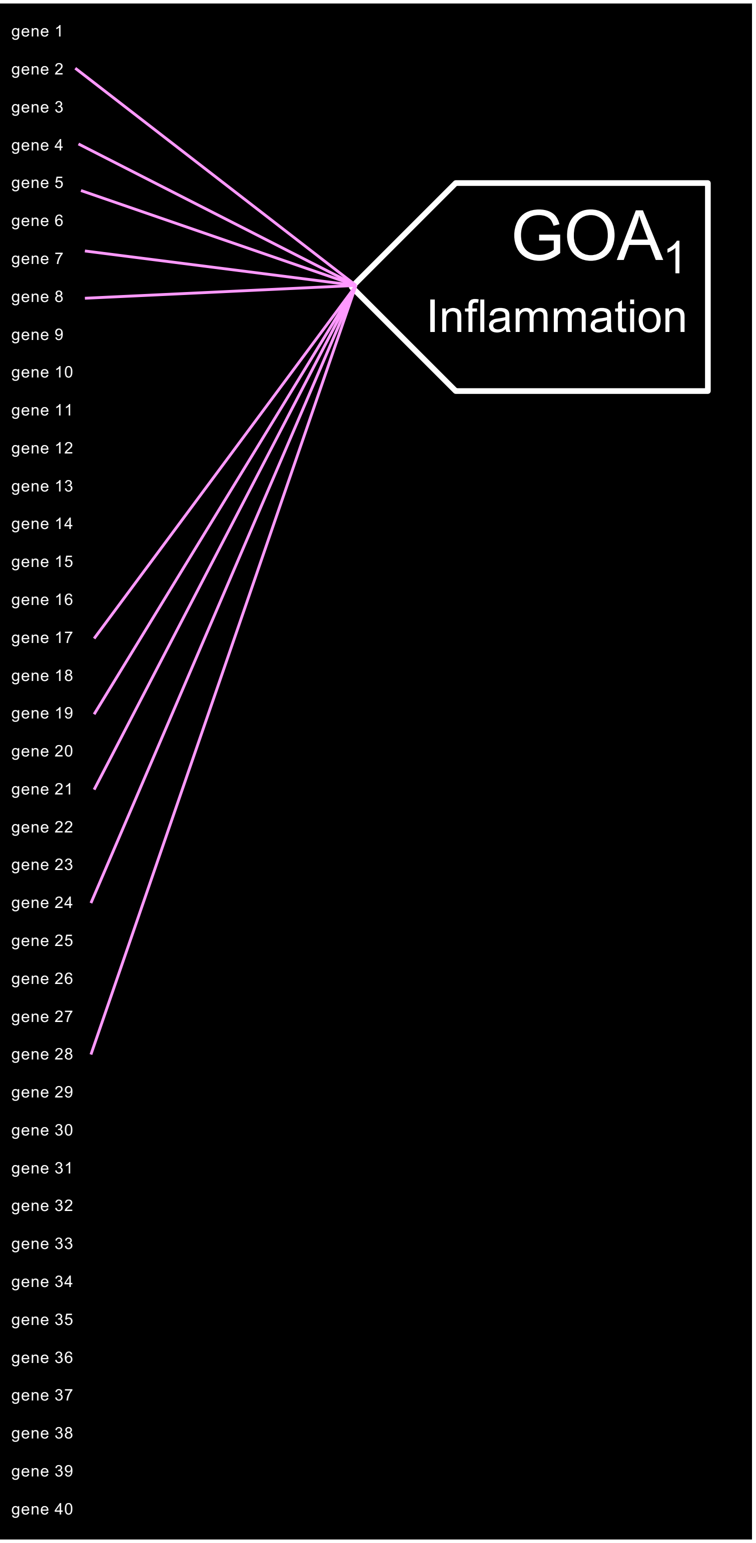
GOA$_1$

Inflammation

Interpreting results within an unbiased “expert annotation” reference space

A statistical caveat: what’s the right reference point for a null hypothesis?

- Genome-wide baseline?
- Expressed transcriptome?
- Up- vs. down-regulated gene sets?



Interpreting results within an unbiased "expert annotation" reference space

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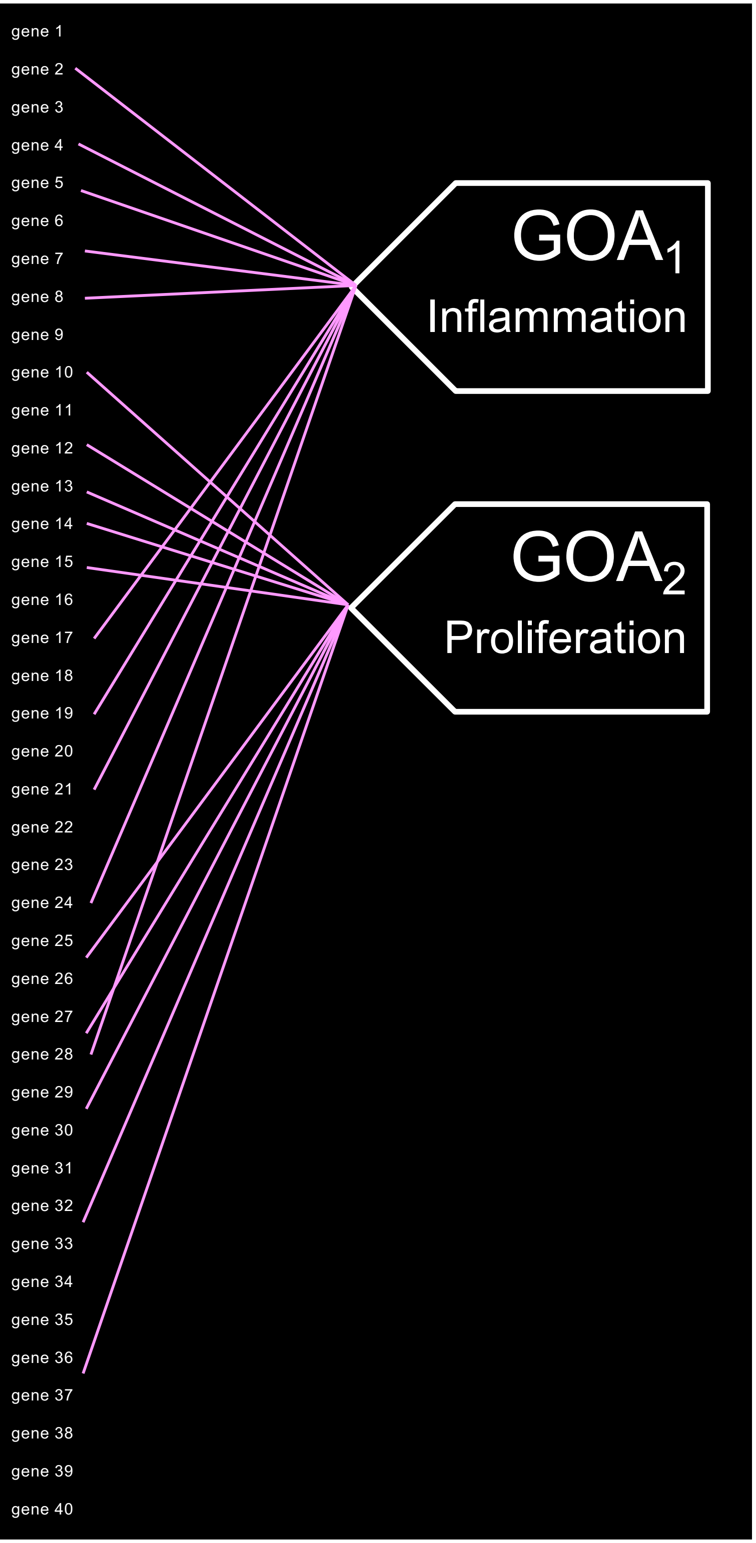

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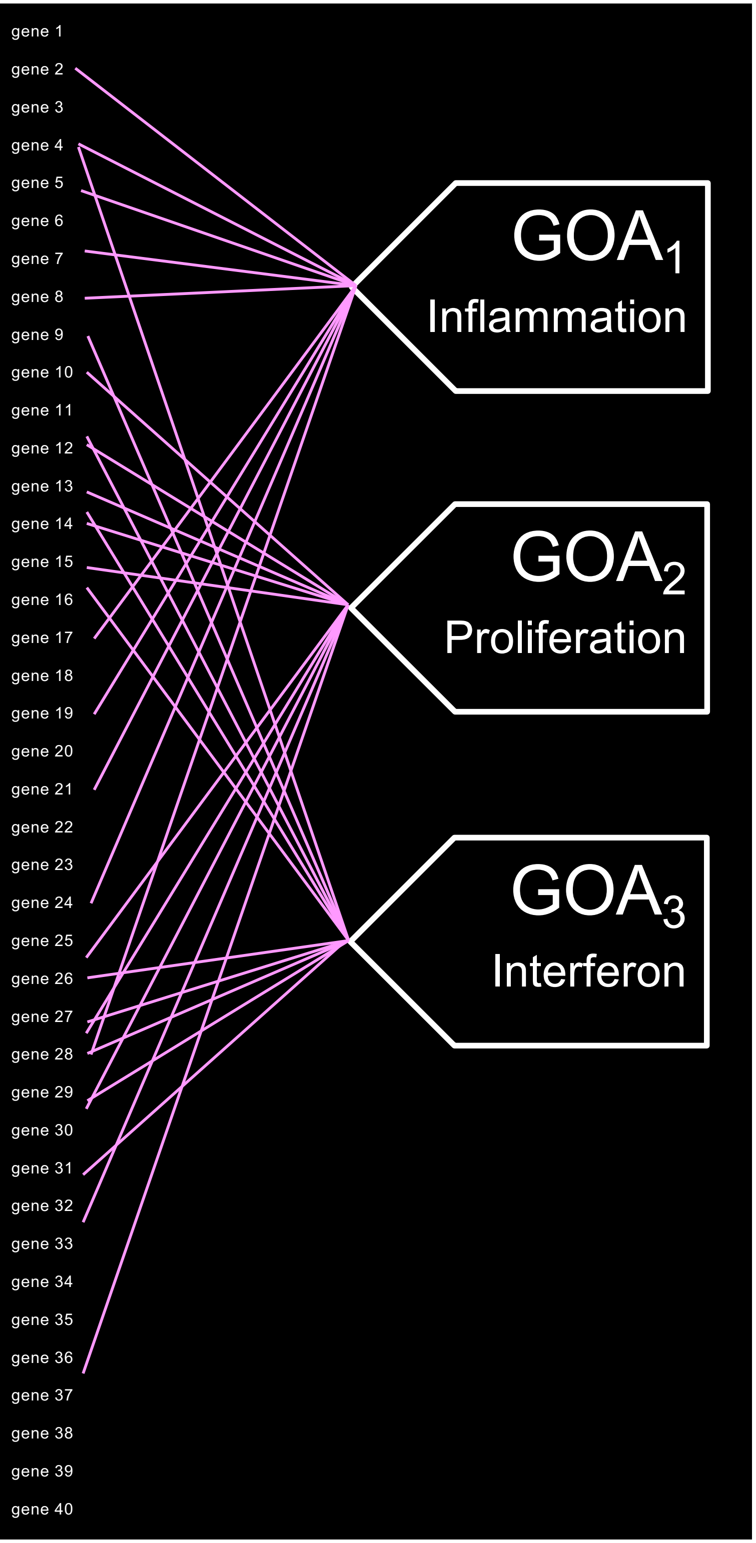

gene 1
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gene 27
gene 28
gene 29
gene 30
gene 31
gene 32
gene 33
gene 34
gene 35
gene 36
gene 37
gene 38
gene 39
gene 40

GOA_1
Inflammation

GOA_2
Proliferation

GOA_3
Interferon

Interpreting results within an unbiased “expert annotation” reference space

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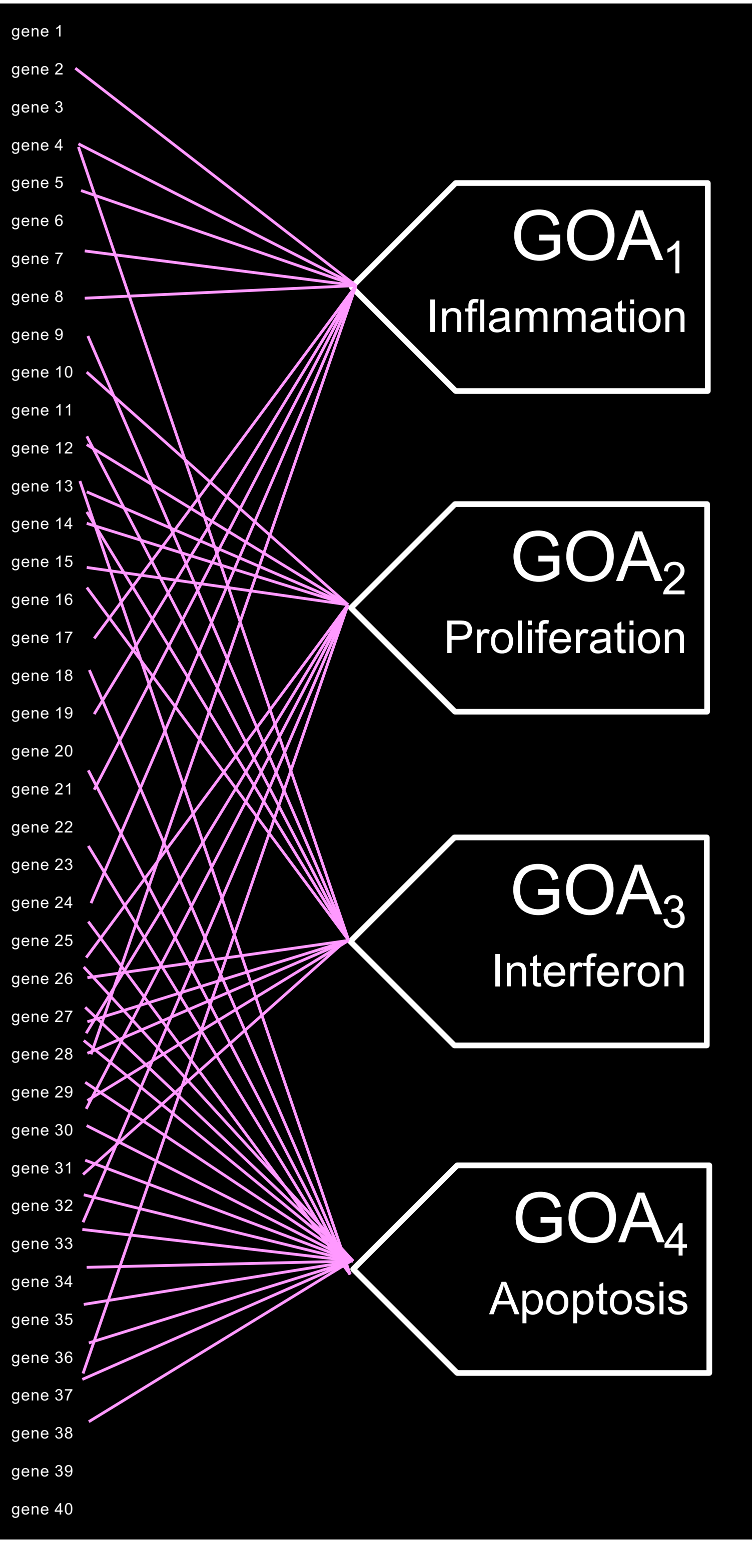
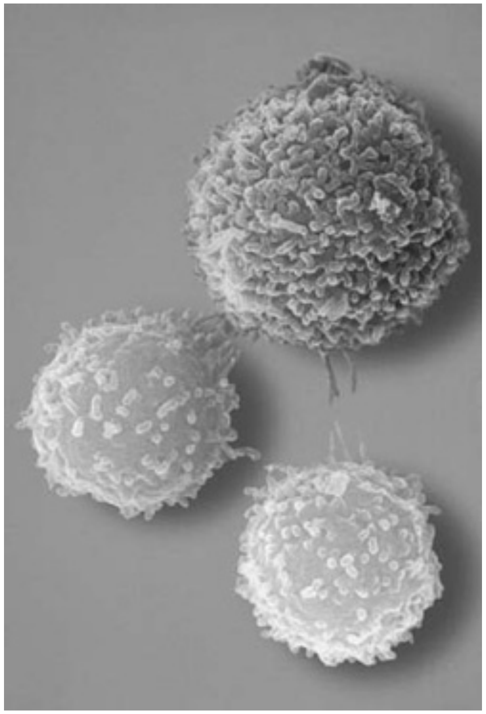


