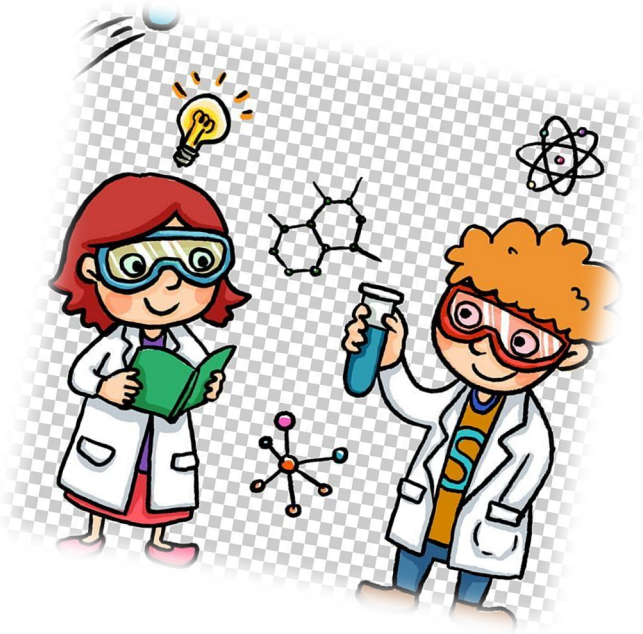
Gene Networks and Drugs

What can we learn by putting together bio- and chemo-informatics?

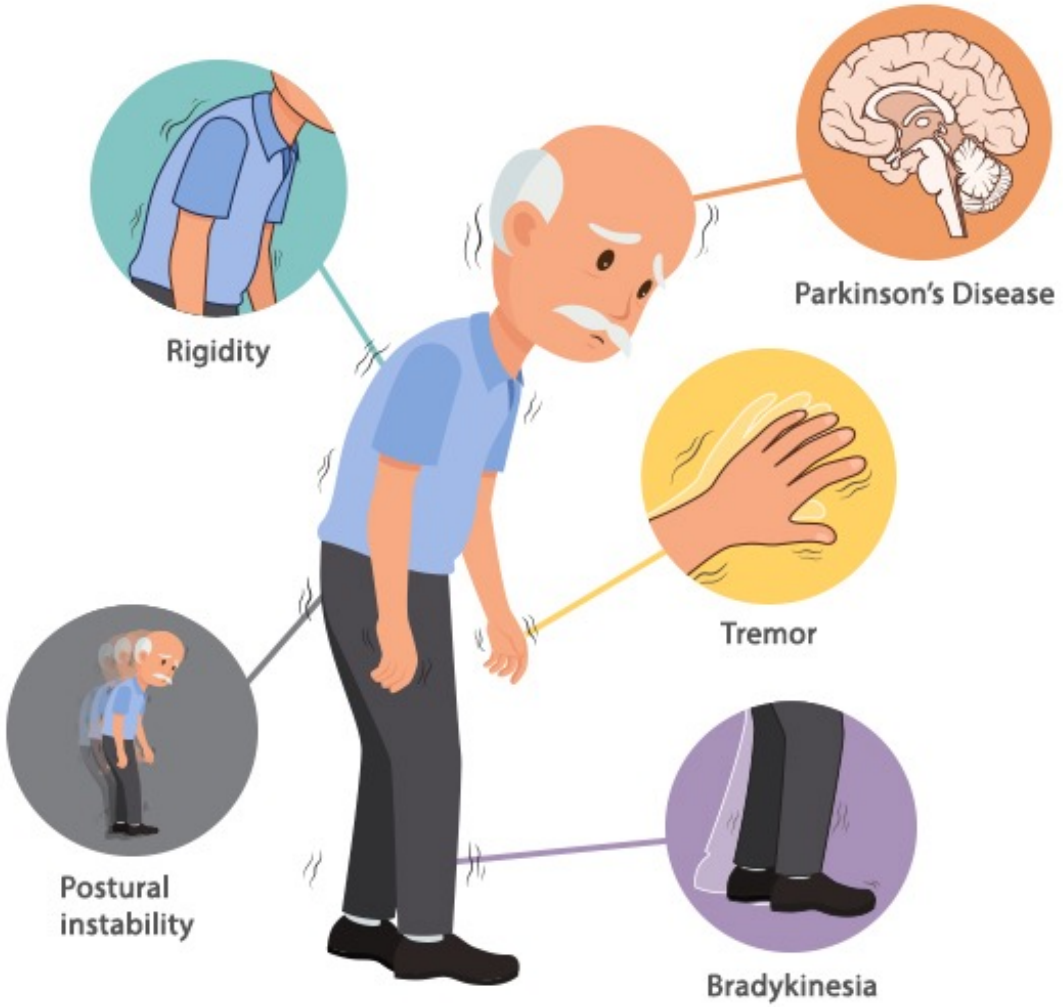


Alexander Kel

geneXplain Germany

Institute of Chemical Biology and Fundamental Medicine, Russia

Parkinson's Disease



Progessive brain disorder that leads to shaking and stiffness
Difficulties with walking, balance and coodination (motor symptoms)
Non-motor symptoms
Degeneration of neurons that synthesise the neurotransmitter dopamine
Norepinephrine-synthesising neurons are also affected
Formation of Lewy bodies in neurons

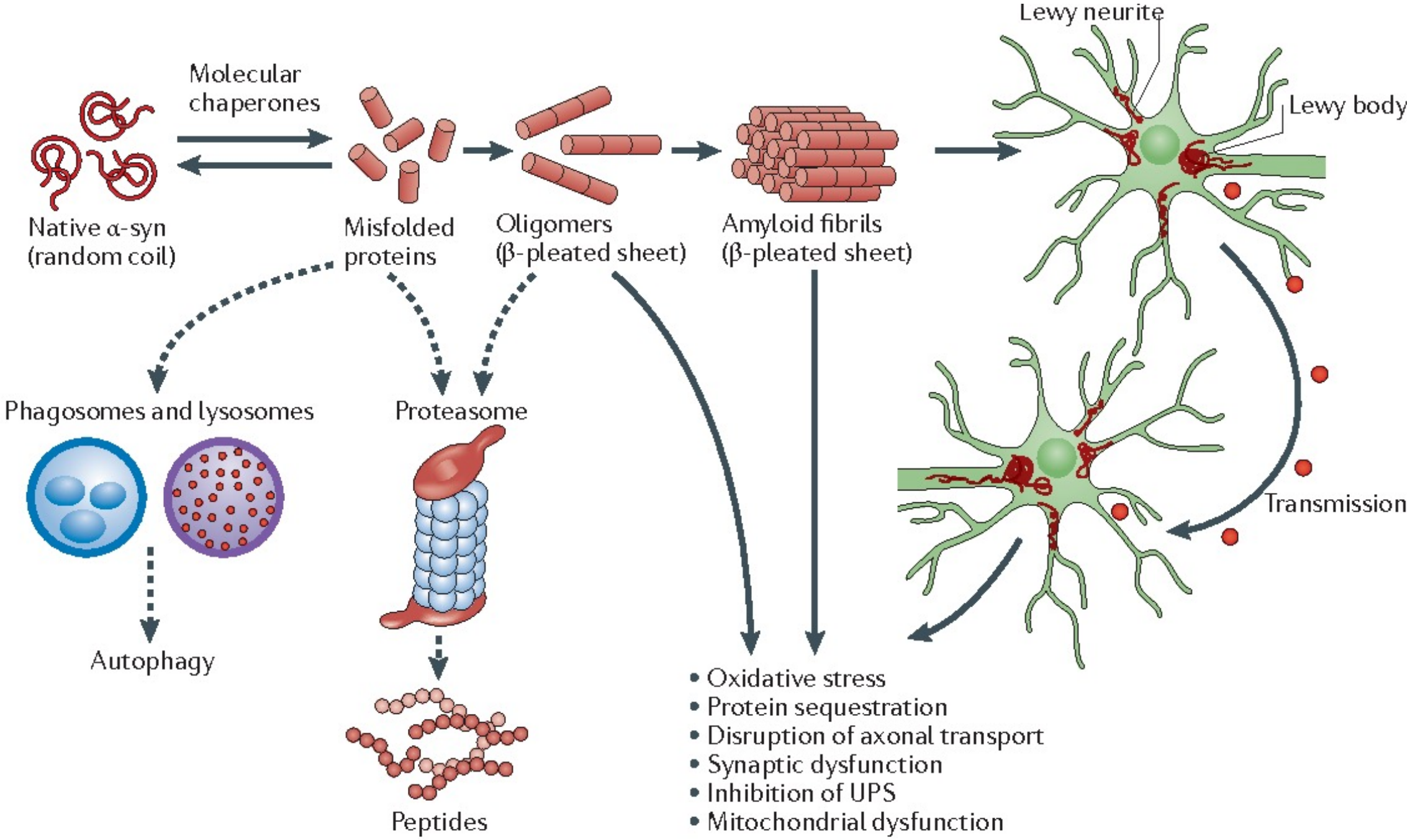
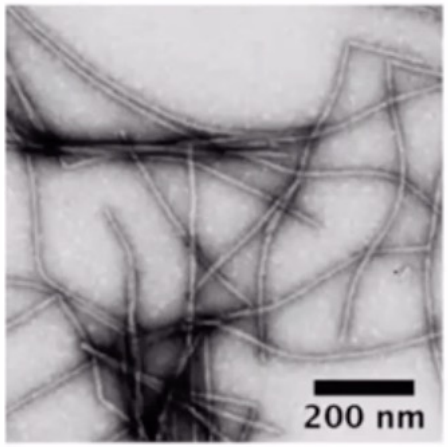
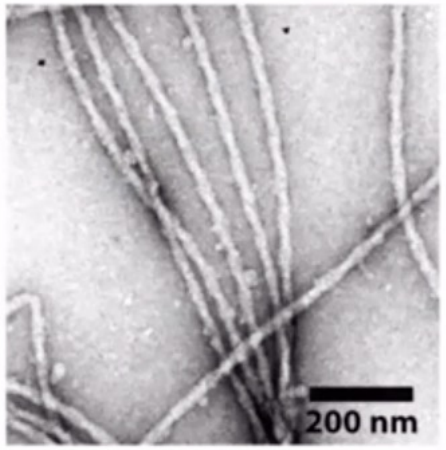


Figure 1 | **Hypothetical model of α-syn toxicity and spread of pathology in PD and PDD.** Under physiological