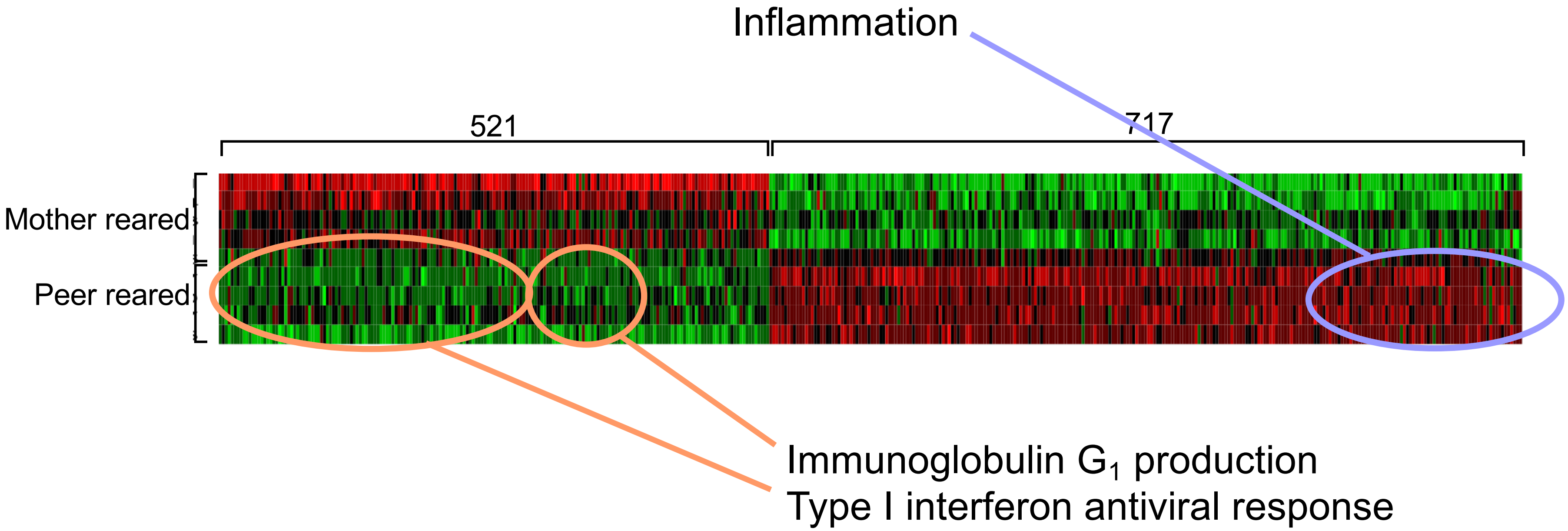
Social instability



Cole et al (2012) PNAS

CTRA – conserved transcriptional response to adversity

Social instability



Inflammation

Immunoglobulin G_1 production

Type I interferon antiviral response

Cole et al (2012) PNAS

Low SES

Social loss / bereavement

Post-traumatic stress

Cancer diagnosis

Social threat

Loneliness

Social instability

Chronic stress

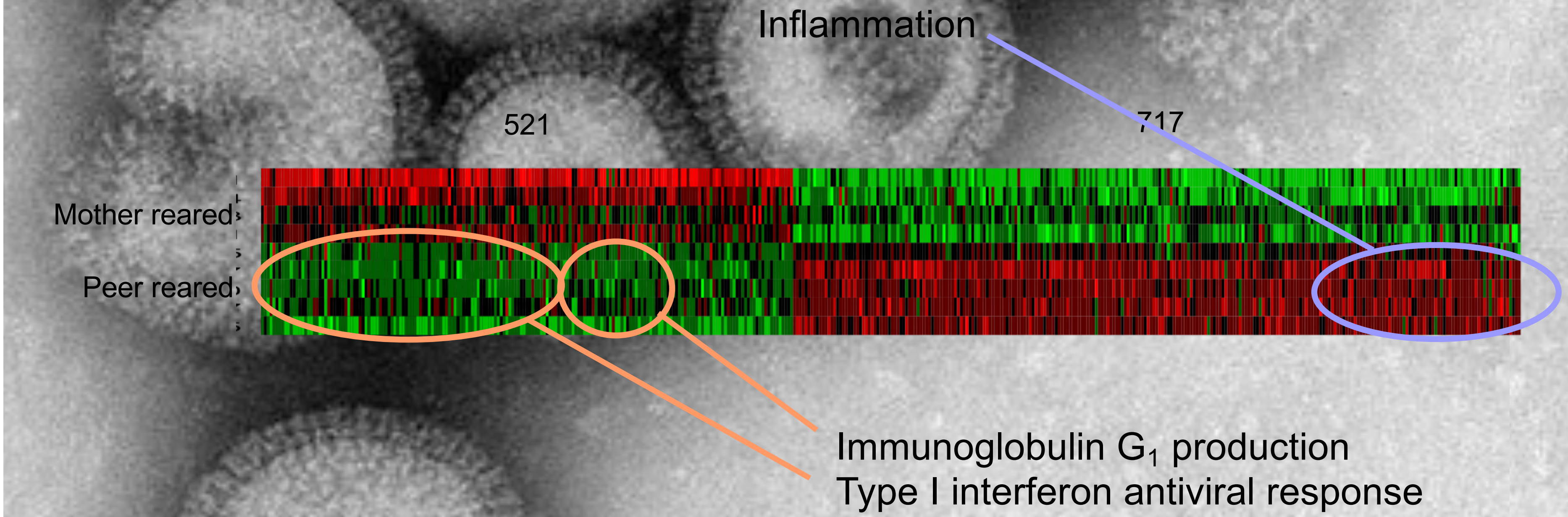
Low social rank

Caregiving for seriously ill

Anxiety

Early life adversity

CTRA – conserved transcriptional response to adversity



Immunoglobulin G_1 production
Type I interferon antiviral response

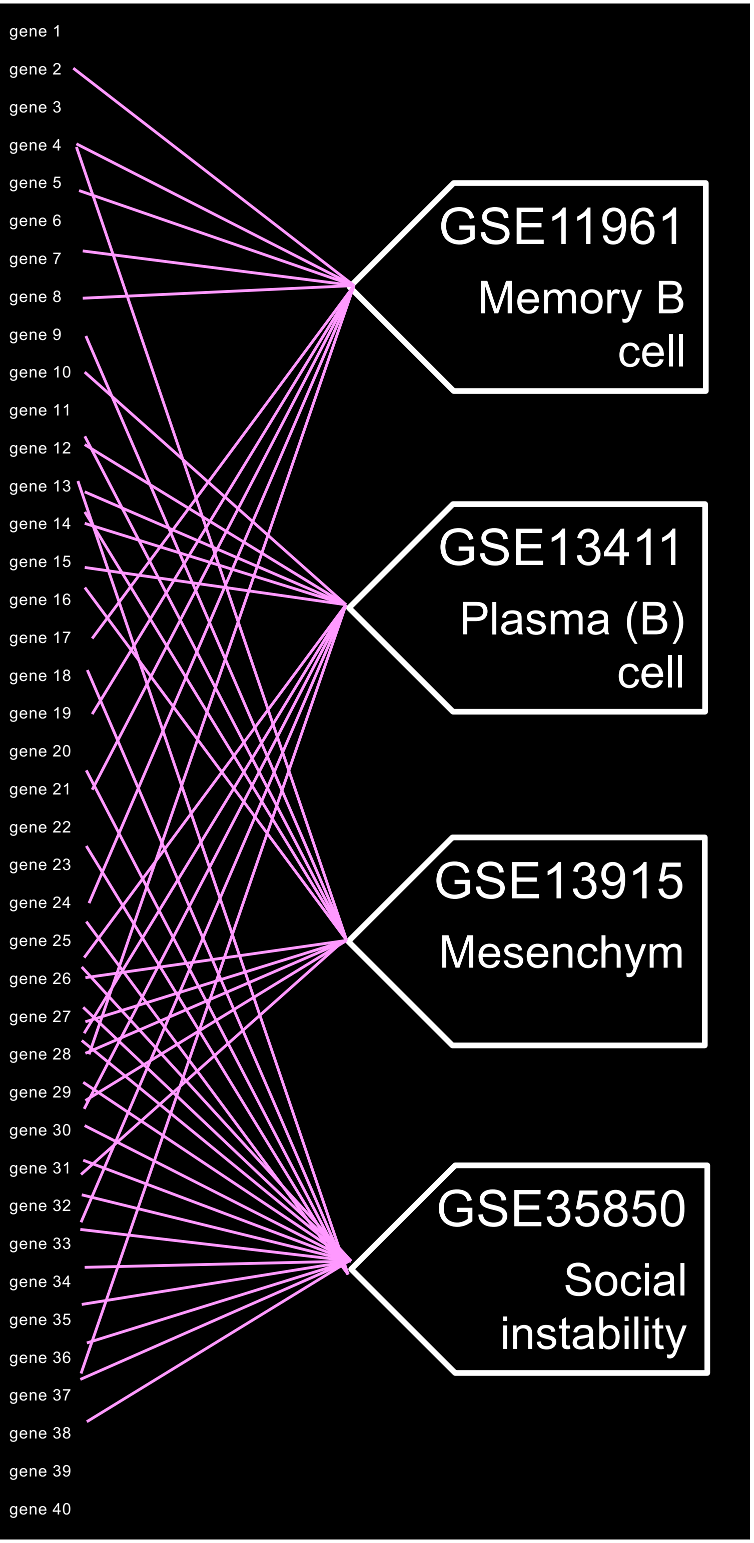
Irwin & Cole, Nature Reviews Immunology 2011
Cole, PLoS Genetics 2014
Nunn & Altizer, Infectious Diseases in Primates 2006

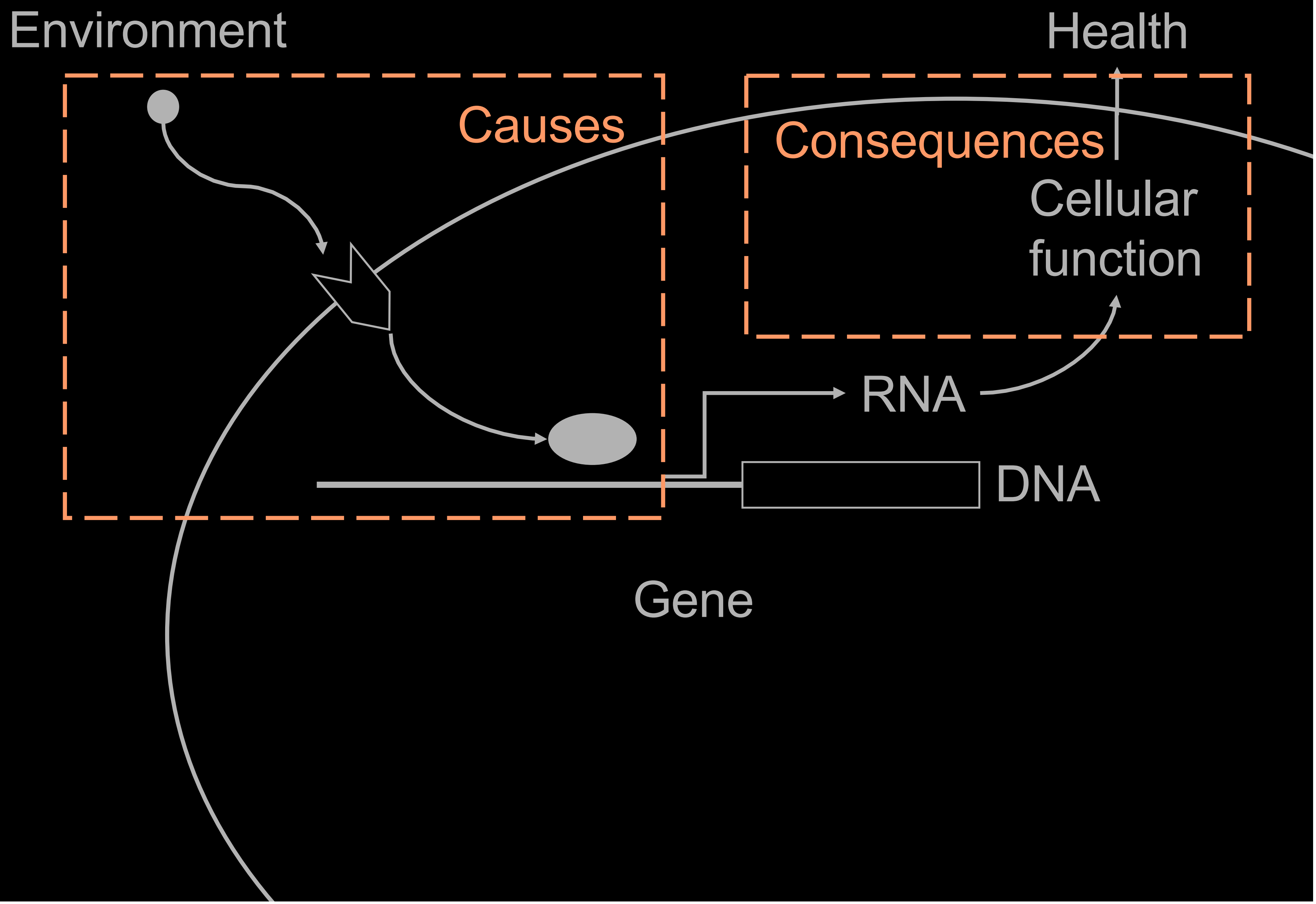
Interpreting results within an empirical transcriptome reference space
(vs. "expert" GO tags)

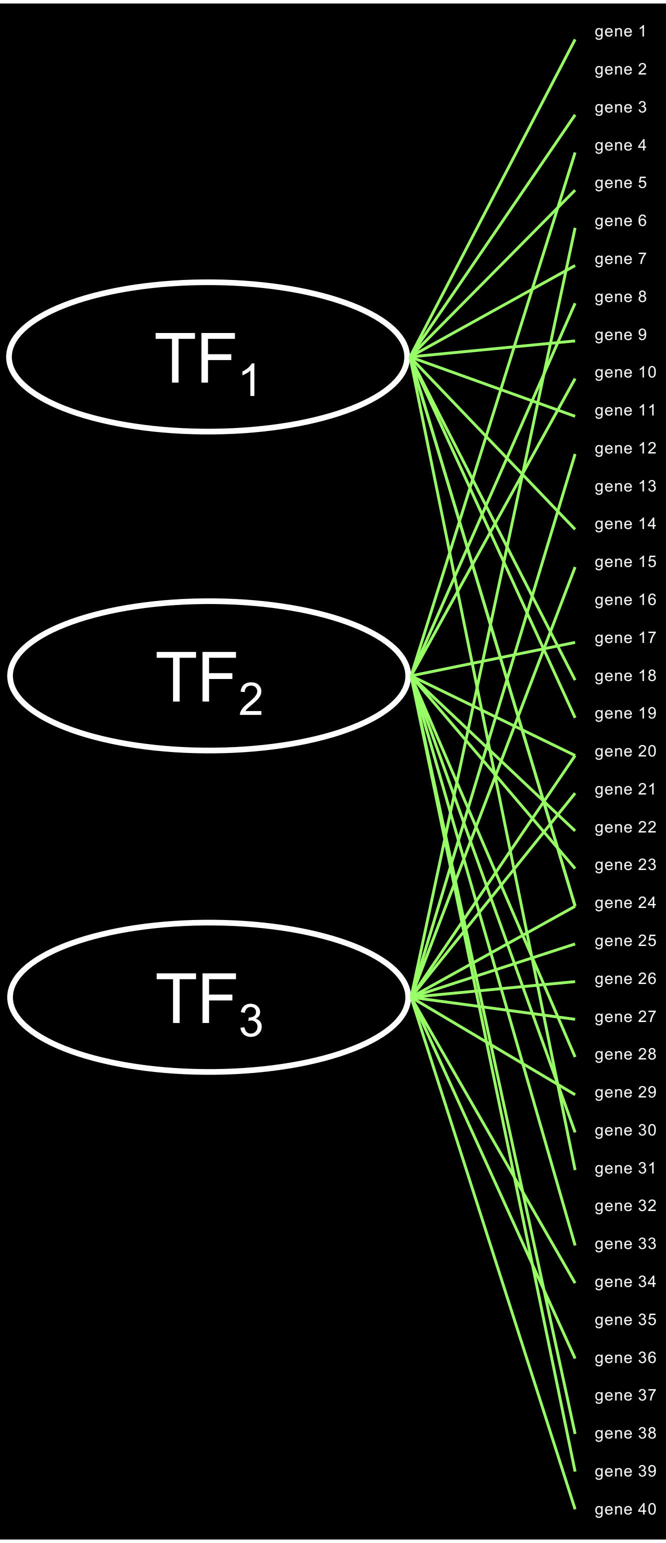
1. GEO search
(or ArrayExpress, GSEA, etc.)

2. Grab the data & compute diagnosticity scores for their experimental "poles"

3. Test for gene set differential expression in your data (either them|you or you|them)




Environment
Health
Causes
Consequences
Cellular function
RNA
DNA
Gene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TF_2
TF_3
gene 1
gene 2
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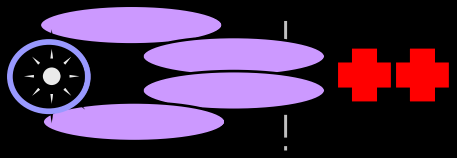
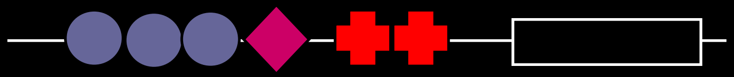
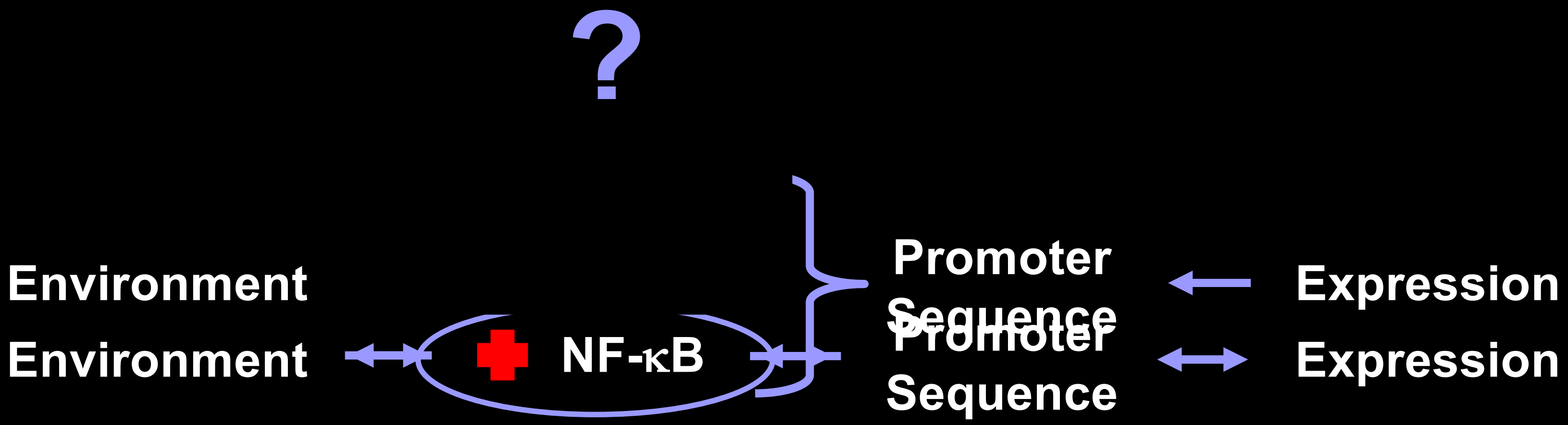






?

Environment

Promoter Sequence

Expression

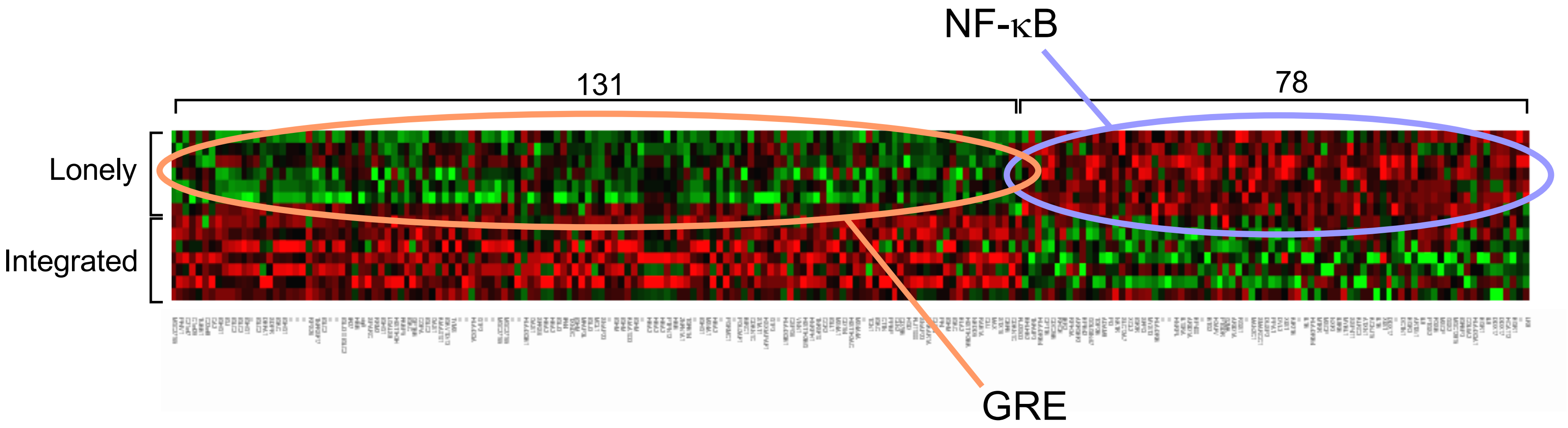
Environment

NF-κB

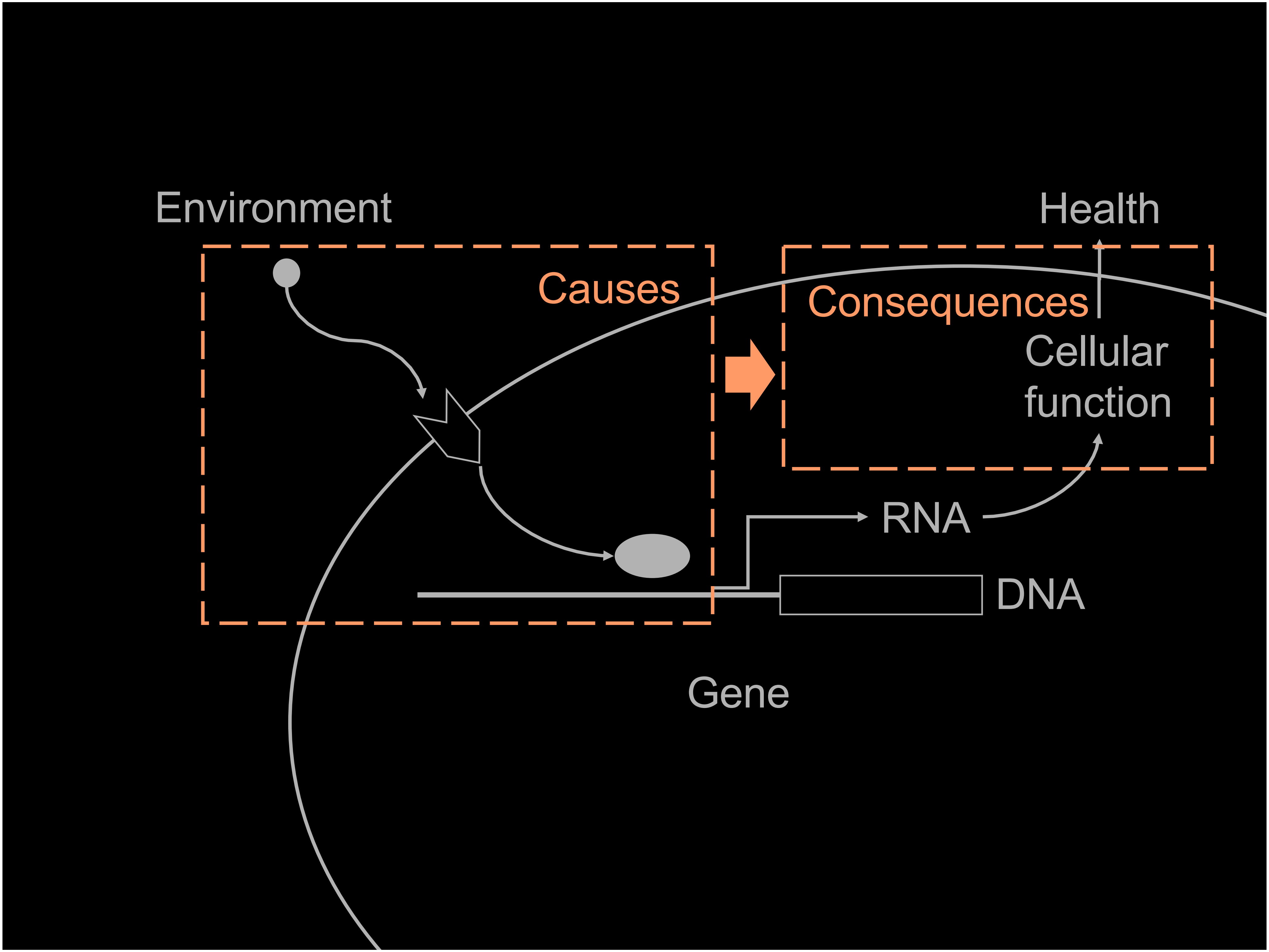
Promoter Sequence

Expression

CTRA – Conserved Transcriptional Response to Adversity



Iriwin & Cole (2011) Nature Reviews Immunology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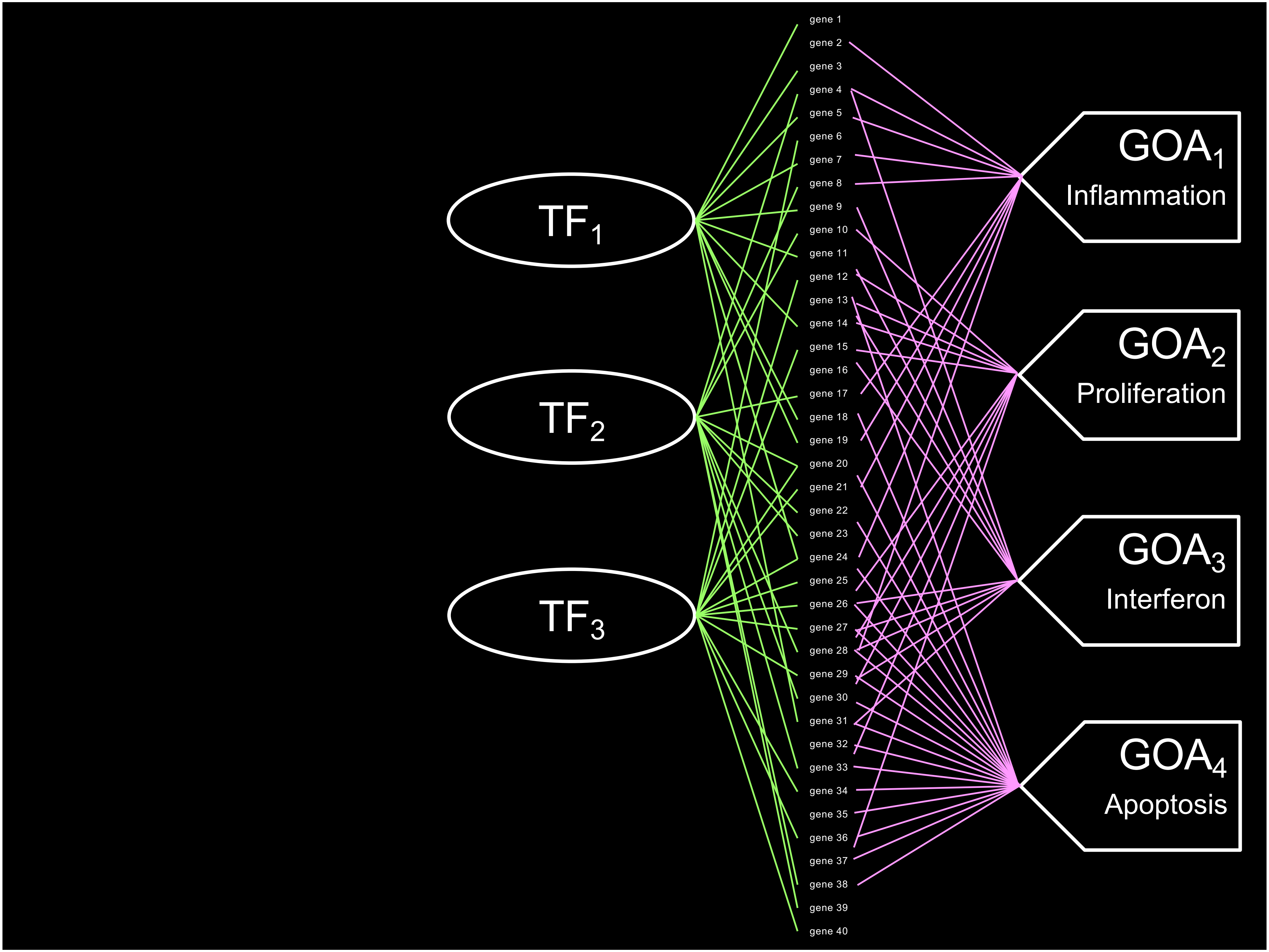
TF$_1$
TF$_2$
TF$_3$
gene 1
gene 2
gene 3
gene 4
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gene 11
gene 12
gene 13
gene 14
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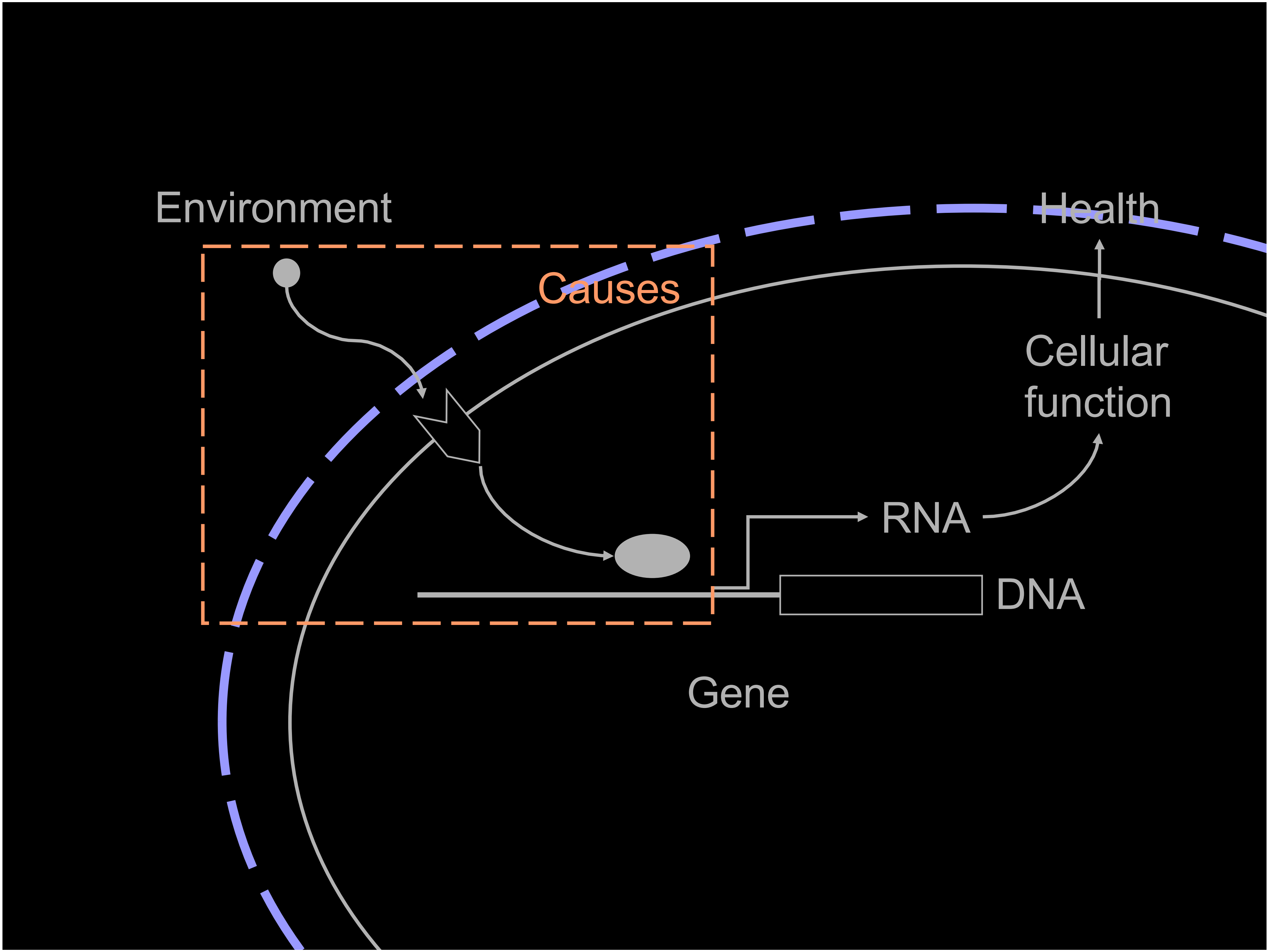
gene 40
GOA$_1$
Inflammation
GOA$_2$
Proliferation
GOA$_3$
Interferon
GOA$_4$
Apoptosis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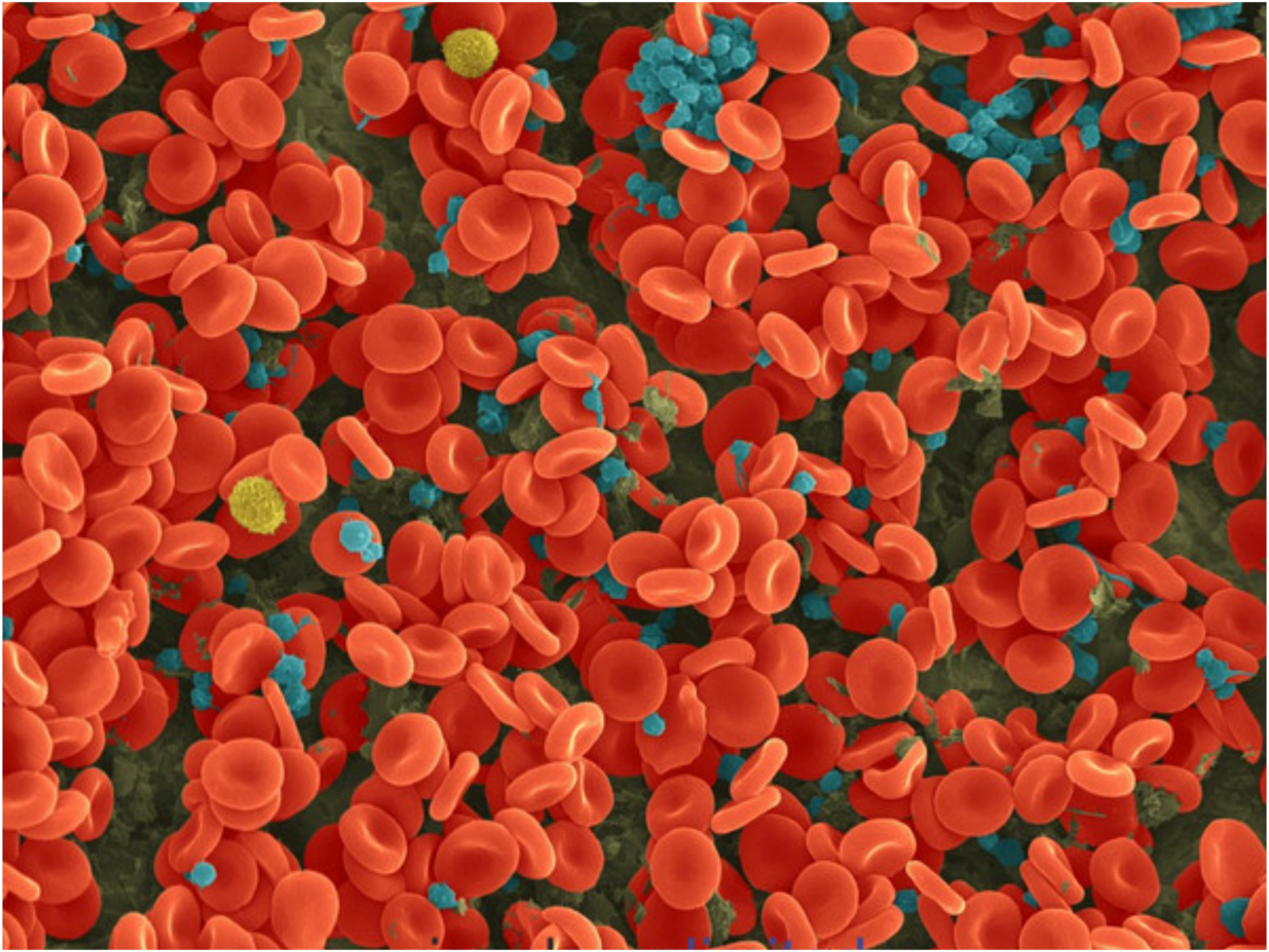
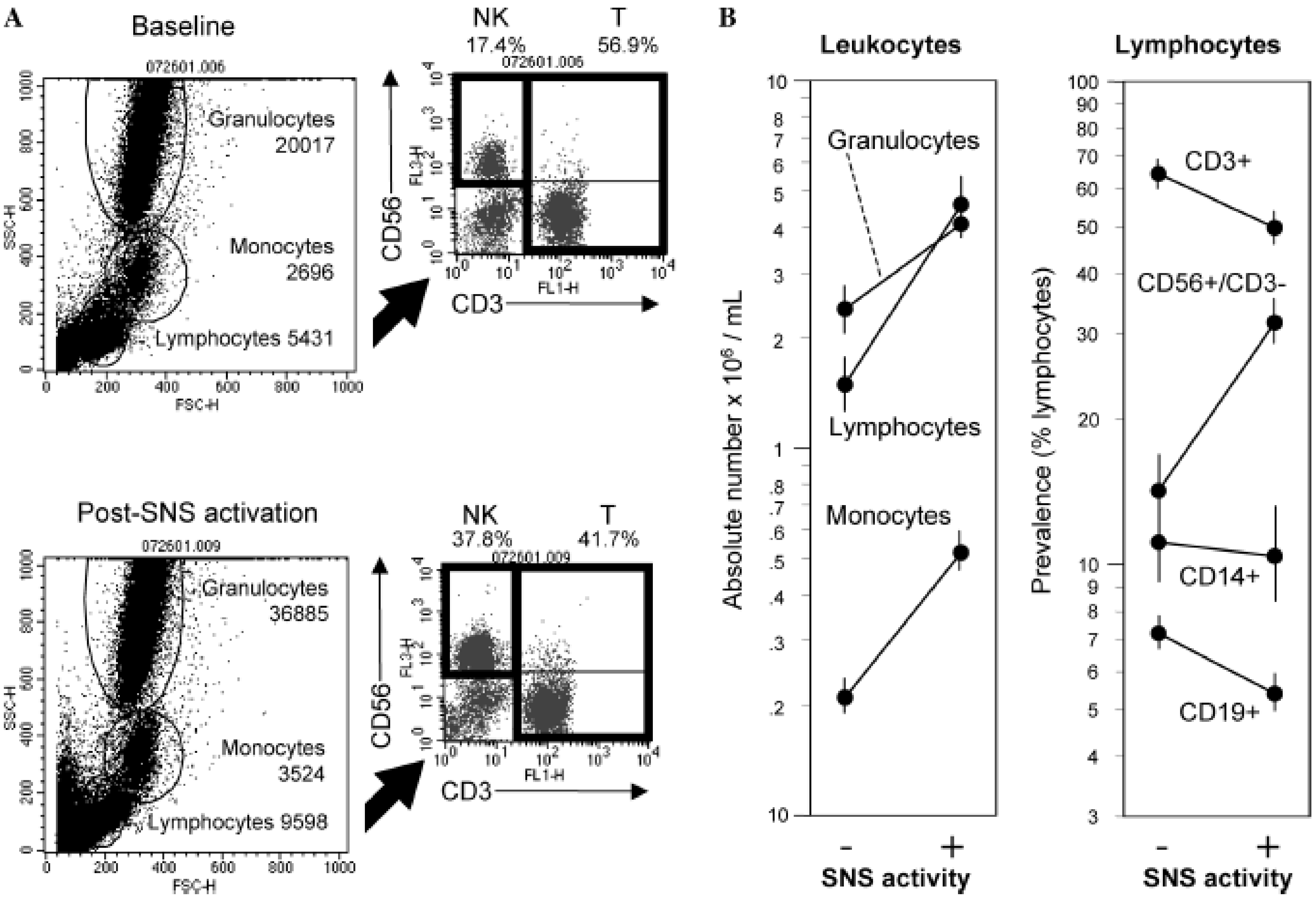
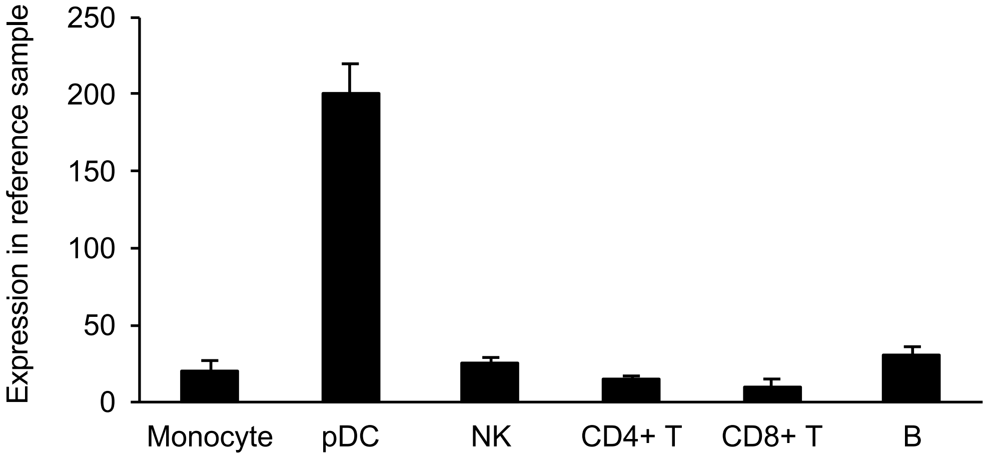