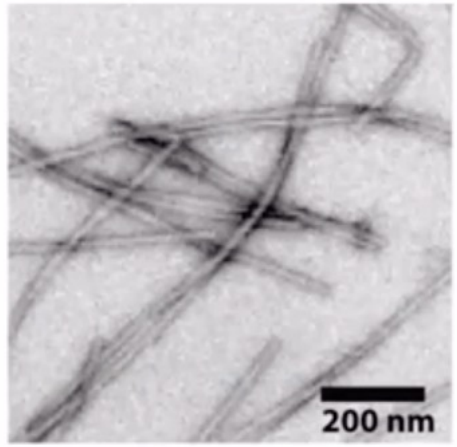
αSyn fibrils come in many forms



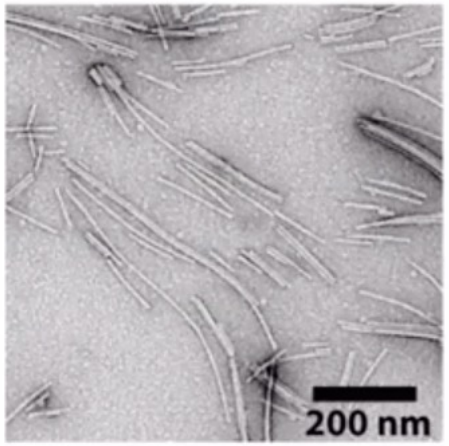
αSyn Fibrils



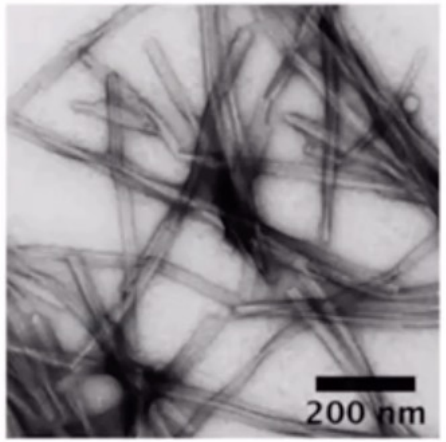
αSyn Fibrils 65



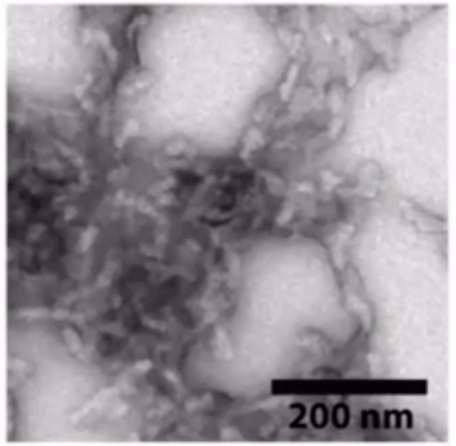
αSyn Fibrils 91



αSyn Fibrils 110



αSyn Ribbons



αSyn assemblies derived from a DLB case

> Sci Rep. 2018 Nov 1;8(1):16165. doi: 10.1038/s41598-018-34490-9.

The small molecule alpha-synuclein misfolding inhibitor, NPT200-11, produces multiple benefits in an animal model of Parkinson's disease

Diana L Price [1], Maya A Koike [2 3], Asma Khan [2], Wolfgang Wrasidlo [2], Edward Rockenstein [4], Eliezer Masliah [4], Douglas Bonhaus [2]

Affiliations + expand

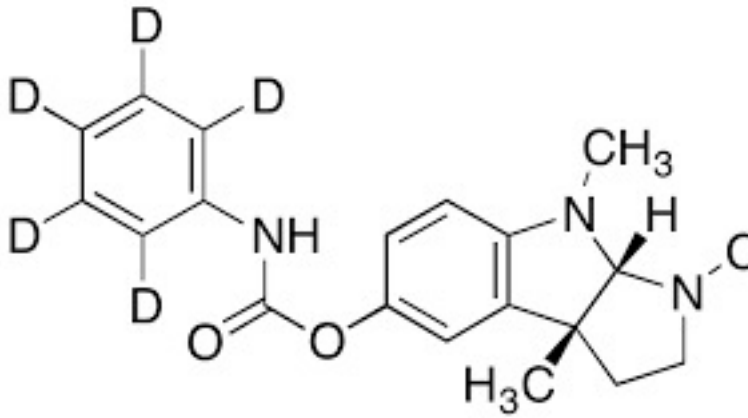
PMID: 30385782 PMCID: PMC6212487 DOI: 10.1038/s41598-018-34490-9

Free PMC article

Abstract

Accumulation of alpha-synuclein (ASYN) in neurons and other CNS cell types may contribute to the underlying pathology of synucleinopathies including Parkinson's disease (PD), dementia with Lewy bodies (DLB) and Multiple Systems Atrophy (MSA). In support of this hypothesis for PD, ASYN

What were the results of the clinical study?



In 2019, UCB initiated a US-based multicenter Phase Ib clinical trial of UCB0599 in Parkinson's. 31 people with Parkinson's (Hoehn-Yahr stage 1–3, aged 40–80 years) were recruited and they received two doses of either UCB0599 (n=21) or placebo (n=10) over four weeks (**Click here** to read the details of the trials). This was the first time the drug was tested in people with PD.

The results of the study indicate that UCB0599 was safe and well tolerated in the study. There was little difference between the UCB0599- and placebo-treated groups in terms of treatment-emergent adverse events (headache being the most common event in both groups).

PLOS GENETICS

OPEN ACCESS PEER-REVIEWED

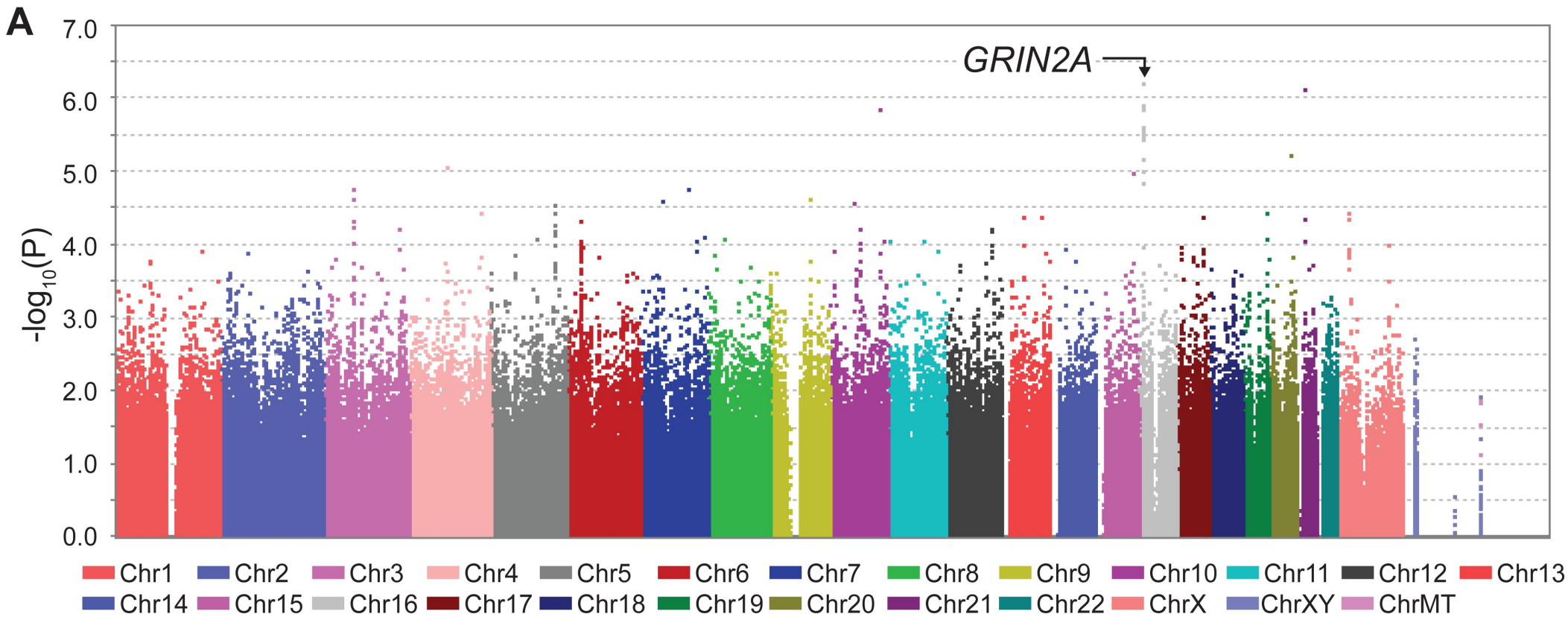
RESEARCH ARTICLE

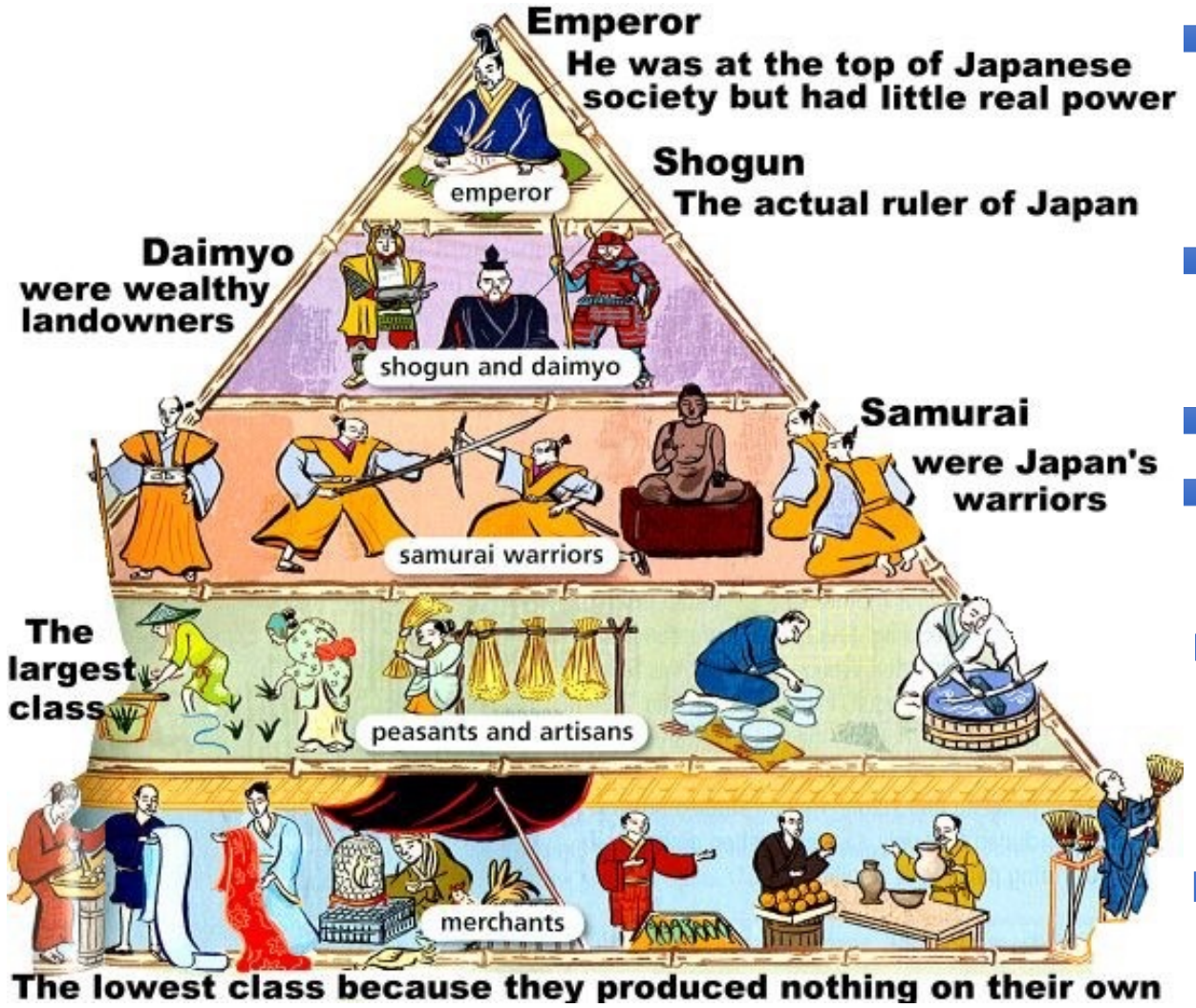
Genome-Wide Gene-Environment Study Identifies Glutamate Receptor Gene *GRIN2A* as a Parkinson's Disease Modifier Gene via Interaction with Coffee