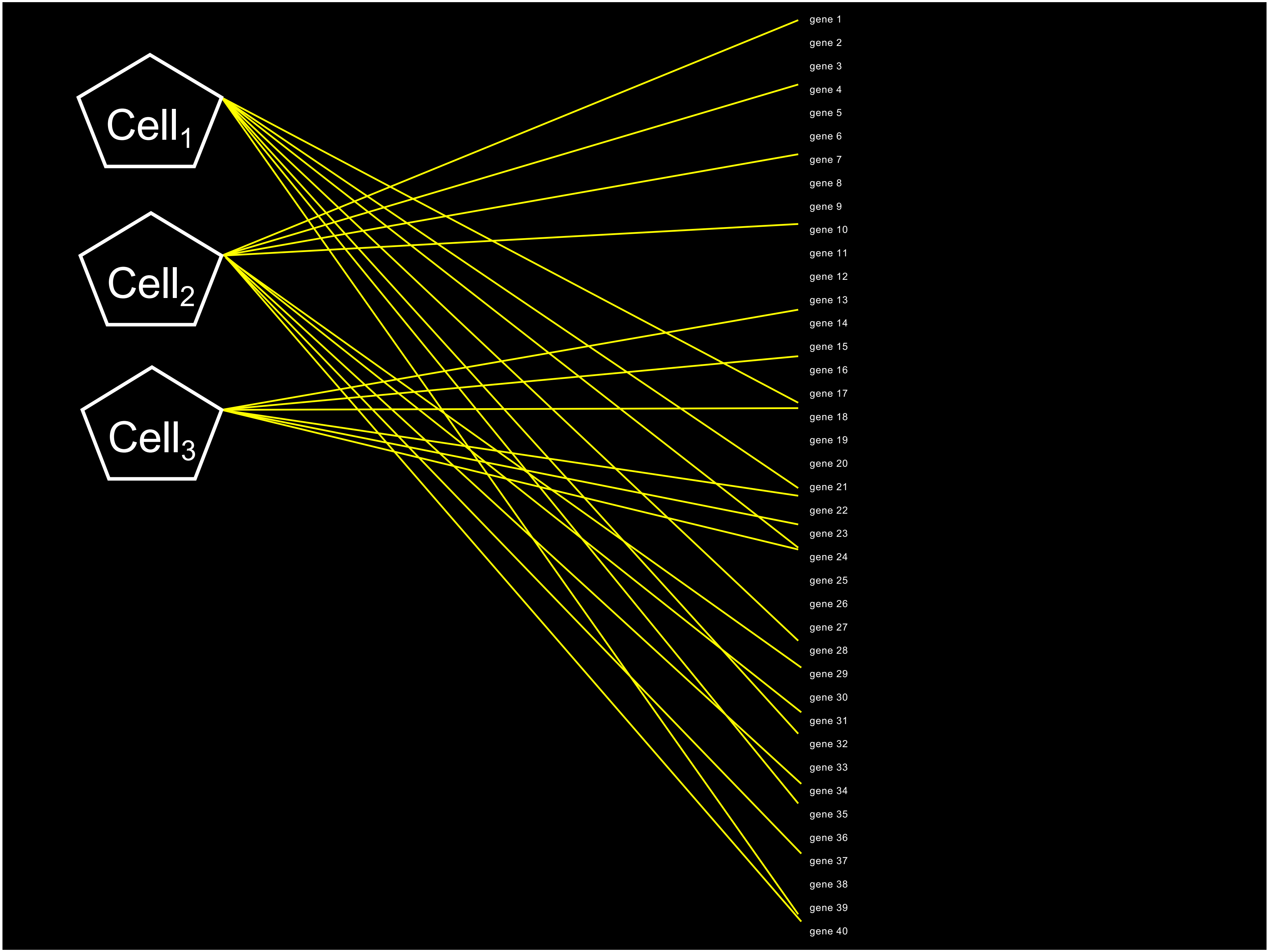
Richlin et al. Brain, Behavior & Immunity (2004)

Transcript origin analysis



TOA *Z*-score $_{gc}$ = -0.4 4.9 -0.3 -0.5 -0.6 -0.3

Cole et al (2011) PNAS


$Cell_1$
$Cell_2$
$Cell_3$
gene 1
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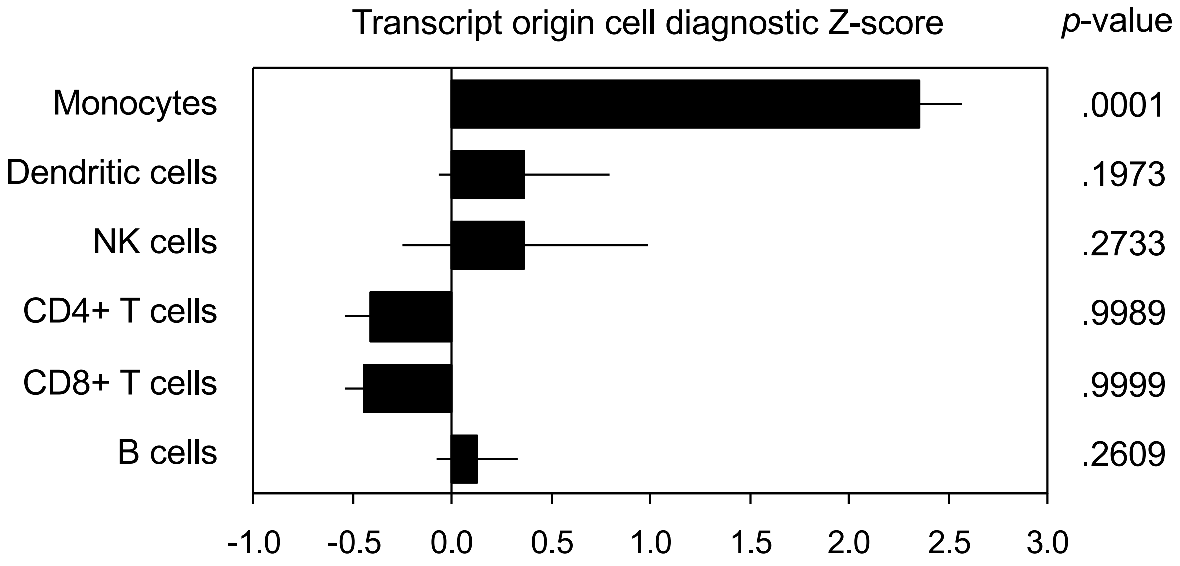
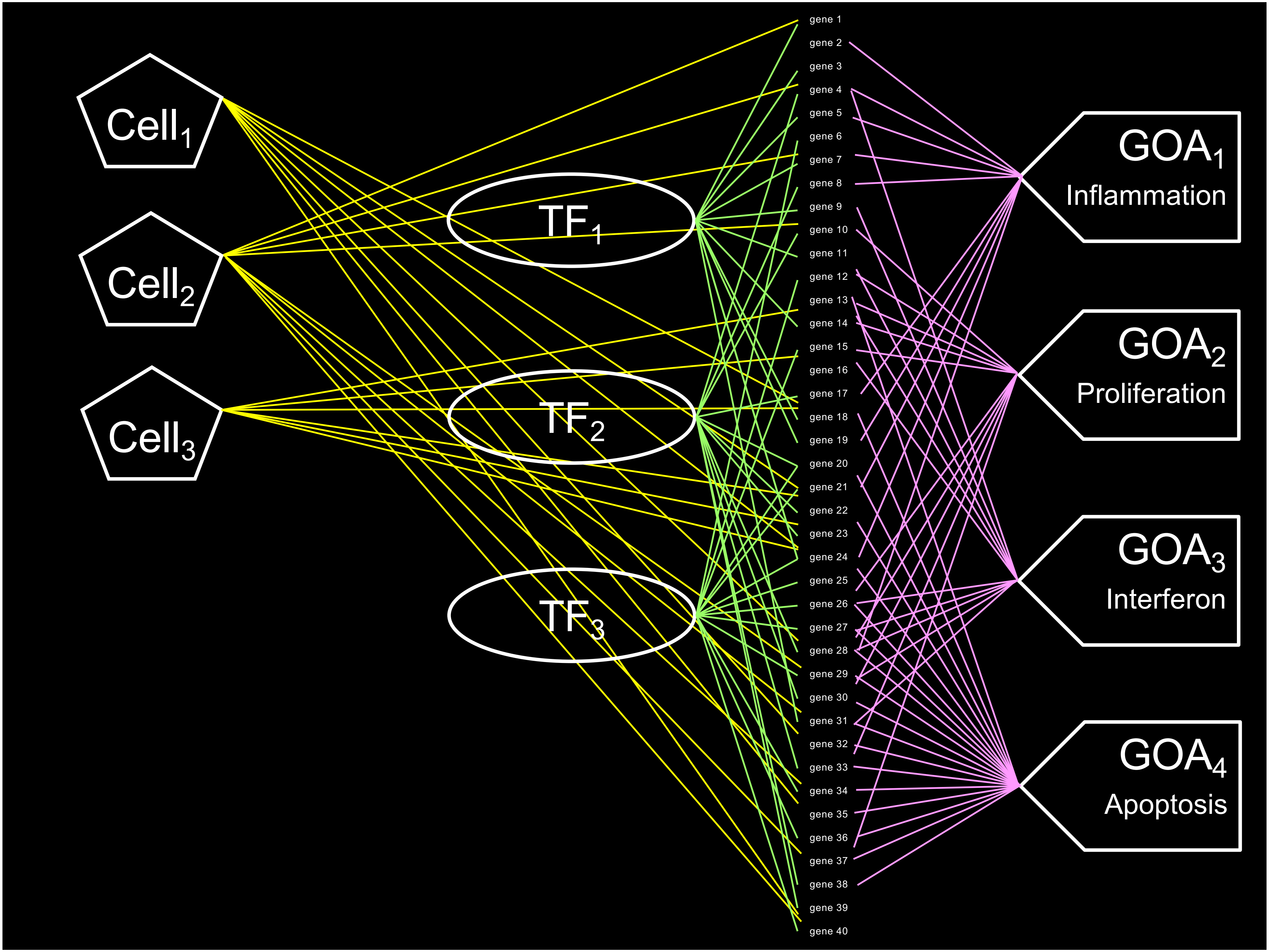
gene 38
gene 39
gene 40

Cellular target of social adversity



Cole et al (2011) PNAS


Cell$_1$
Cell$_2$
Cell$_3$
TF$_1$
TF$_2$
TF$_3$
gene 1
gene 2
gene 3
gene 4
gene 5
gene 6
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GOA$_1$
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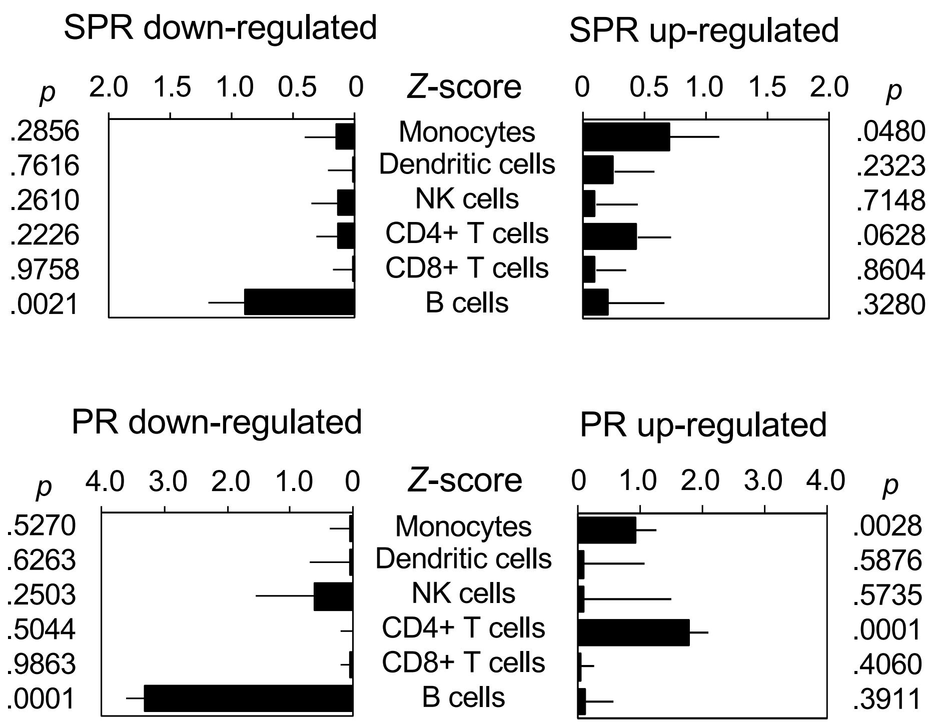
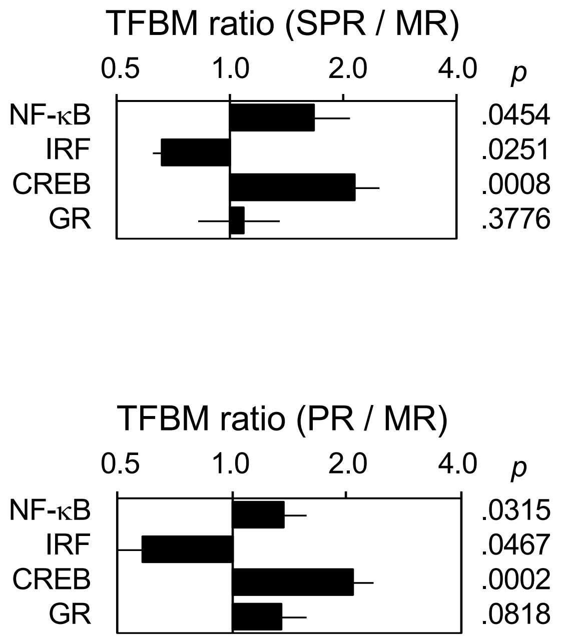
GOA$_2$
Proliferation
GOA$_3$
Interferon
GOA$_4$
Apoptosis

Social instability

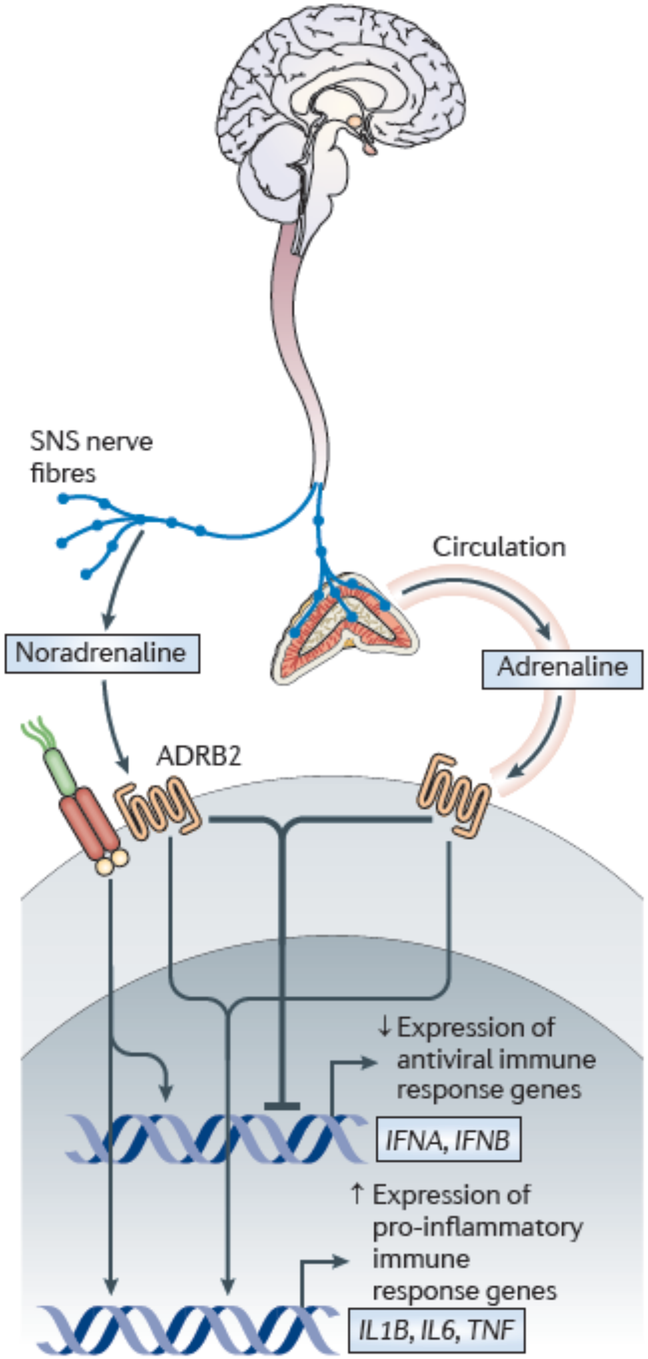
Cellular origin



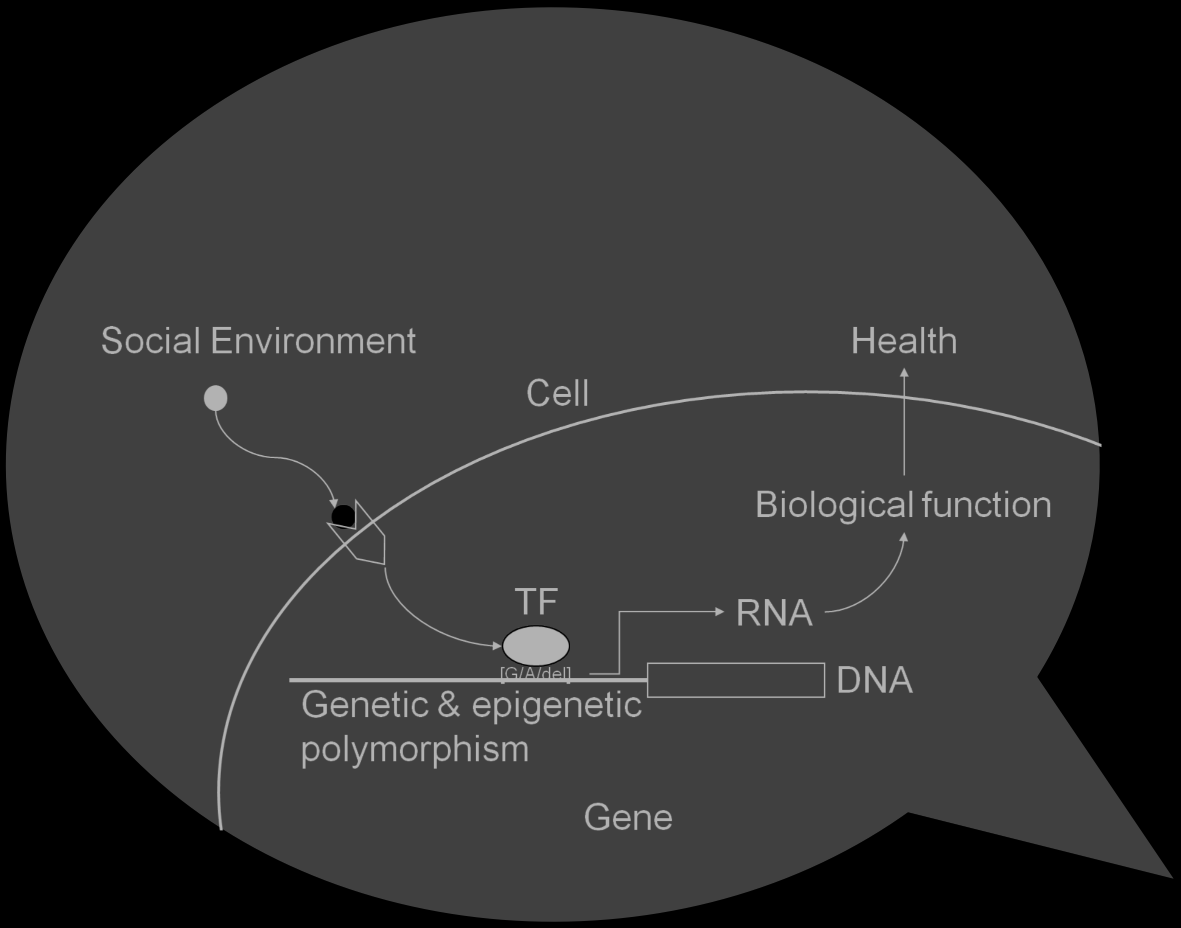
Transcription factor



Cole et al (2012) PNAS



SNS nerve fibres
Circulation
Noradrenaline
Adrenaline
ADRB2
↓ Expression of antiviral immune response genes
IFNA, IFNB
↑ Expression of pro-inflammatory immune response genes
IL1B, IL6, TNF



Social Environment

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Health

Biological function

TF

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[G/A/del]

DNA

Genetic & epigenetic polymorphism

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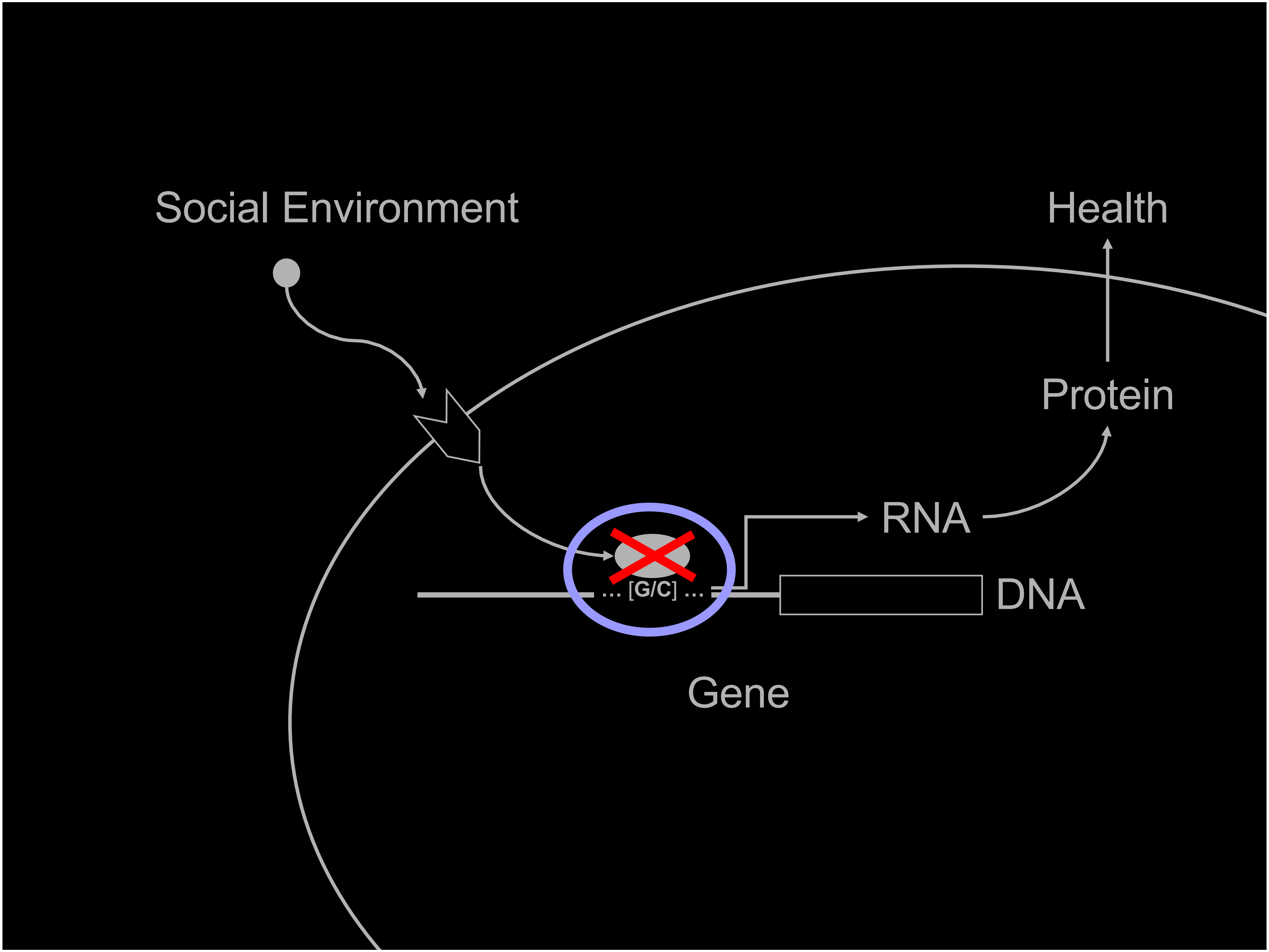
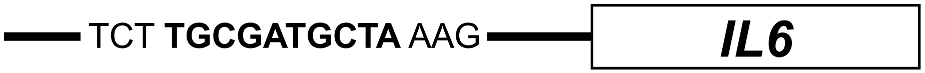

Social Environment
Health
Protein
RNA
... [G/C] ...
DNA
Gene

Gene x Environment Interaction

In silico

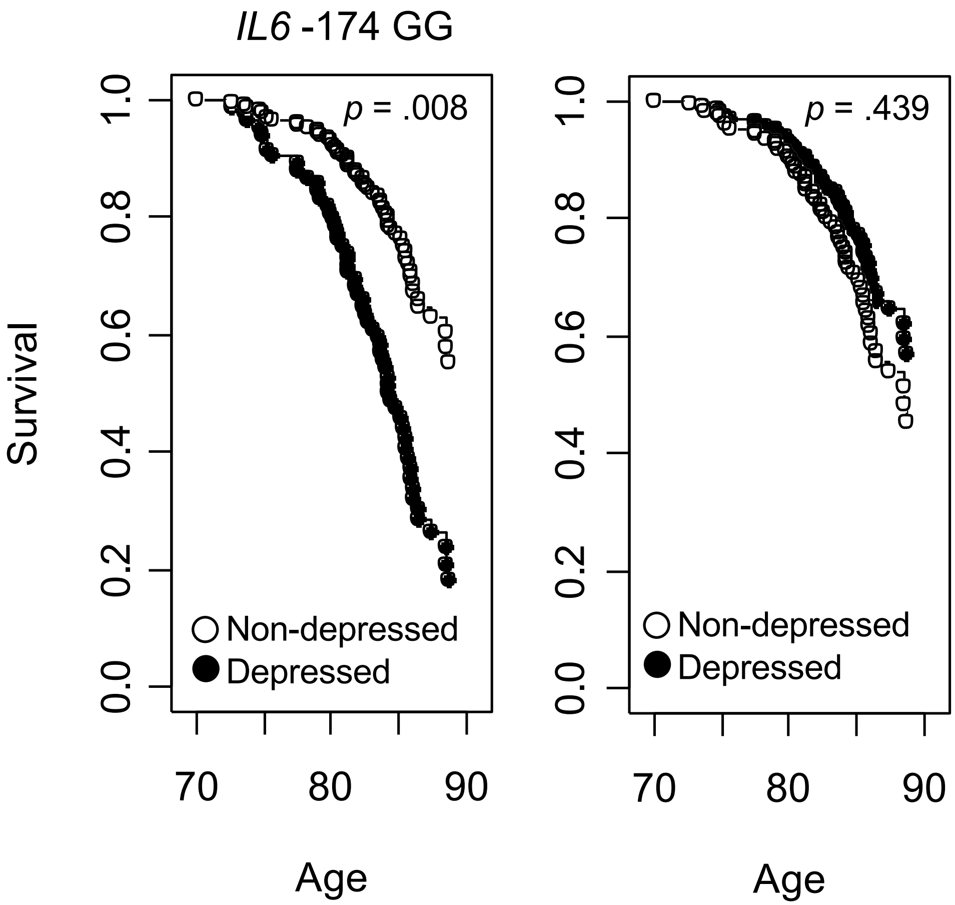


TCT **TGCGATGCTA** AAG

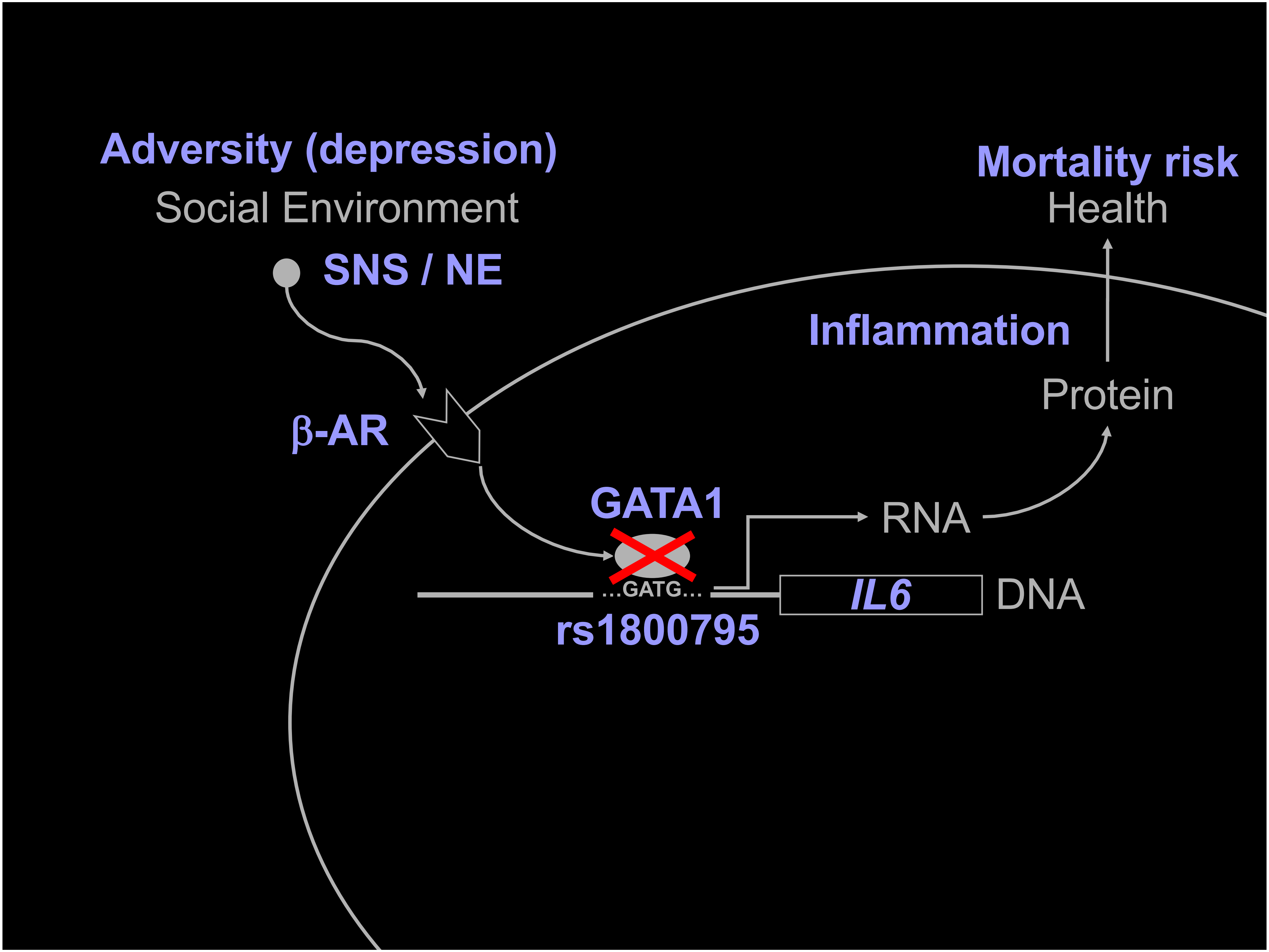
IL6

Cole et al. (2010) PNAS

Gene x Environment Interaction



Cole et al. (2010) PNAS



Adversity (depression)