Taye H. Hamza, Honglei Chen, Erin M. Hill-Burns, Shannon L. Rhodes, Jennifer Montimurro, Denise M. Kay, Albert Tenesa, Victoria I. Kusel, Patricia Sheehan, Muthukrishnan Eaaswarkh Haydeh Payami [view all]

Published: August 18, 2011 • https://doi.org/10.1371/journal.p

Epidemiological studies have firmly established that coffee drinking is inversely associated with risk of developing Parkinson disease (PD) [1], and clinical trials of caffeine for treatment of PD have shown symptomatic benefit [2]–[4]. Identifying genes that modulate the efficacy of coffee may therefore have pharmacogenomic potential for prevention and treatment.





Master-regulator

Signal transduction

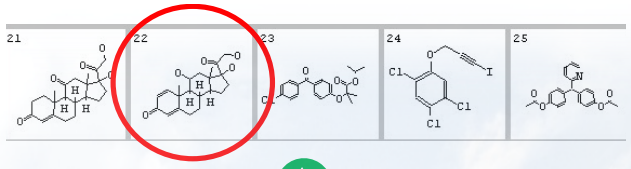
Transcription Factors

miRNAs

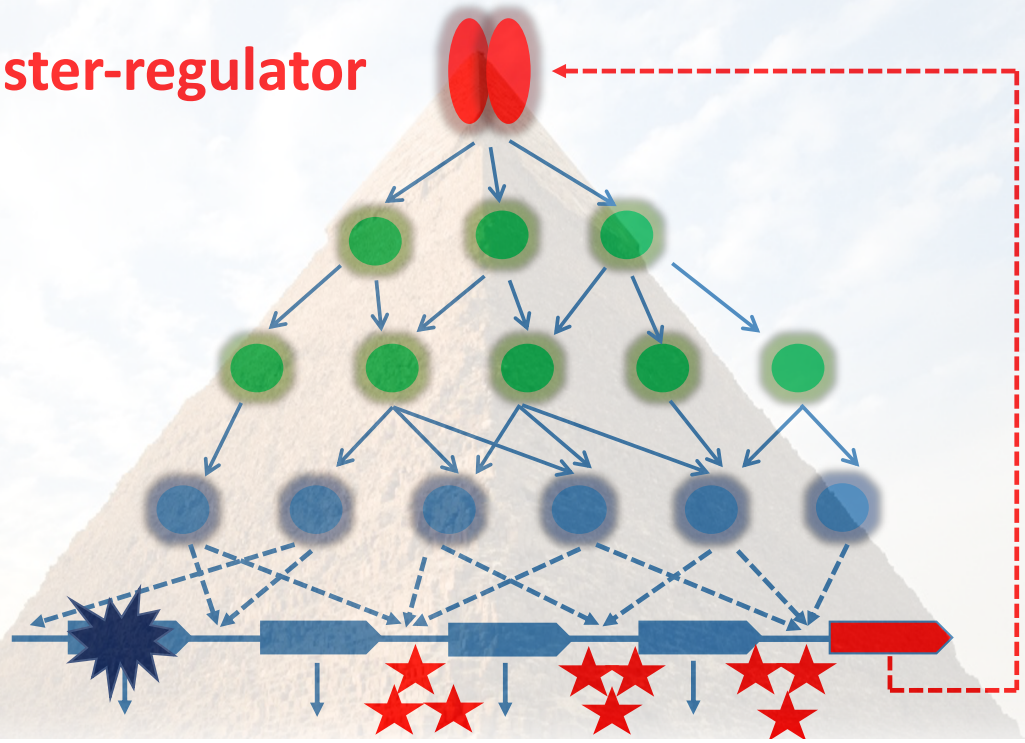
Genes of metabolism

Genes of cell cycle, development, communication

We build a pyramid



Master-regulator

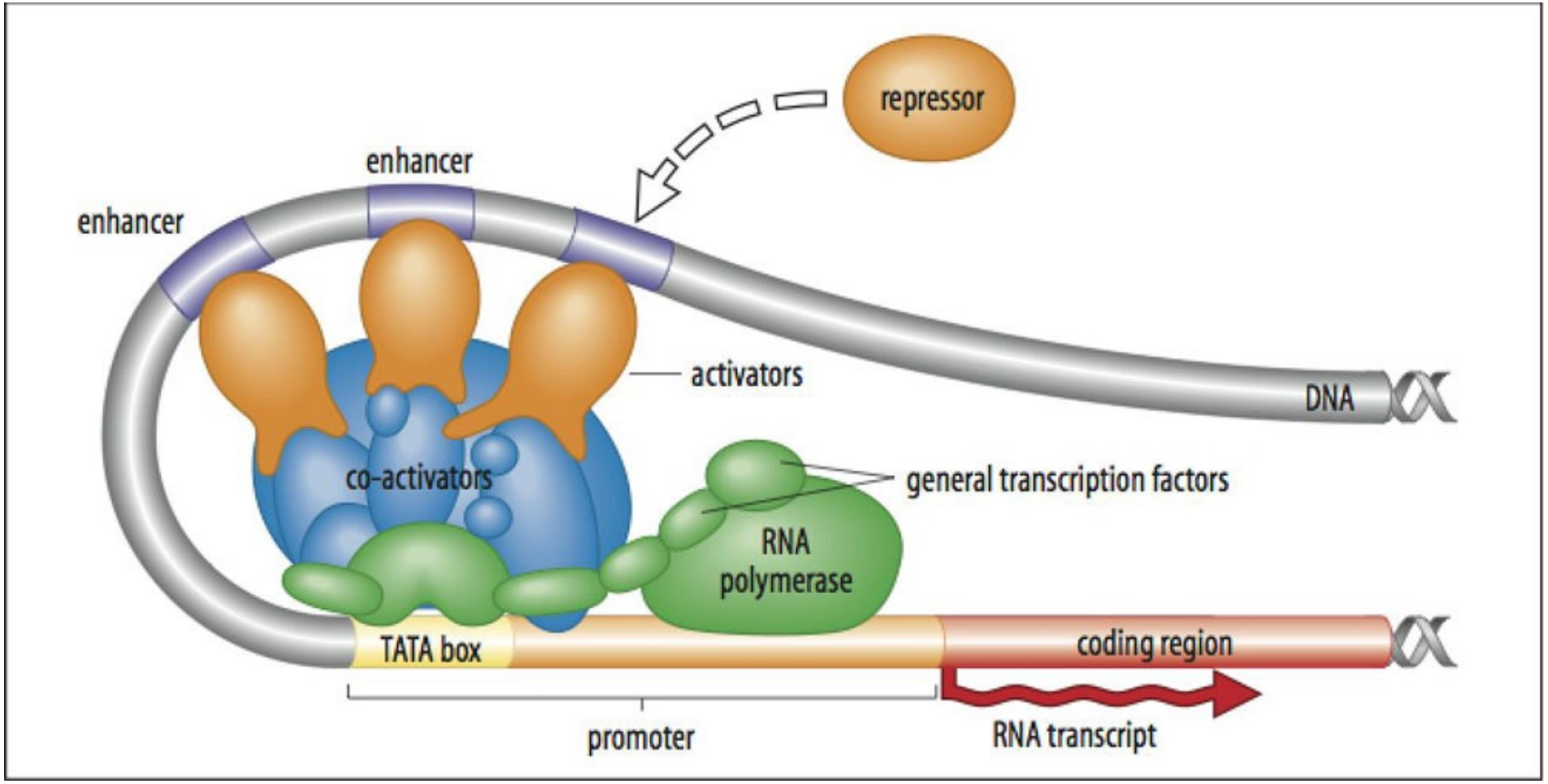


NGS

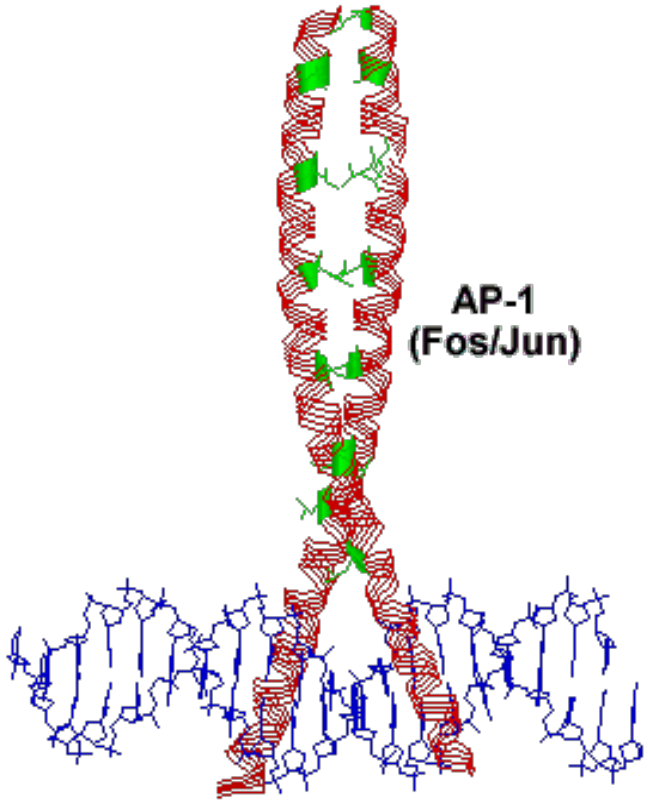
RNA-seq, Exome,
Methylome, ChIP-seq,
Proteome, Metabolome

AI

TFs can read between genes

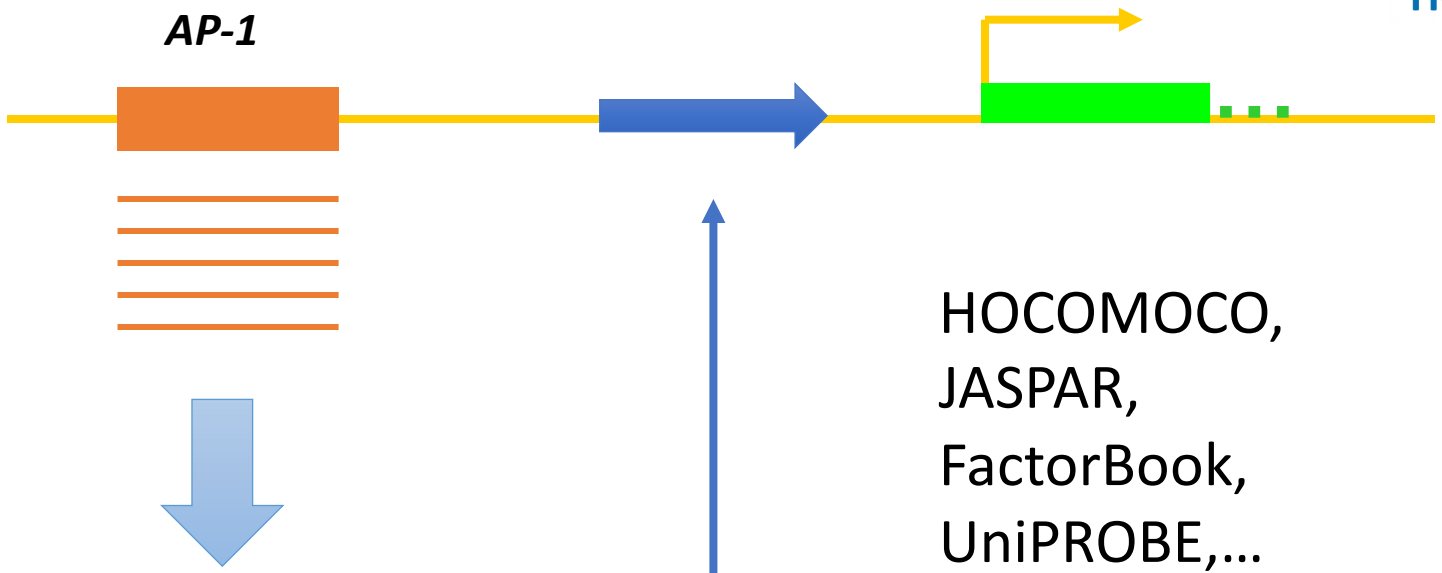


AP-1 (human)

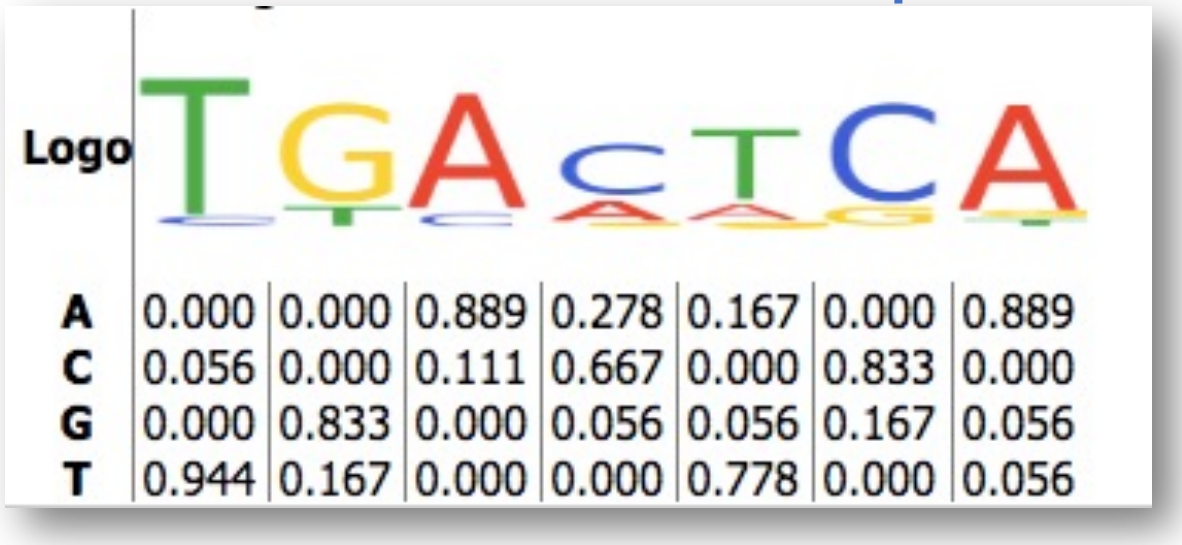


Search for new TF binding sites with PWMs

TRANSFAC 2.0

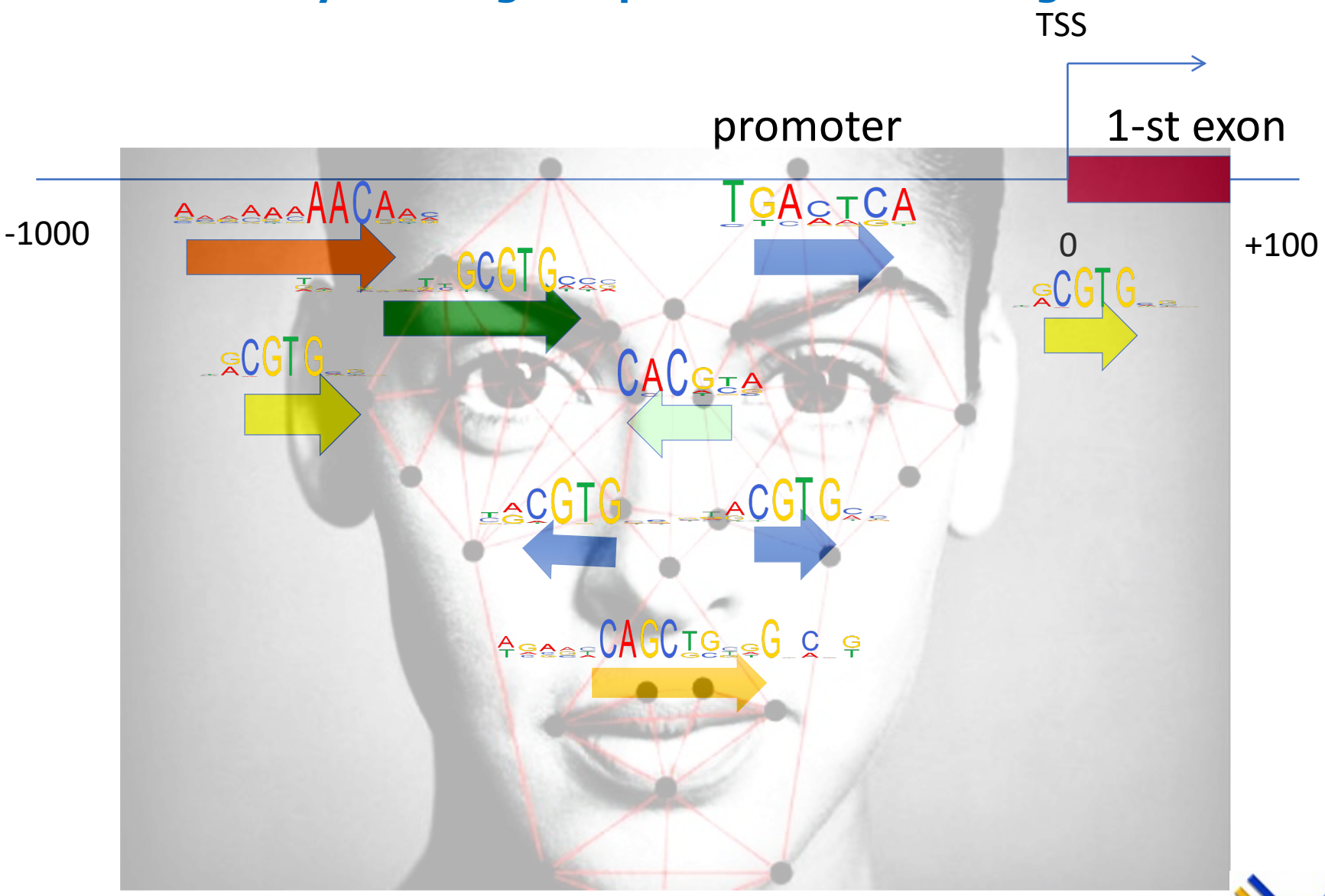


HOCOMOCO,
JASPAR,
FactorBook,
UniPROBE,…
TRANSFAC (**10290 PWMs**)



A	0.000	0.000	0.889	0.278	0.167	0.000	0.889
C	0.056	0.000	0.111	0.667	0.000	0.833	0.000
G	0.000	0.833	0.000	0.056	0.056	0.167	0.056
T	0.944	0.167	0.000	0.000	0.778	0.000	0.056

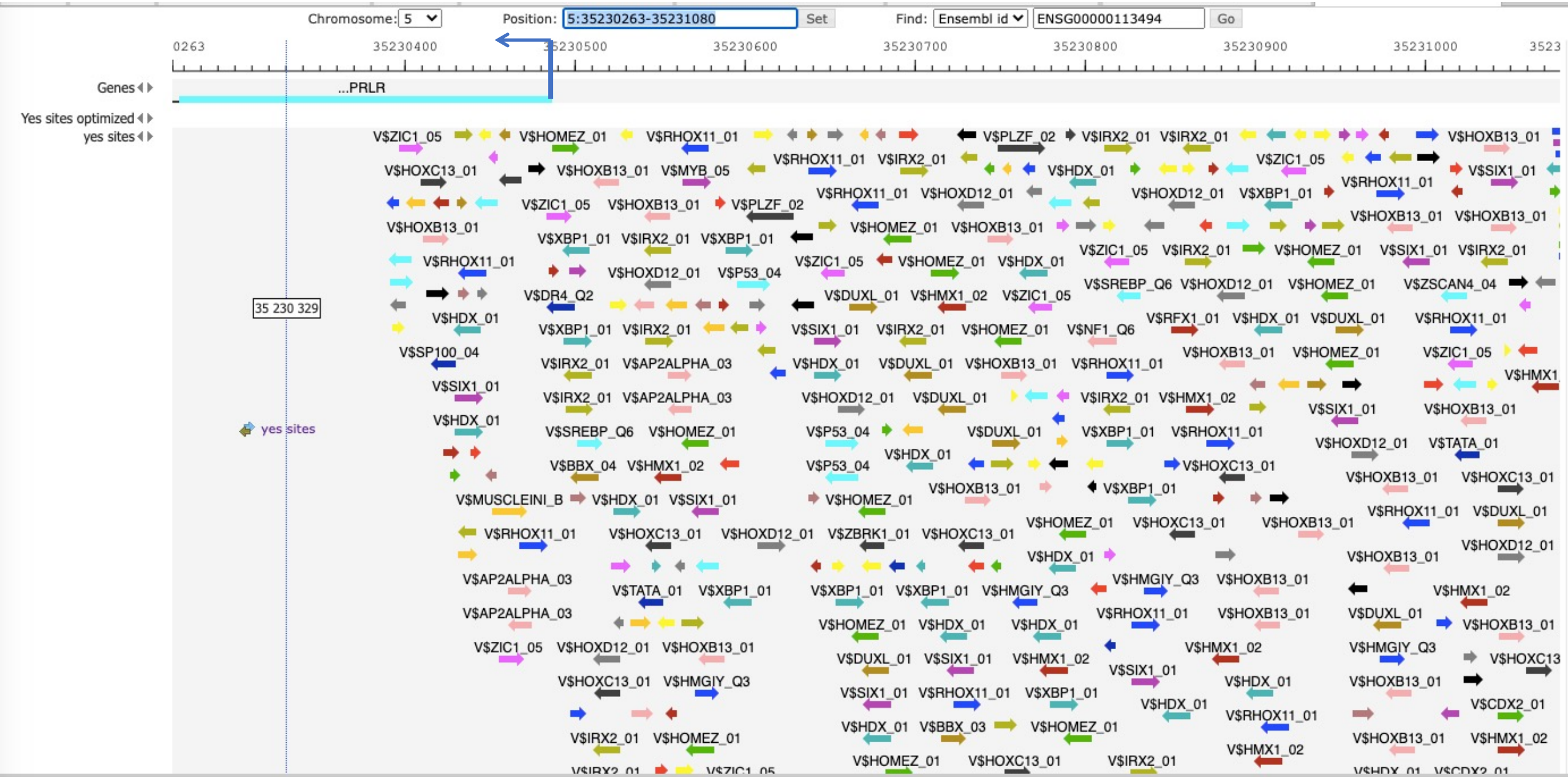
We should try to recognize promoters of active genes in PD