Social Environment

SNS / NE

Mortality risk

Health

Inflammation

β-AR

Protein

GATA1

RNA

…GATG…

IL6

DNA

rs1800795

1205 GRE-modifying SNPs

RHCE -292
RHCE -292
RHCE -292
RHCE -292
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SOC -39
SOC -49
SOC -26
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LAPTM5 -728
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PHC2 -16
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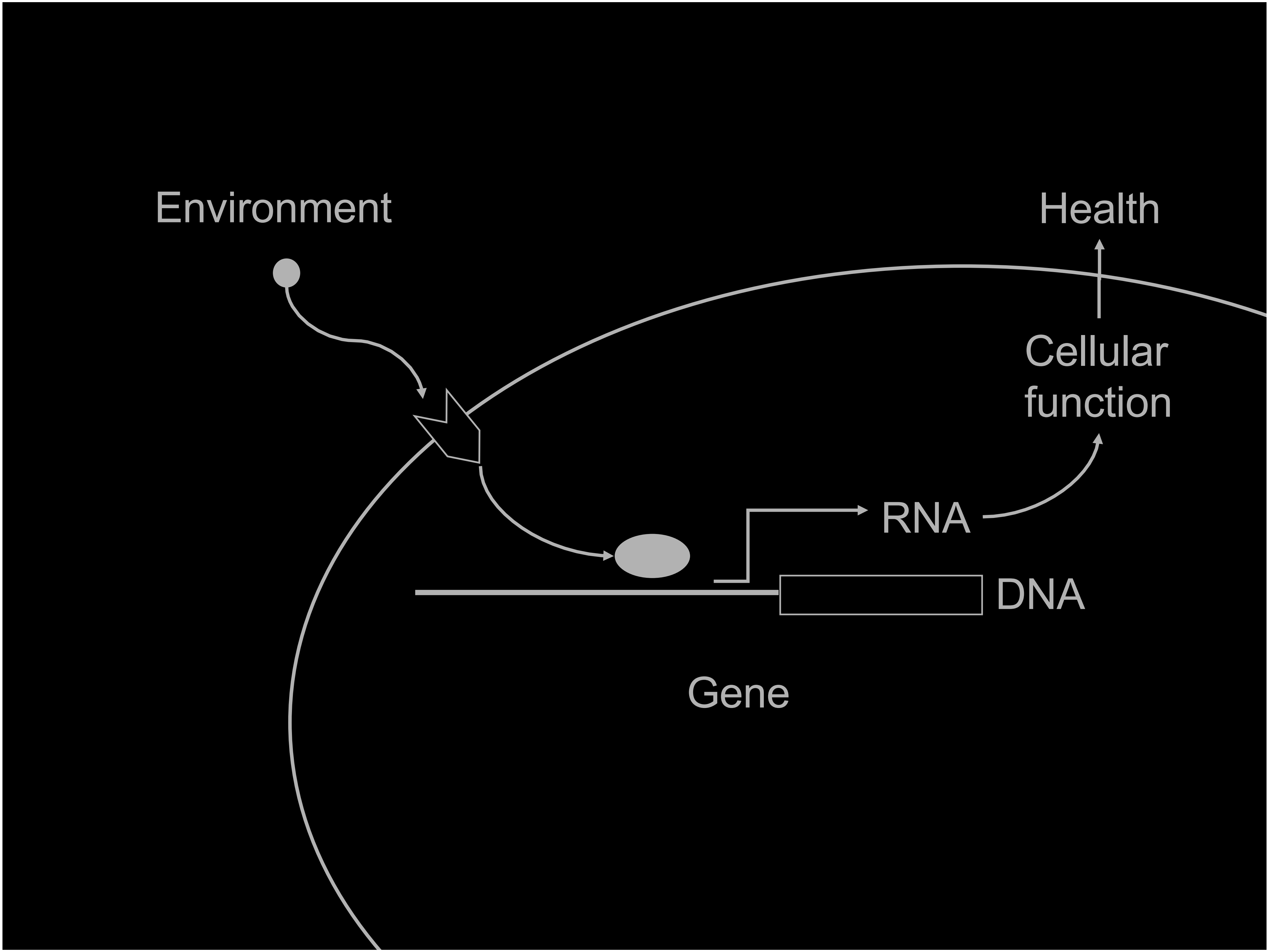
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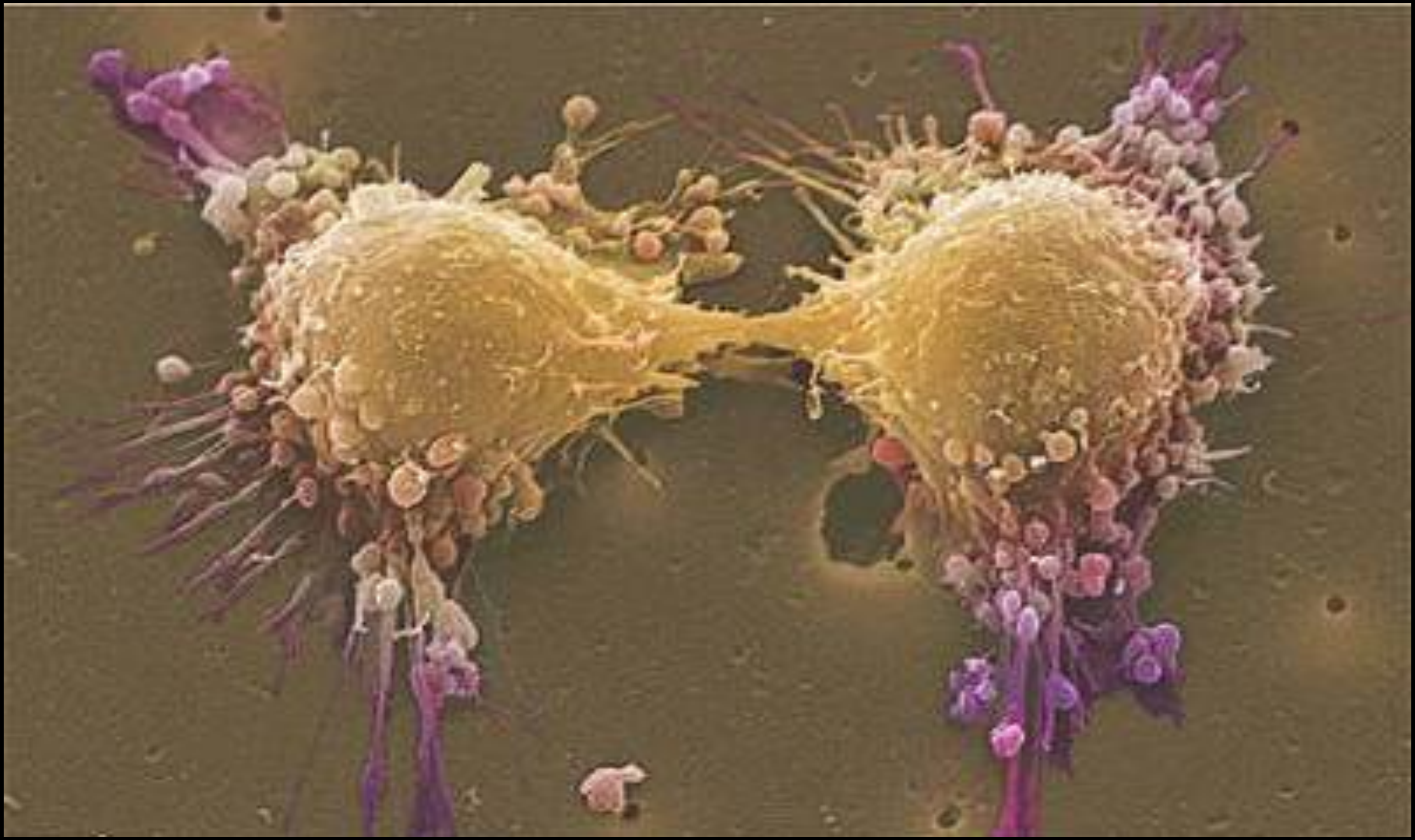

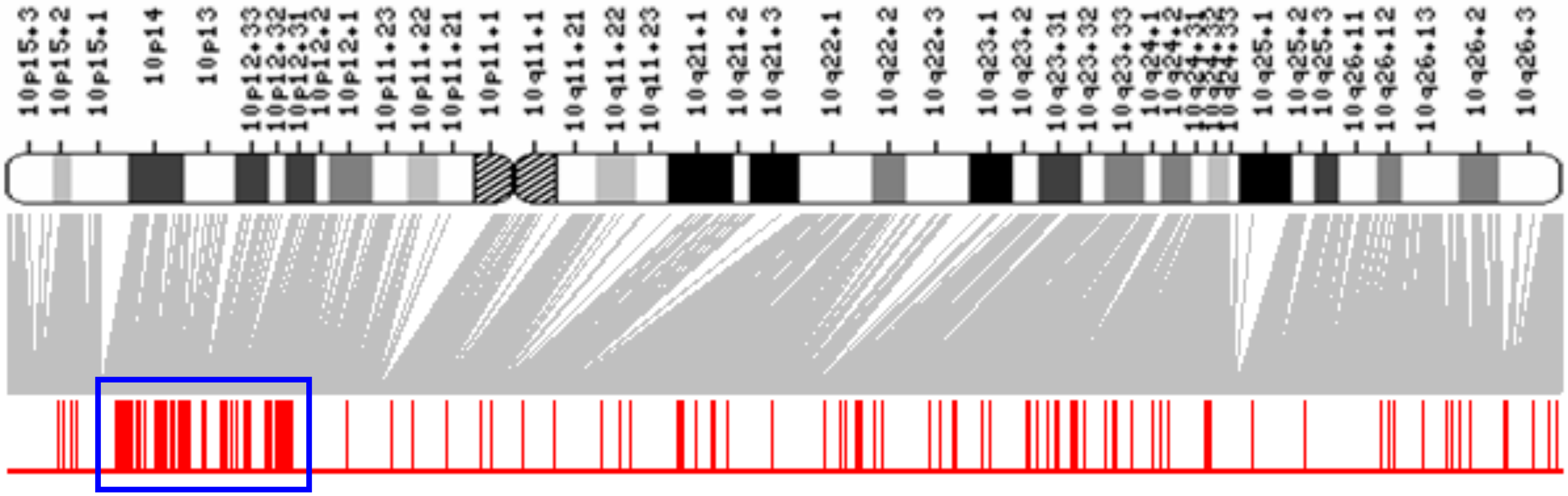
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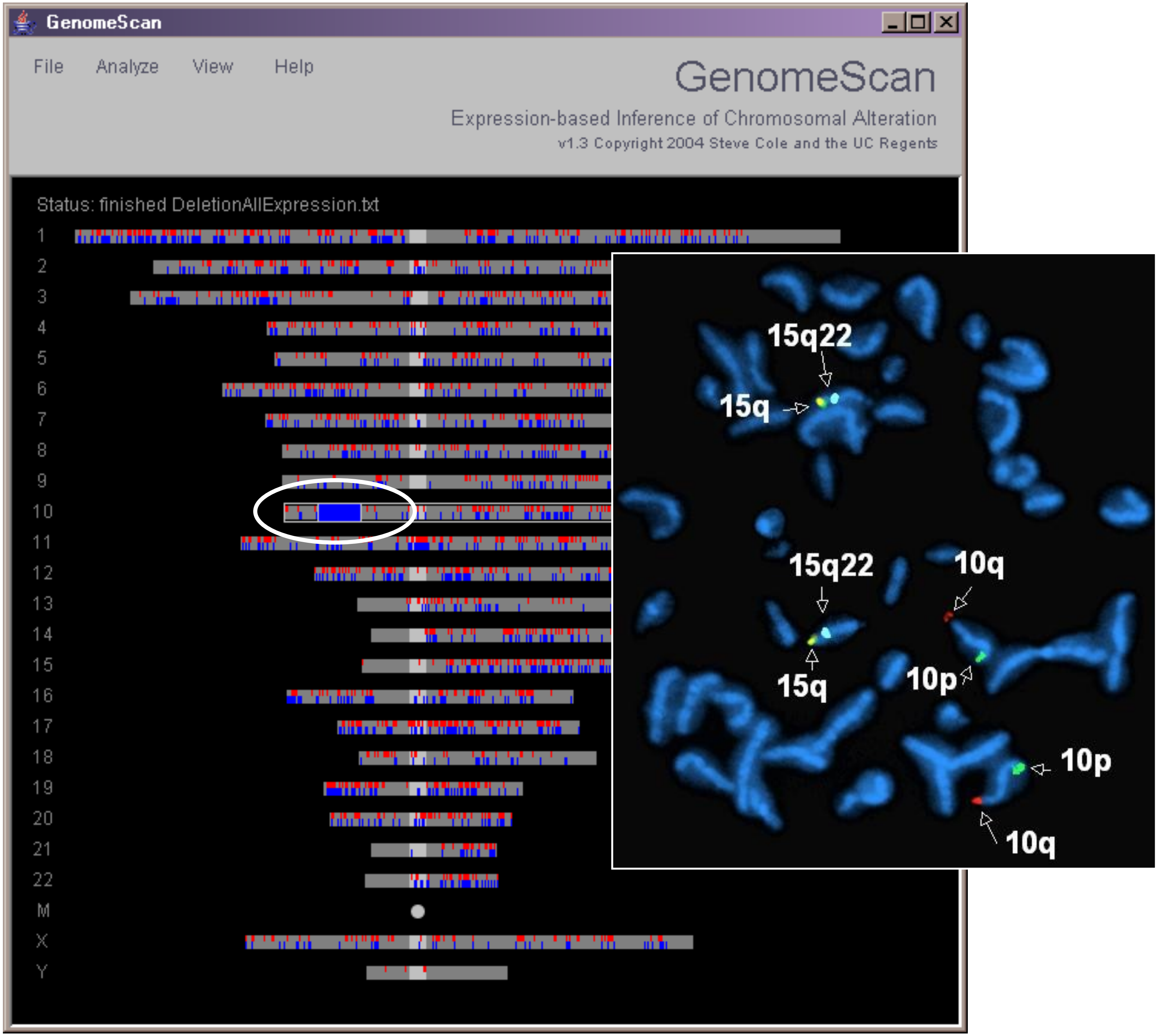


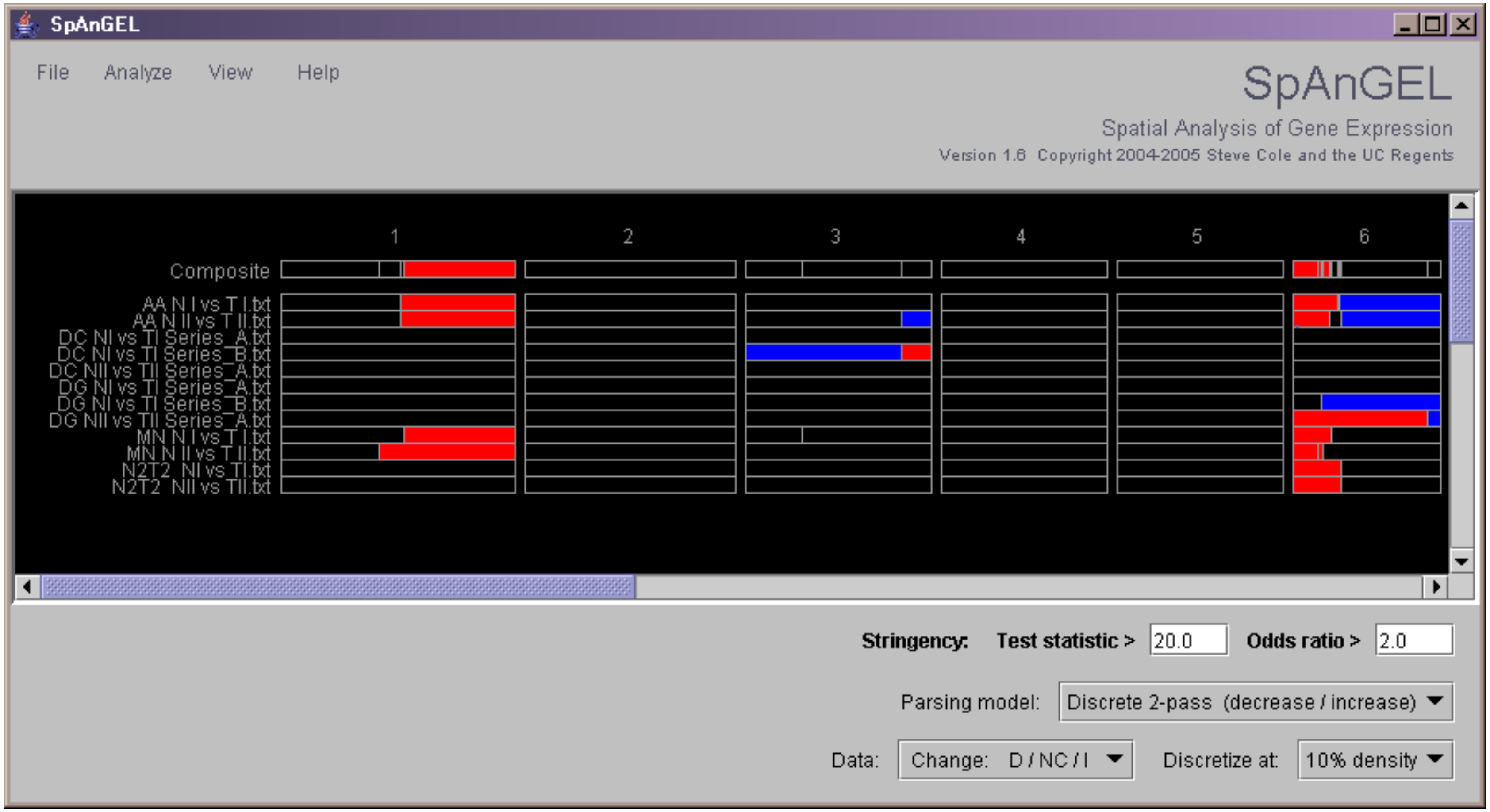
GenomeScan

Expression-based Inference of Chromosomal Alteration

v1.3 Copyright 2004 Steve Cole and the UC Regents

Status: finished DeletionAllExpression.txt

Chromosomal aberration profiles

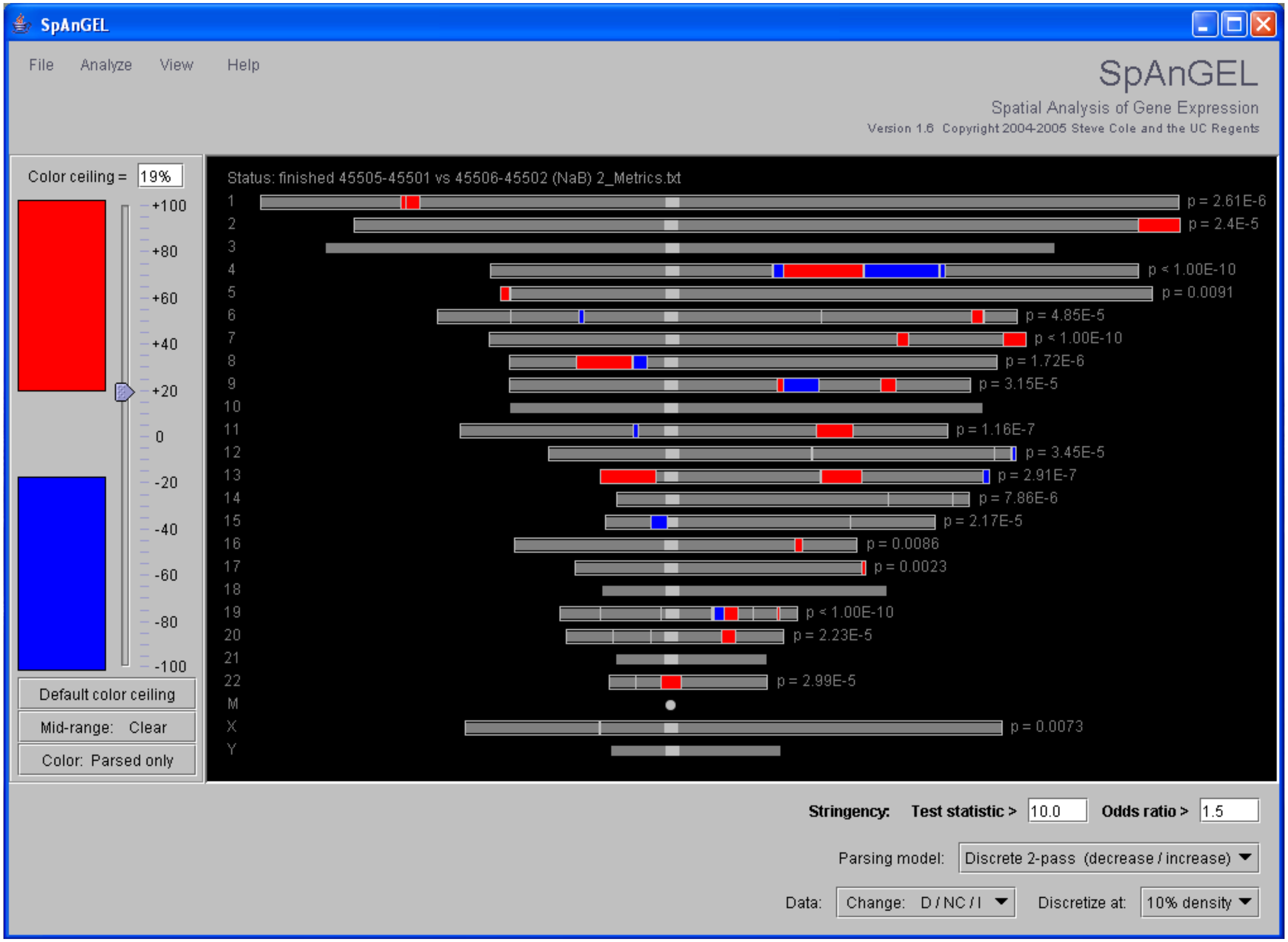


Stringency: Test statistic > 20.0 Odds ratio > 2.0

Parsing model: Discrete 2-pass (decrease / increase)