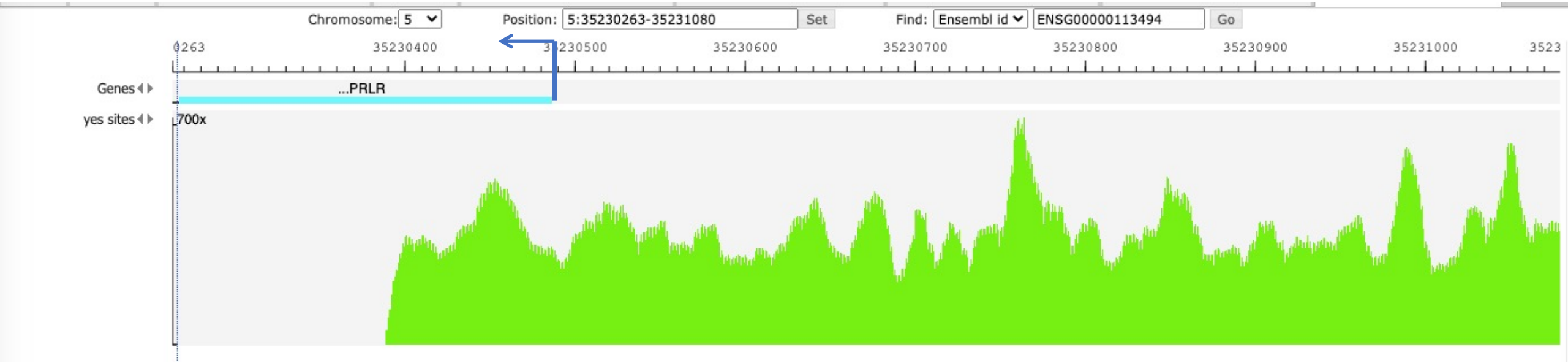
Promoter face

TRANSFAC

TFBS of 168 TF motifs

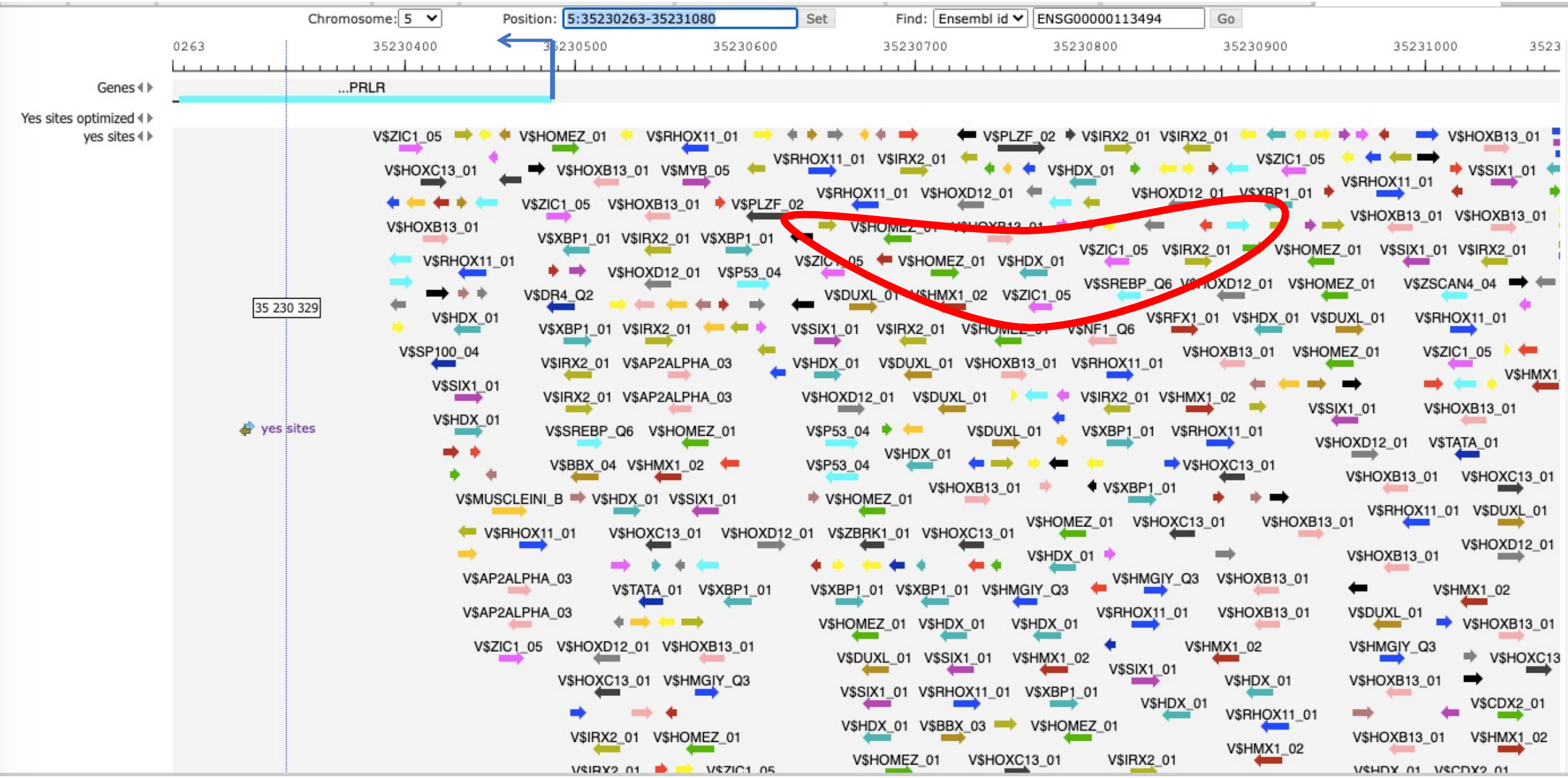


TFBS of 5260 TF motifs



What is common between all these faces?

Find a subset of TF sites out of all 5260 TFs



There are new AI methods available for recognition of human emotions:

😄: 95.69 😠: 1.96 😐: 1.18

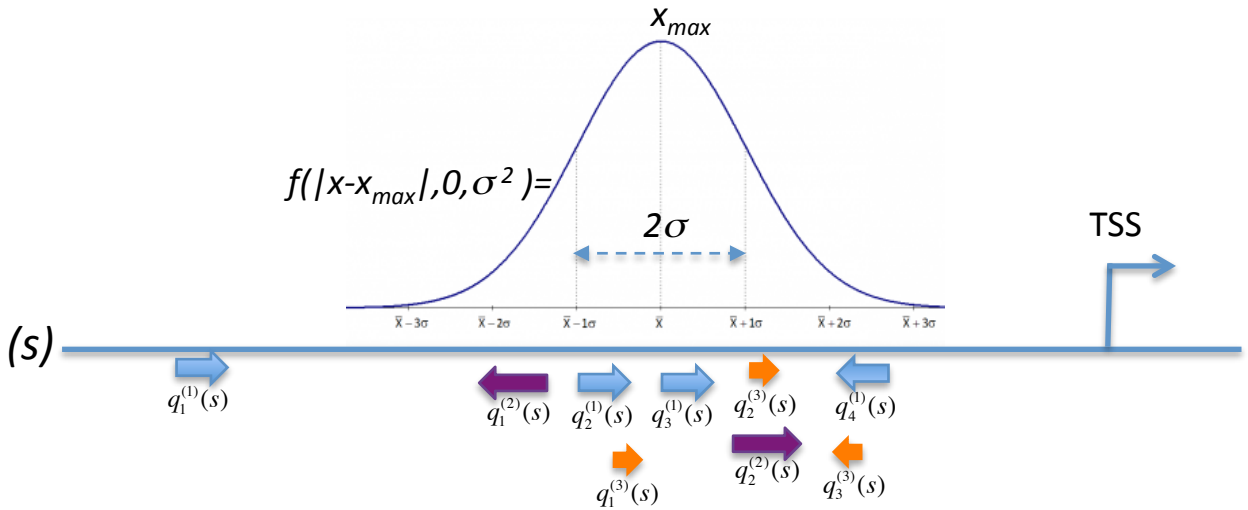
😠: 50.59 😐: 33.73 😞: 9.80

😮: 59.61 😐: 20.78 😄: 14.51

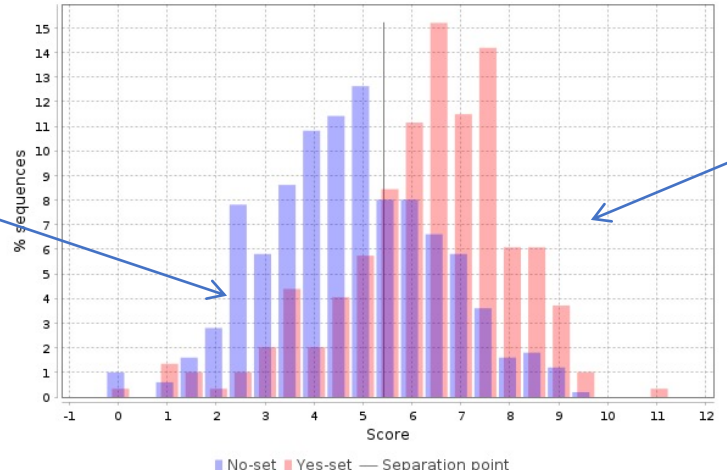
😐: 83.92 😞: 7.45 😮: 5.10

We are going to use such algorithms for recognizing promoter “emotions” – promoter “smile” or PD enhancer “grin”.

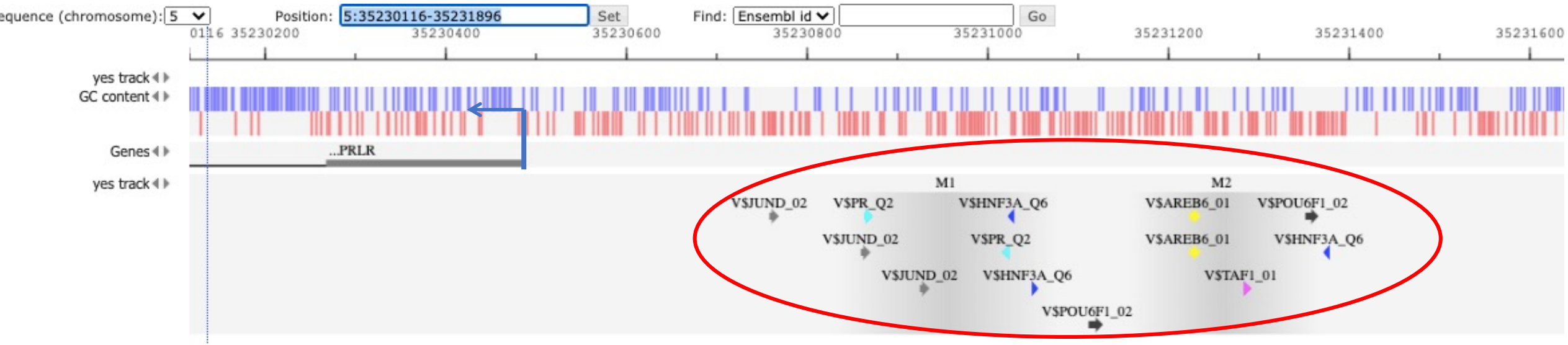
Composite model



500
Non changed
genes

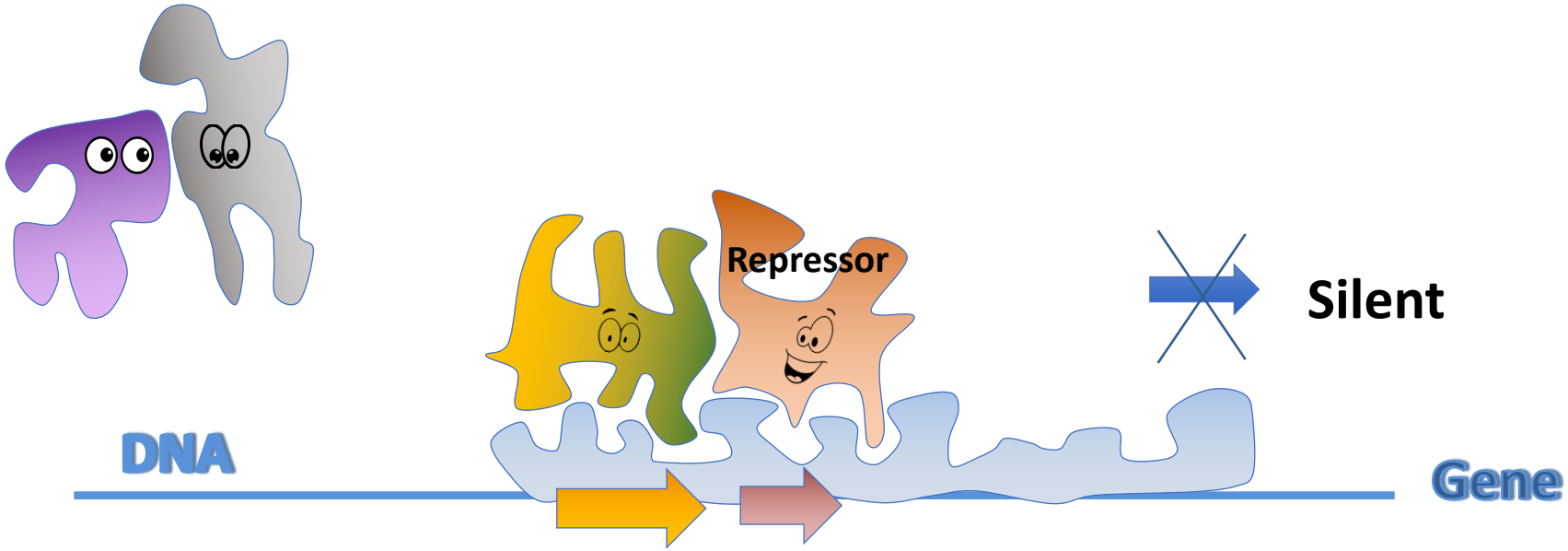


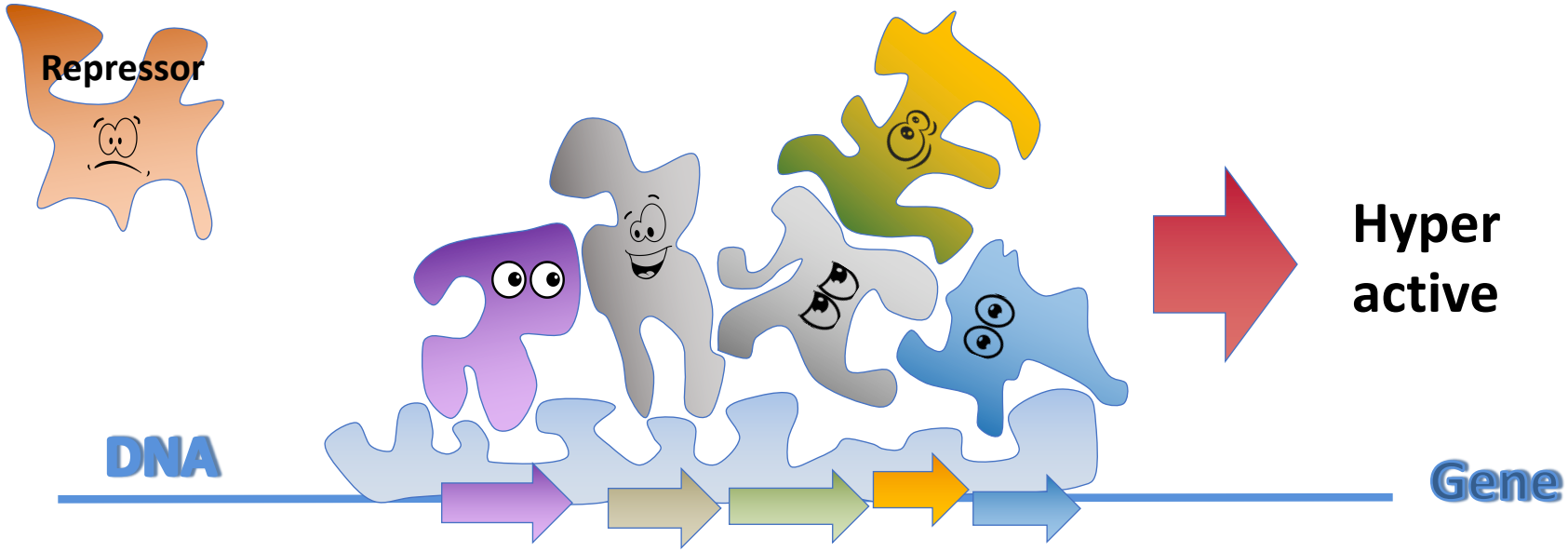
296 top
UP-regulated
genes
with TF
clusters

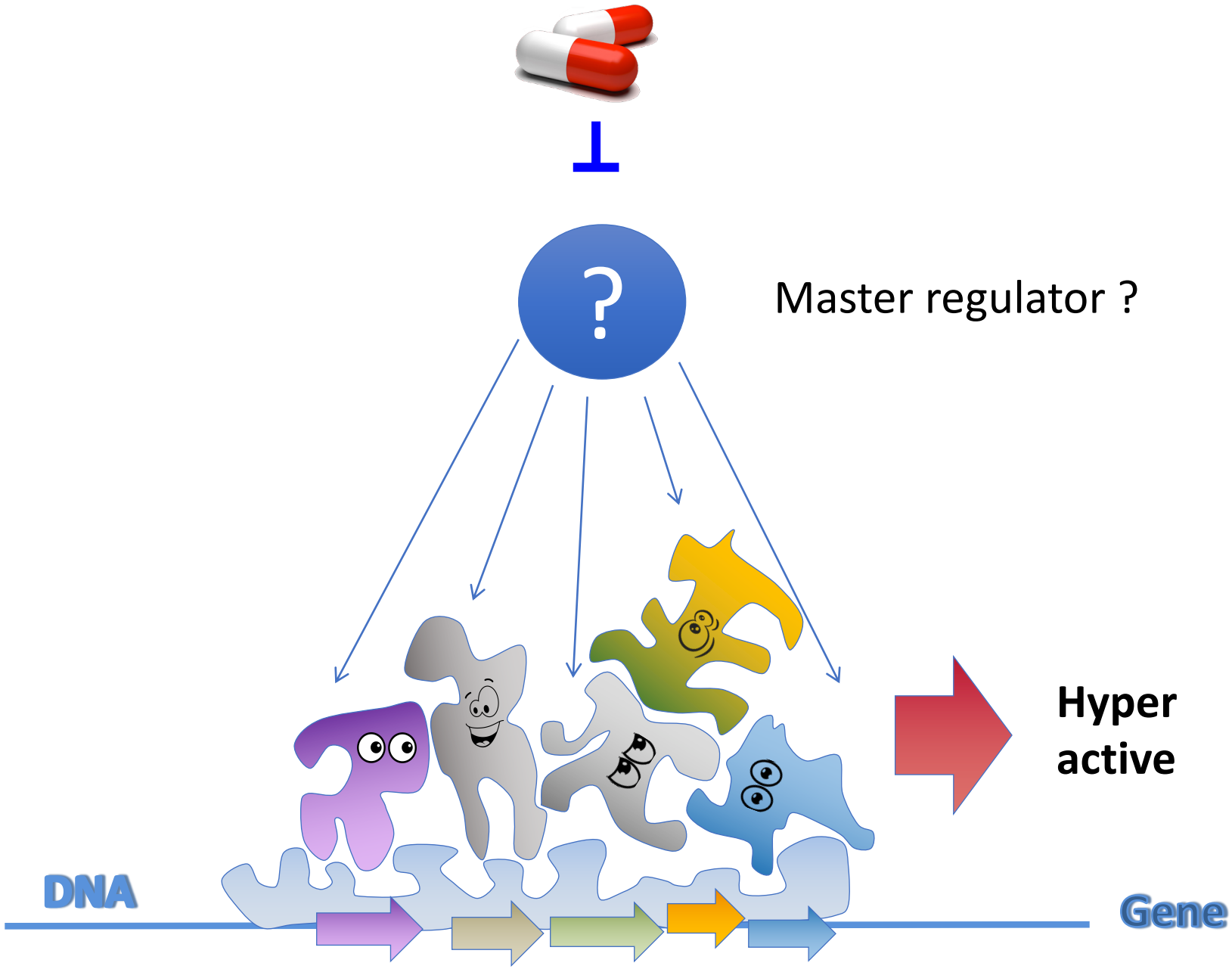

equence (chromosome): 5
Position: 5:35230116-35231896
Set
Find: Ensembl id
Go
35230200
35230400
35230600
35230800
35231000
35231200
35231400
35231600
yes track
GC content
Genes
..PRLR
yes track
M1
M2
V$JUND_02
V$PR_Q2
V$HNF3A_Q6
V$AREB6_01
V$POU6F1_02
V$JUND_02
V$PR_Q2
V$AREB6_01
V$HNF3A_Q6
V$JUND_02
V$HNF3A_Q6
V$TAF1_01
V$POU6F1_02