Data: Change: D / NC / I Discretize at: 10% density

Epigenetics, chromatin accessibility, & RIDGEs



Color ceiling = 19%

Mid-range: Clear

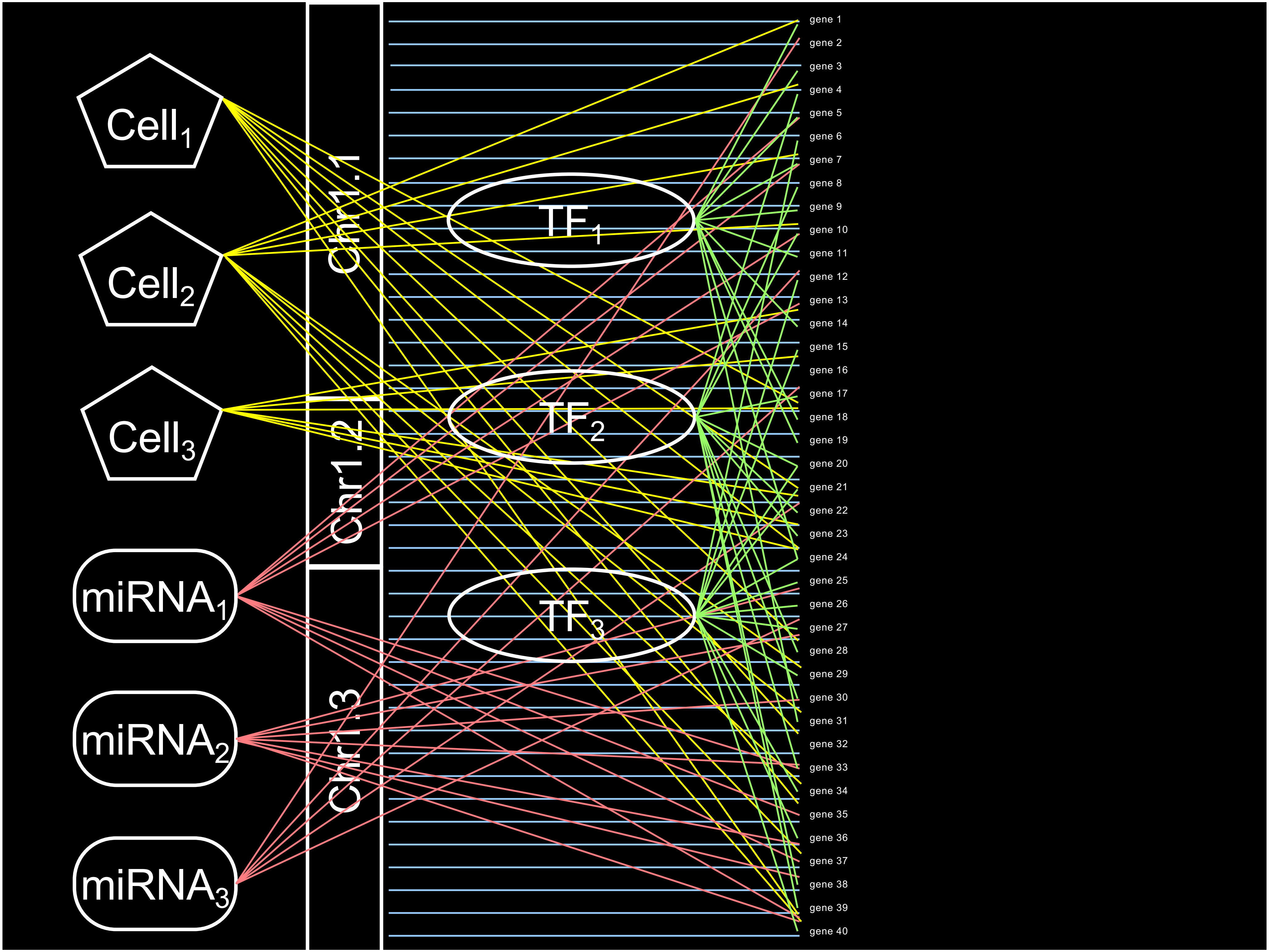
Color: Parsed only

Status: finished 45505-45501 vs 45506-45502 (NaB) 2_Metrics.txt

Stringency: **Test statistic >** 10.0 **Odds ratio >** 1.5

Parsing model: Discrete 2-pass (decrease / increase)

Data: Change: D / NC / I Discretize at: 10% density



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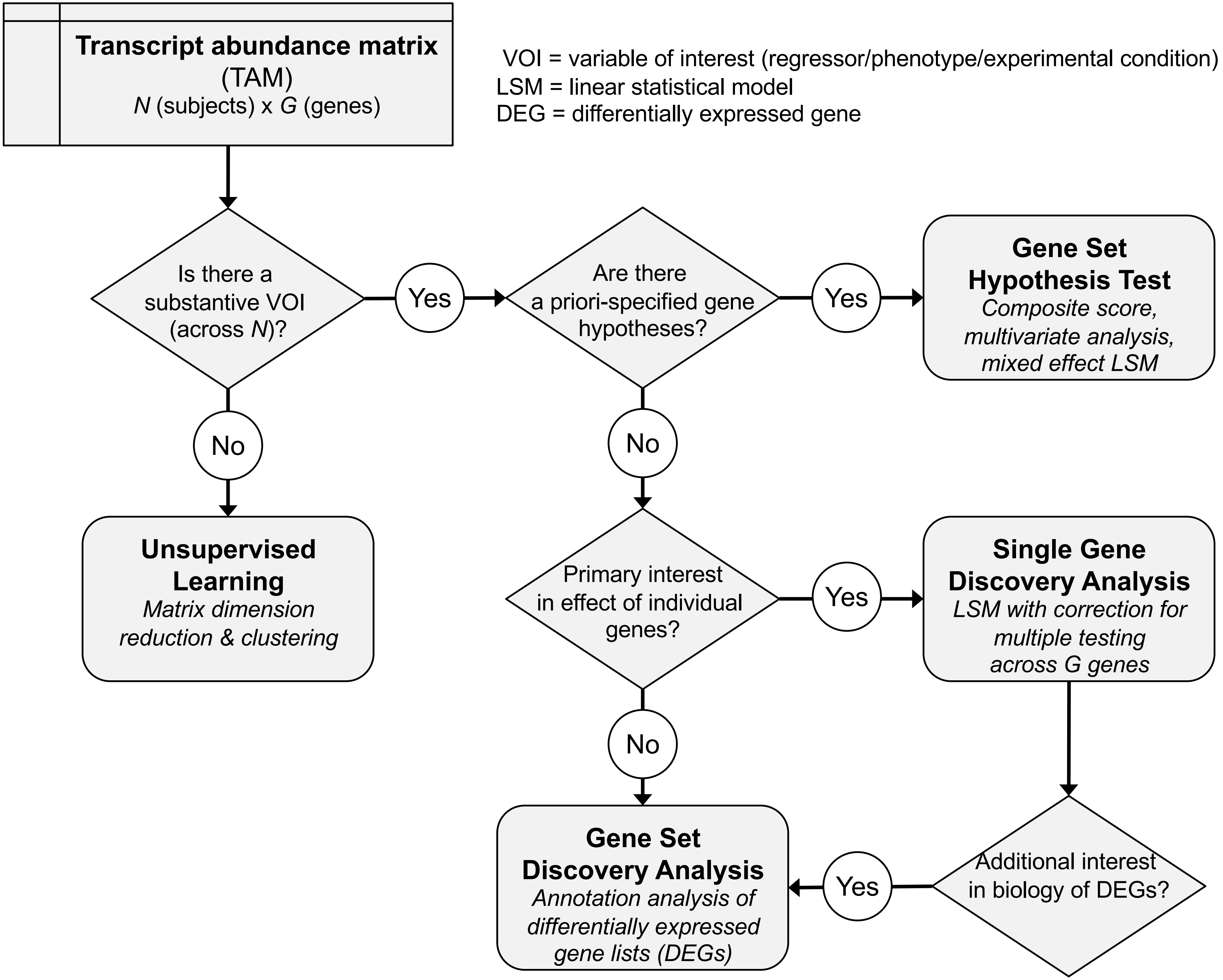
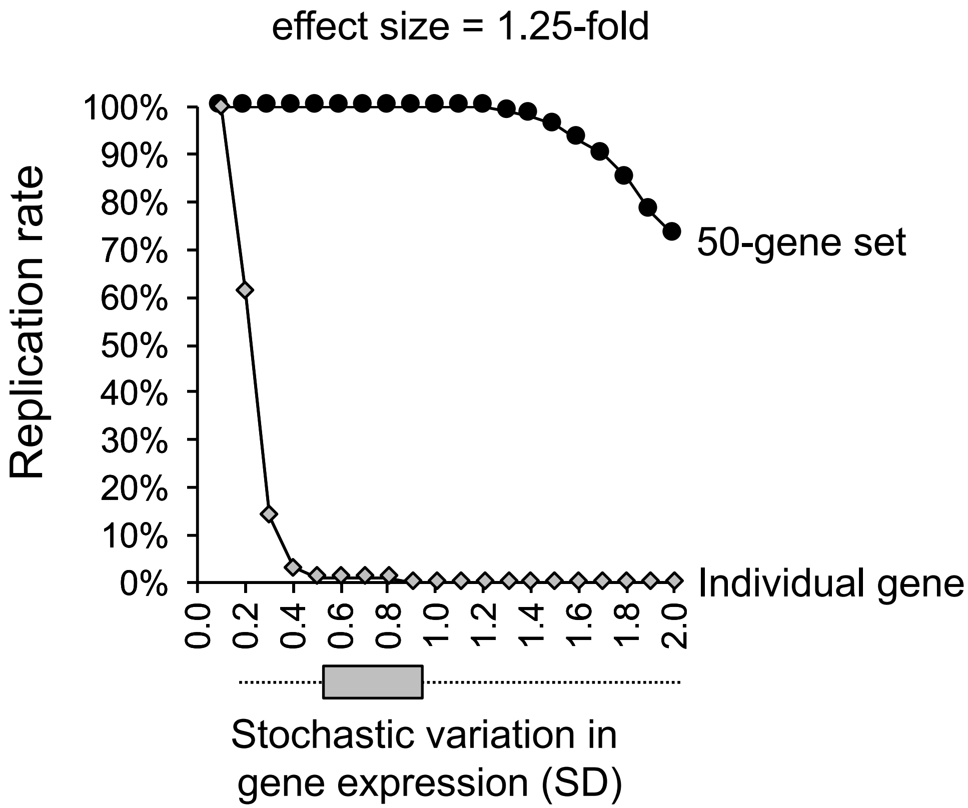
Some notes on statistical testing for gene list analysis


Transcript abundance matrix
(TAM)
N (subjects) x G (genes)
VOI = variable of interest (regressor/phenotype/experimental condition)
LSM = linear statistical model
DEG = differentially expressed gene
Is there a substantive VOI (across N)?
Yes
No
Unsupervised Learning
Matrix dimension reduction & clustering
Are there a priori-specified gene hypotheses?
Yes
Gene Set Hypothesis Test
Composite score, multivariate analysis, mixed effect LSM
No
Primary interest in effect of individual genes?
Yes
Single Gene Discovery Analysis
LSM with correction for multiple testing across G genes
No
Additional interest in biology of DEGs?
Yes
Gene Set Discovery Analysis
Annotation analysis of differentially expressed gene lists (DEGs)

Painful lesson #1: If you want replicable results, focus on functionally related ***sets*** of genes (not individual gene transcripts)

Differential expression of an a priori gene set

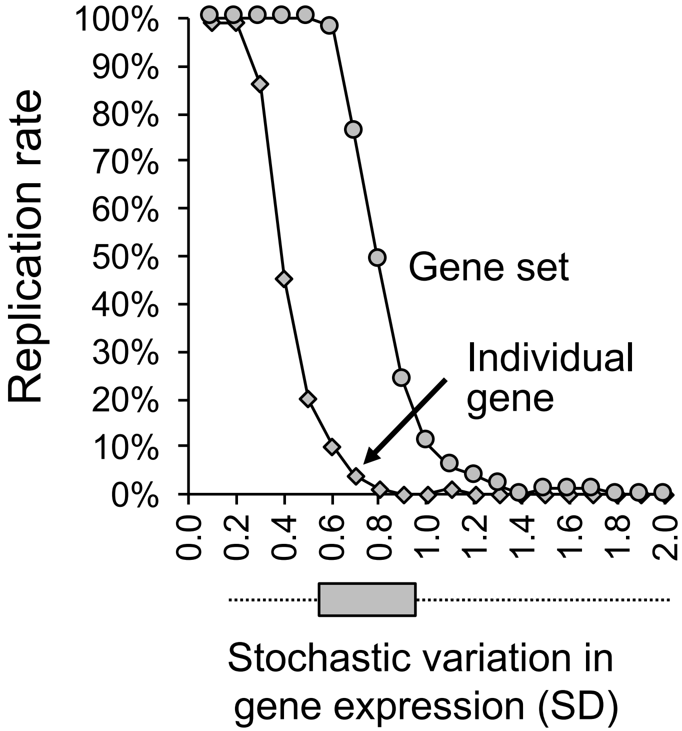


Fredrickson et al (2013) PNAS - SI

Painful lesson #2: If you want replicable results, conduct 2nd stage bioinformatics on gene lists derived from point estimates of ***effect size*** (not *p*/*q*-values)