Module 1
V$IPF1_07
0.82; N=2
V$LEF1_12
0.82; N=3
V$YY1_12
0.79; N=3
V$PAX5_Q6
0.98; N=3
V$SREBP_Q3
0.85; N=2
Module width: 126
Module 2
V$HOXB6_05
0.98; N=3
V$FOXO6_02
1.00; N=1
V$GR_Q6_01
0.99; N=2
V$ZEB1_05
0.99; N=2
V$FOXK1_13
0.89; N=2
Module width: 49

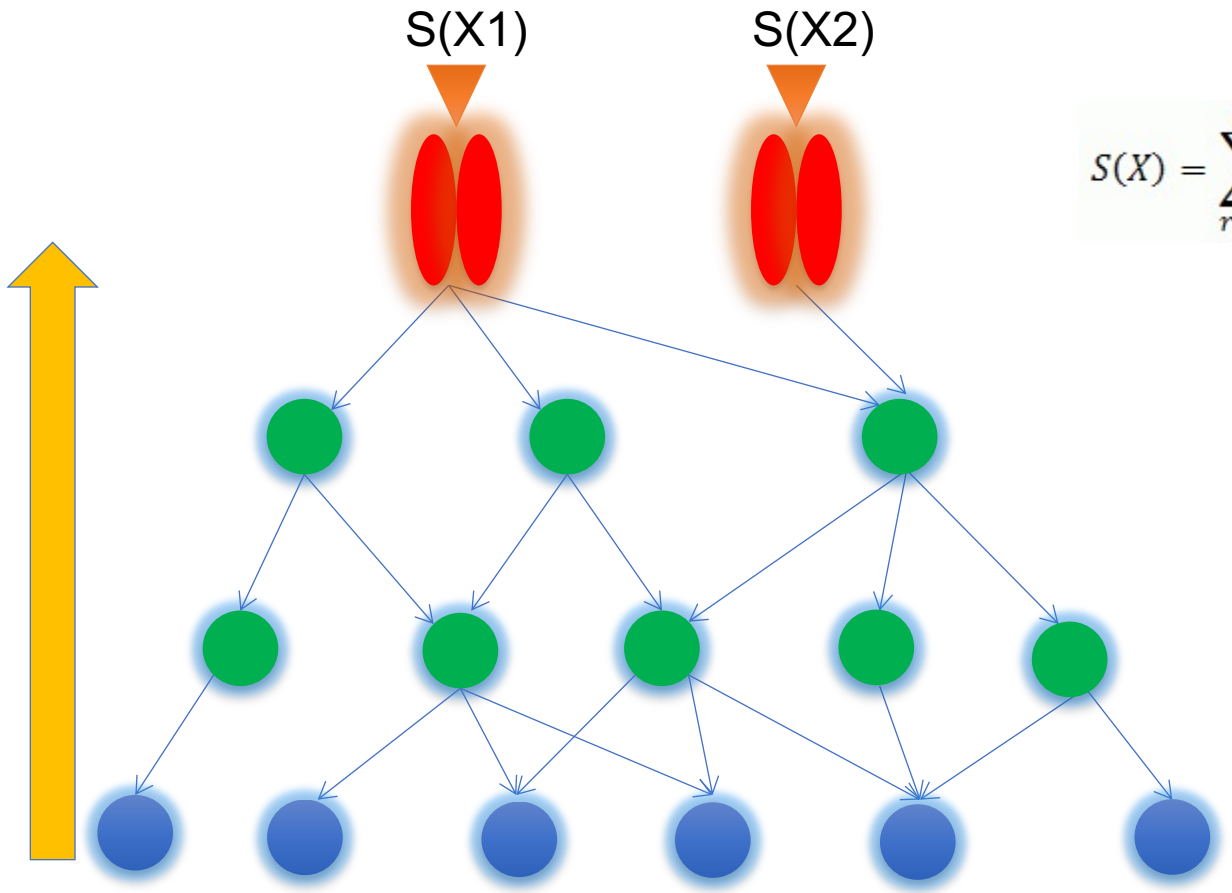
It’s a fuzzy puzzle!