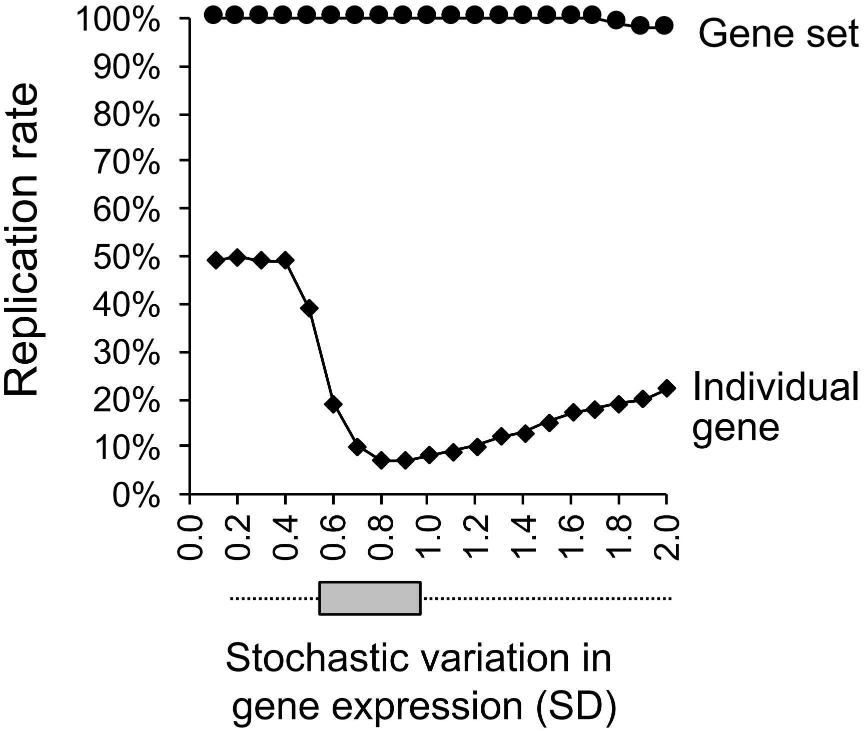
Gene set enrichment analysis

Low level input: *p*-value gene list

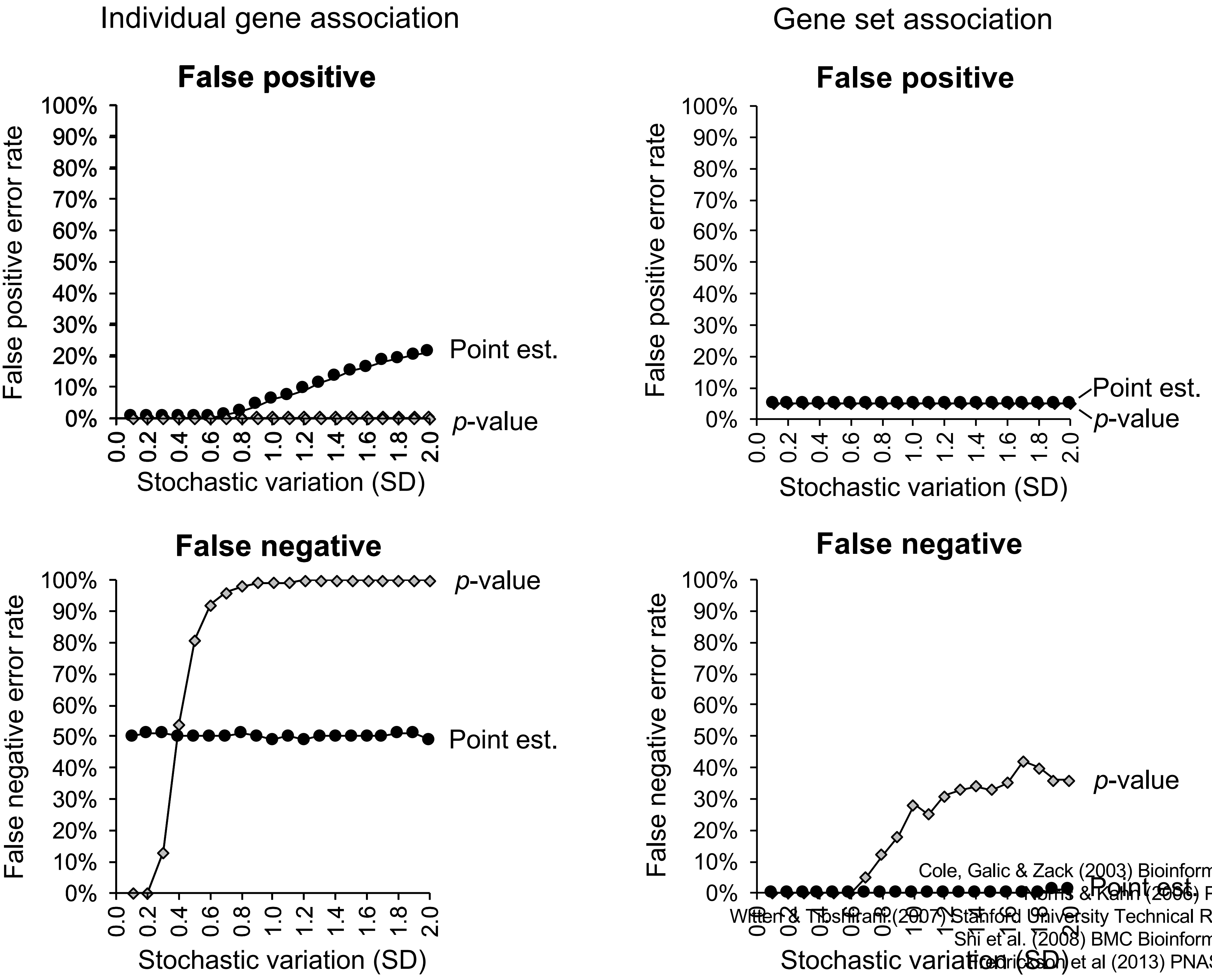


Gene set enrichment analysis

Low level input: point estimate gene list

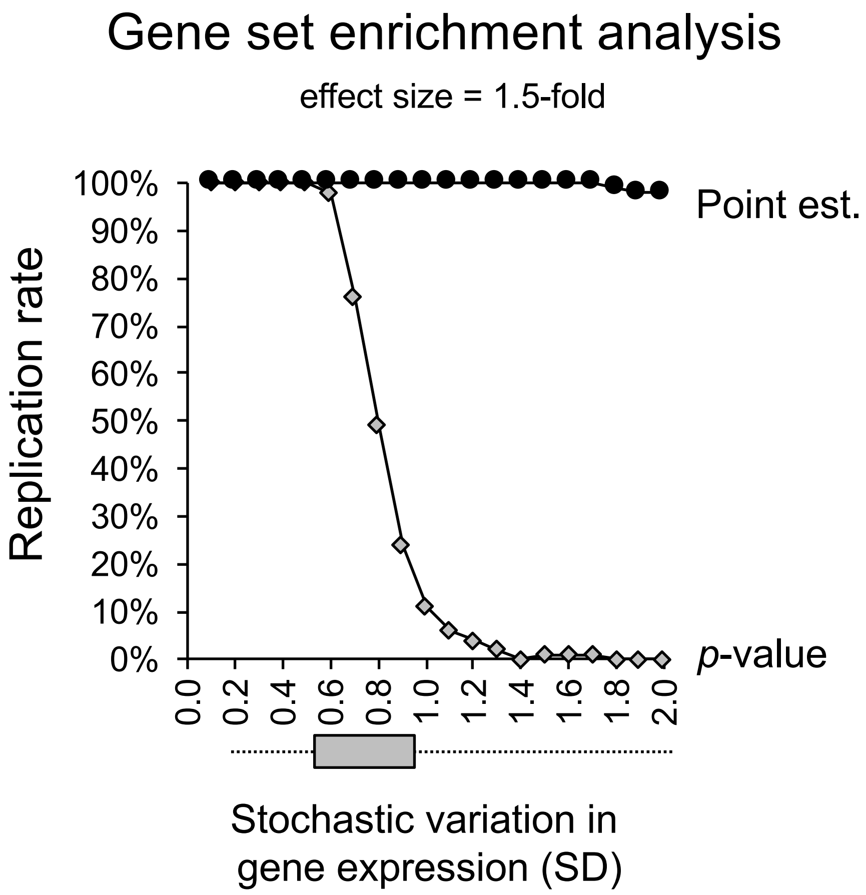


Fredrickson et al (2013) PNAS - SI



Cole, Galic & Zack (2003) Bioinformatics
Norris & Kahn (2006) PNAS
Witten & Tibshirani (2007) Stanford University Technical Report
Shi et al. (2008) BMC Bioinformatics
Fredriksson et al (2013) PNAS - SI

Implication of false negative errors for result replication



Cole, Galic & Zack (2003) Bioinformatics
Norris & Kahn (2006) PNAS
Witten & Tibshirani (2007) Stanford University Technical Report
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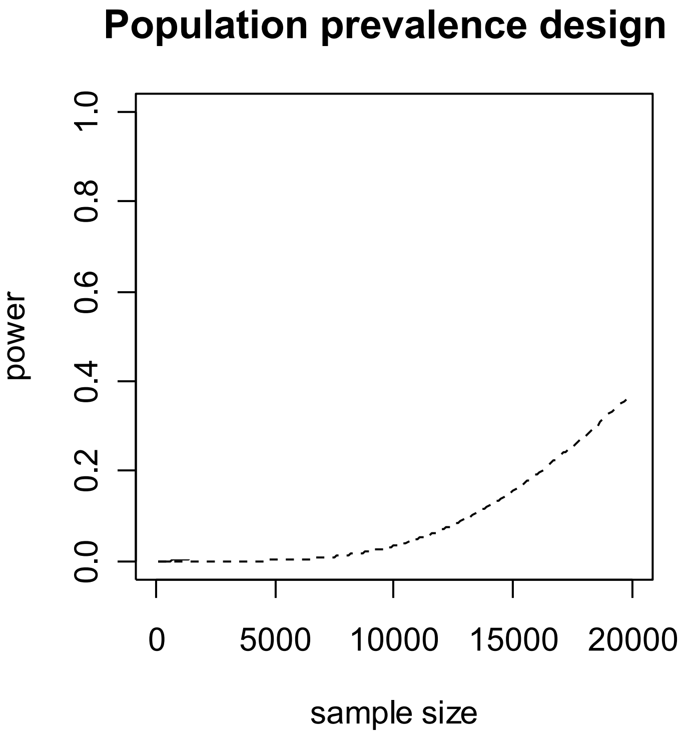
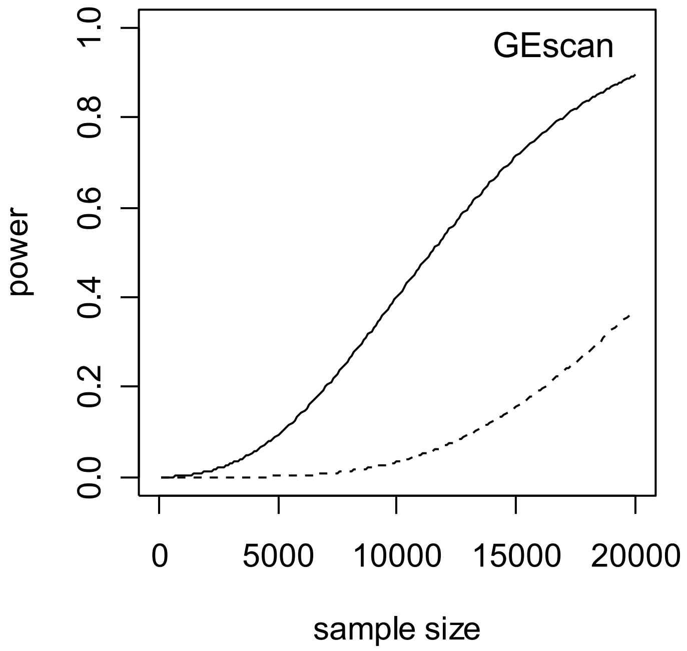
Painful lesson #3: Hypotheses are ***extremely*** valuable for statistical power in genomics. Don't pretend you know nothing (unless you really do).

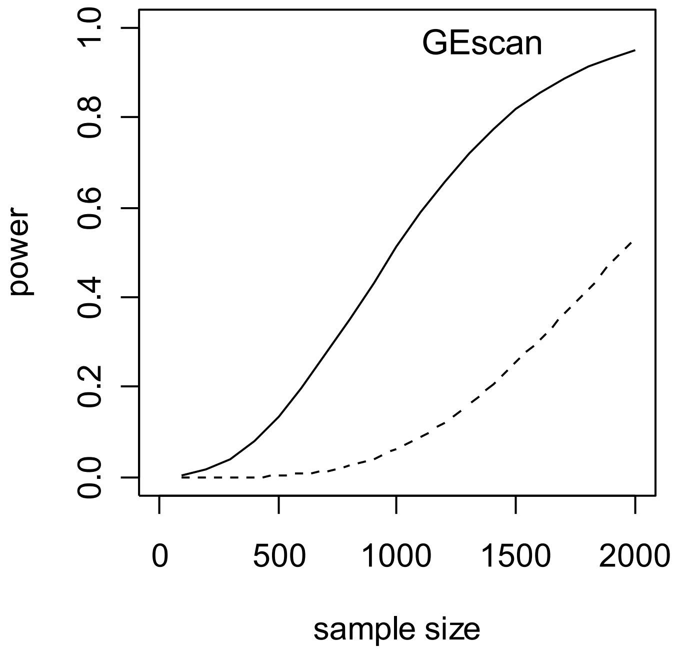


Painful lesson #3: Hypotheses are ***extremely*** valuable for statistical power in genomics. Don’t pretend you know nothing (unless you really do).

Population prevalence design

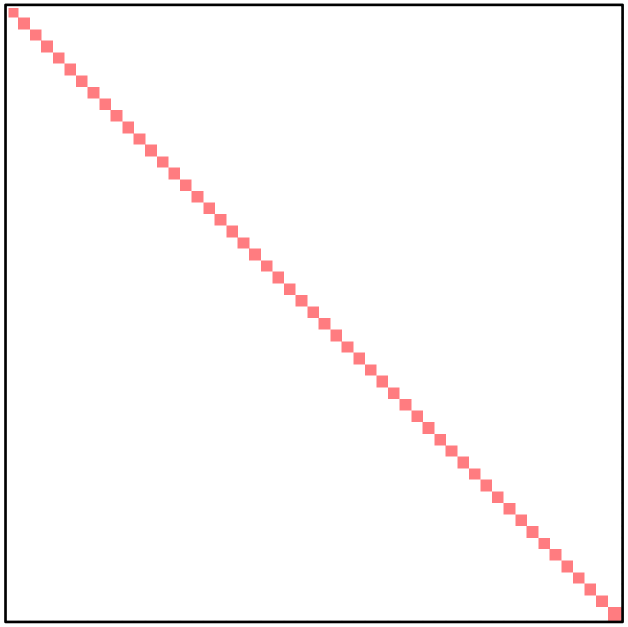


Outcome-stratified design

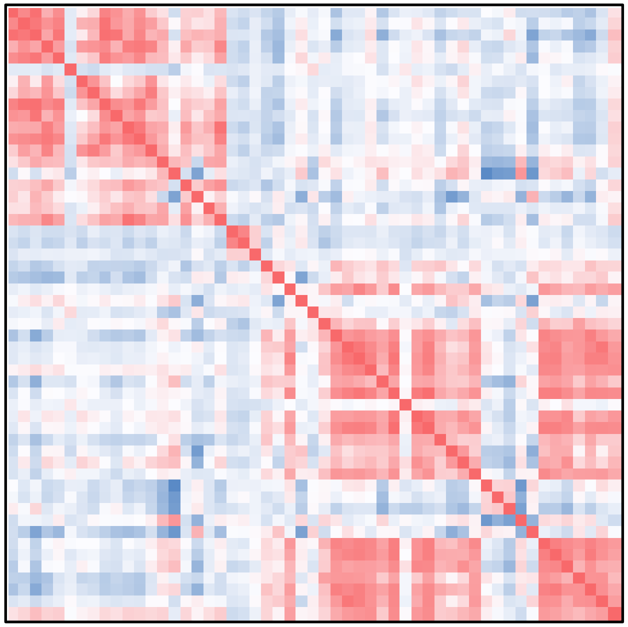


Painful lesson #4: Most *p*- and *q*-values are wrong (due to non-independence). Don’t trust them.

Inter-gene correlation assuming independence



Empirical inter-gene correlation



Efron (2010) J Am Stat Assoc

Painful lesson #1: If you want replicable results, analyze functionally related ***sets*** of genes (not individual gene transcripts)

Sets derive from a biological model of mass action

(i.e., environmental conditions, pathogens, distinct cell types, differentiation states, TFs, chromosomal & epigenetic alterations, genetic polymorphisms, etc.)

Painful lesson #2: If you want replicable results, conduct interpretive bioinformatics on gene lists derived from point estimates of ***effect size*** (not *p*/*q*-values)

Effect sizes (not SNRs) reflect mass biological processes

(i.e., environmental conditions, pathogens, cells, differentiation states, TFs, chromosomal & epigenetic alterations, genetic polymorphisms, etc.)

Painful lesson #3: Hypotheses are ***extremely*** valuable for statistical power, and that is the limiting resource in genomics. Don’t pretend you know nothing.

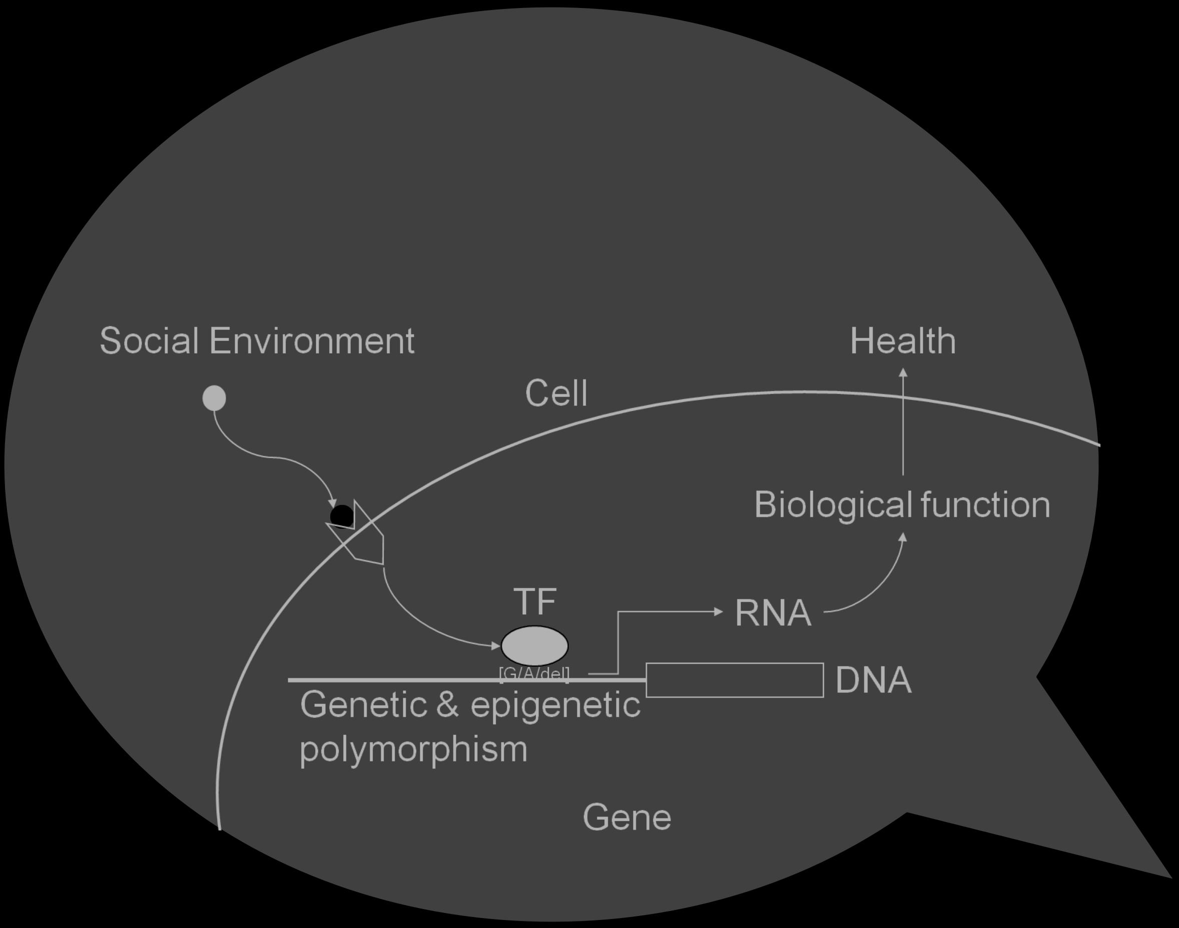
Hypotheses derive from a biological model

(i.e., or perhaps at least a set of ~100 imaginable models << 20,000 genes)

Painful lesson #4: *p/q*-values are inaccurate due to mass action correlation.

Model the biological processes that create the correlation

(work with the gene sets, not against them)



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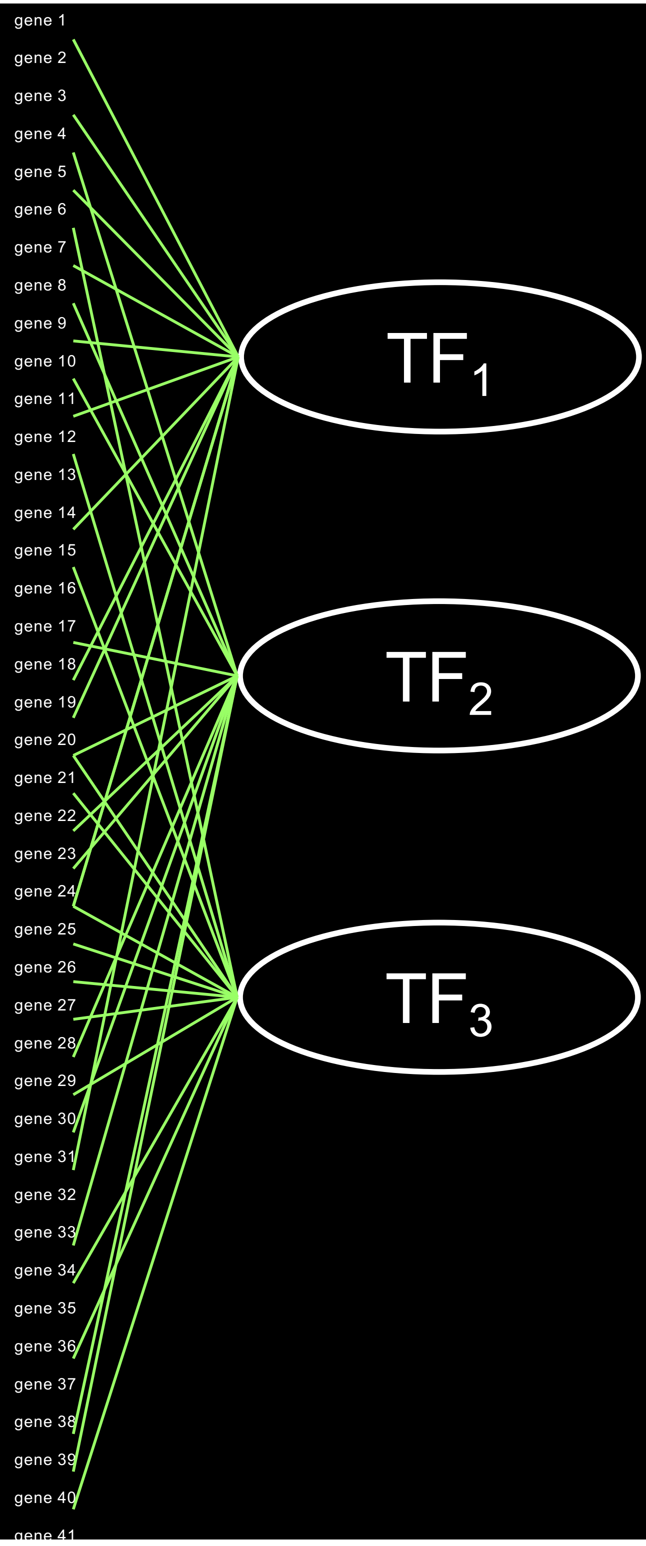

Statistical power

100x narrowed search space

Increased reliability

100x indicators

Substantive understanding

Move from *what happened* to *why*