?
Master regulator ?
Hyper
active
DNA
Gene

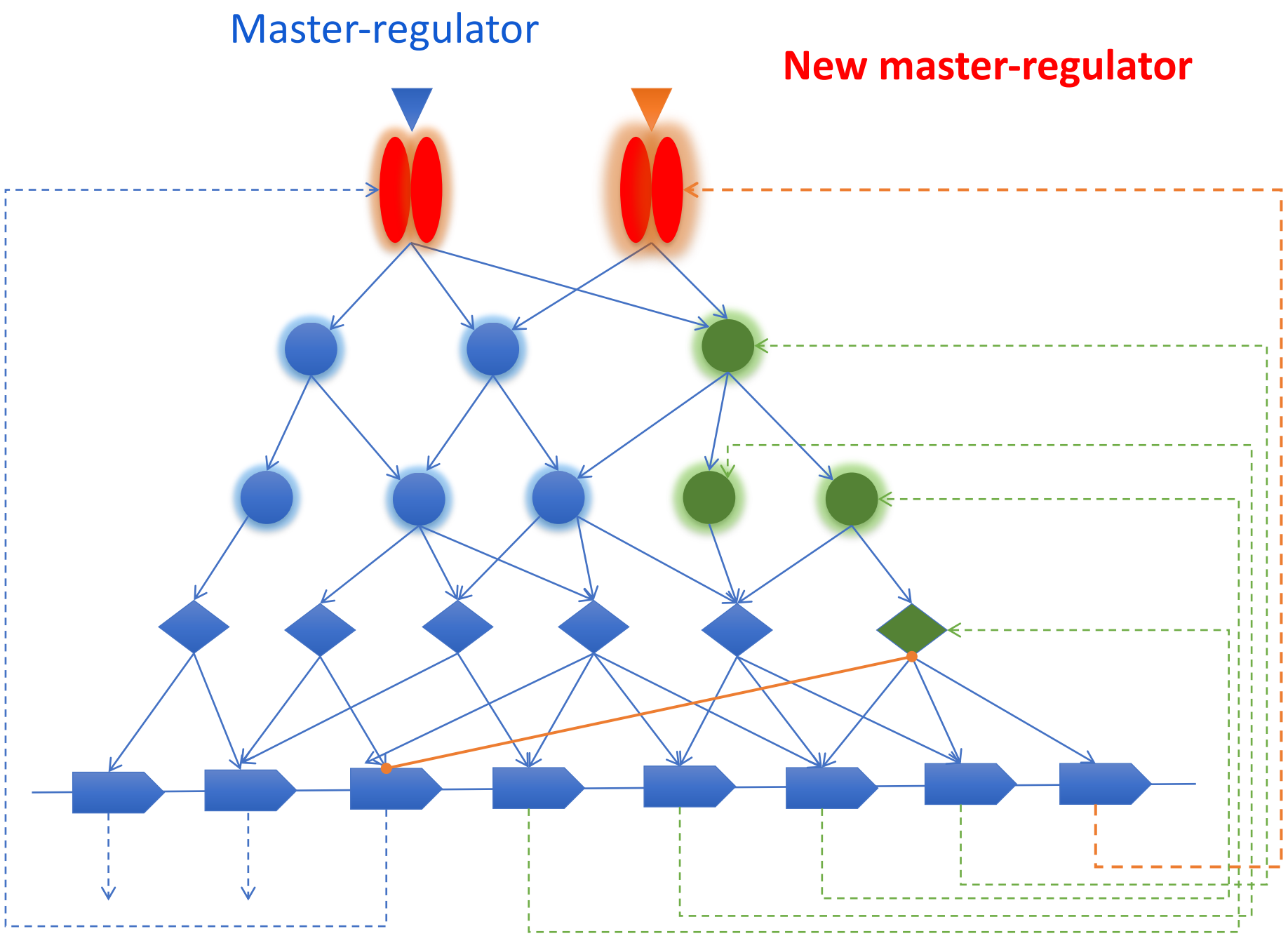
Search for master regulators

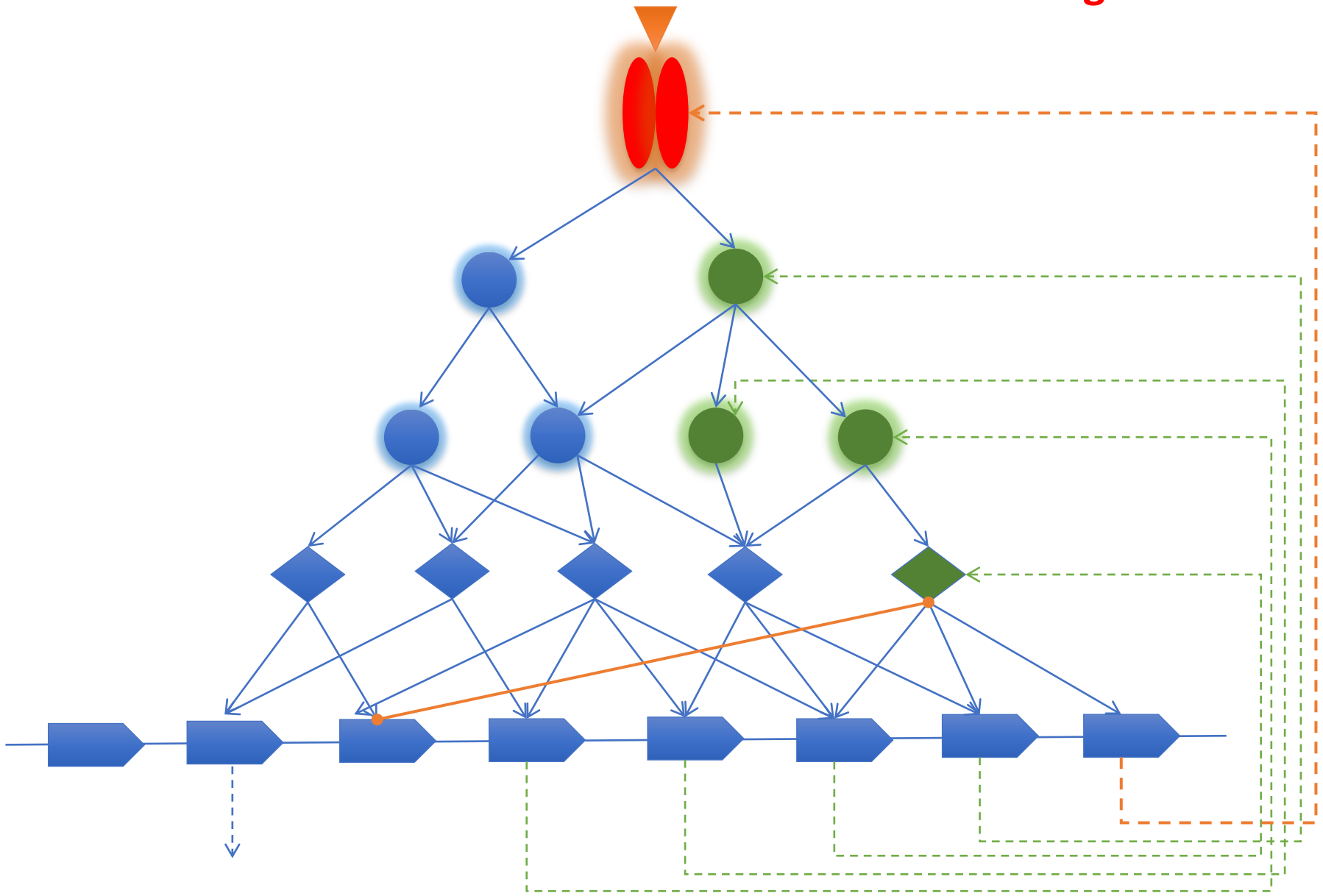


$$S(X) = \sum_{r=1}^{R} \frac{M(X,r)}{M_{max}(r)} \cdot \frac{1}{1 + pN(X,r)/N_{max}(r)}$$

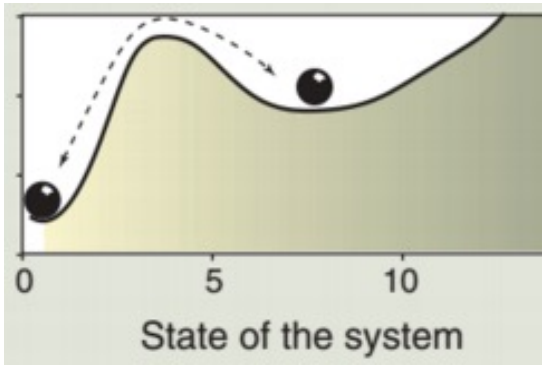
Where:
R - Max radius (input parameter)
p - Penalty (input parameter)
N(X,r) - total number of molecules reachable from key molecule X within the radius r.
N_{max}(r) - maximal value of *N(X,r)* over all key molecules X found for this radius.
M(X,r) - sum of *w(X)* for all hits reachable from key molecule X within the radius r, where *w(X)* - weight of hit X.
M_{max}(r) - maximal value of *M(X,r)* over all key molecules X found for this radius.

Kel, A., Voss, N., Jauregui, R., Kel-Margoulis, O. and Wingender, E.: Beyond microarrays: Find key transcription factors controlling signal transduction pathways BMC Bioinformatics 7(Suppl. 2), S13 (2006).


Master-regulator
New master-regulator

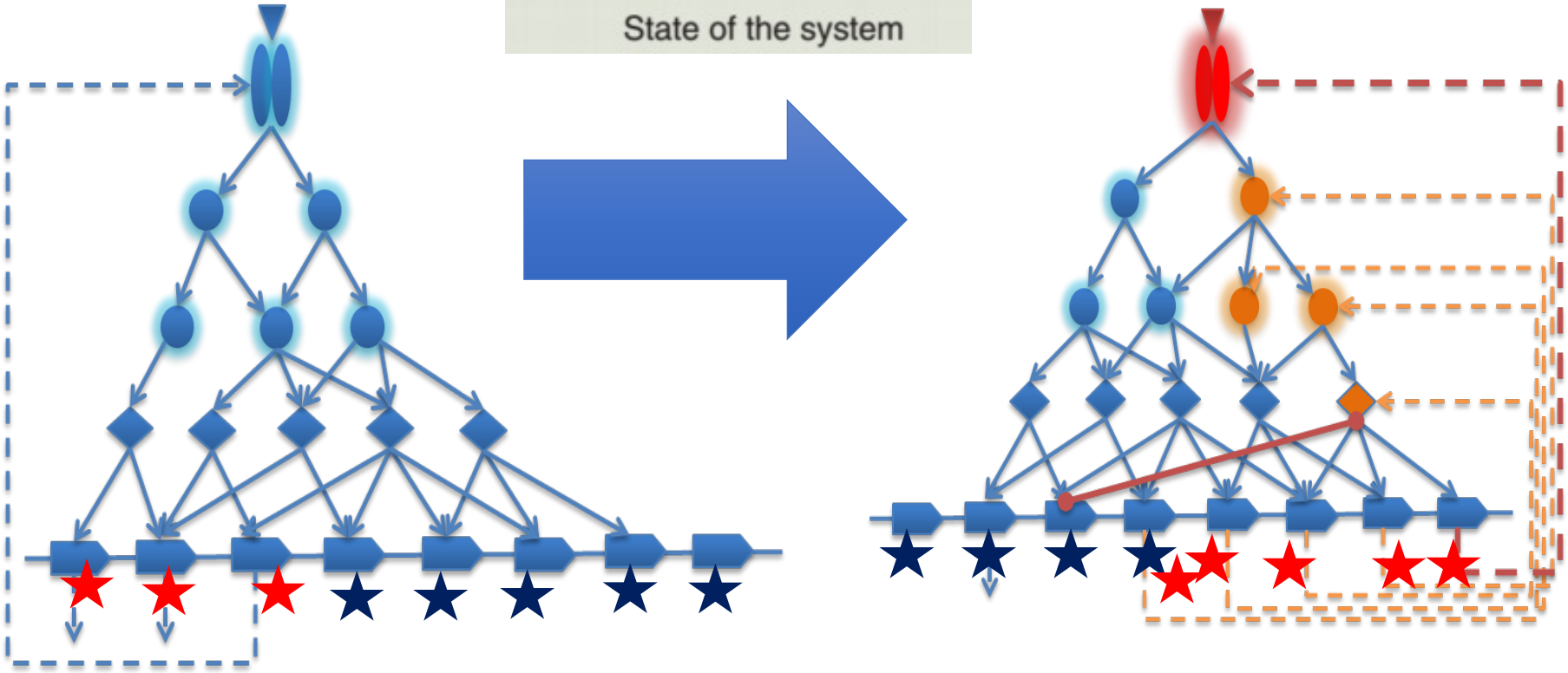

New master-regulator

Pathway corruption

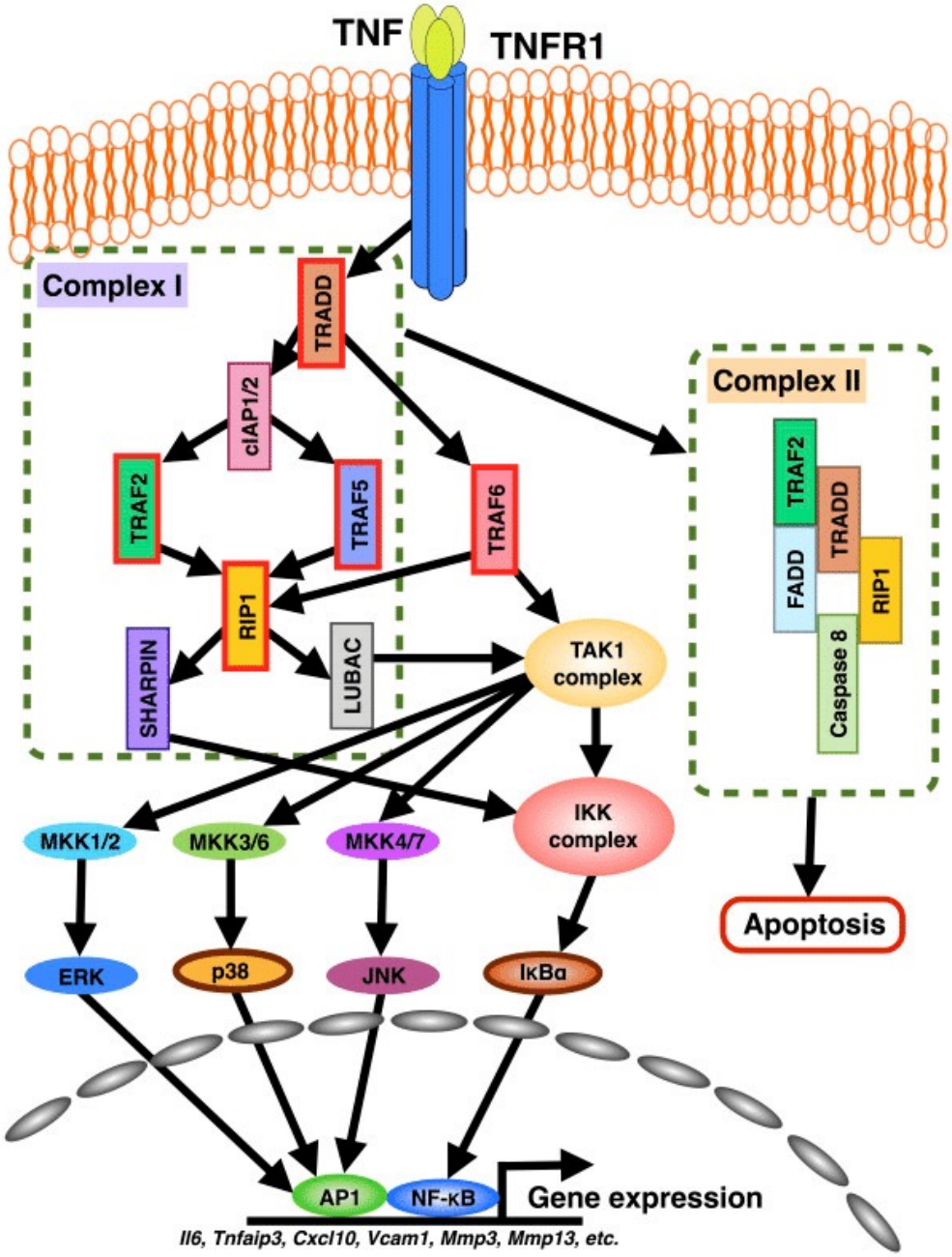


Healthy

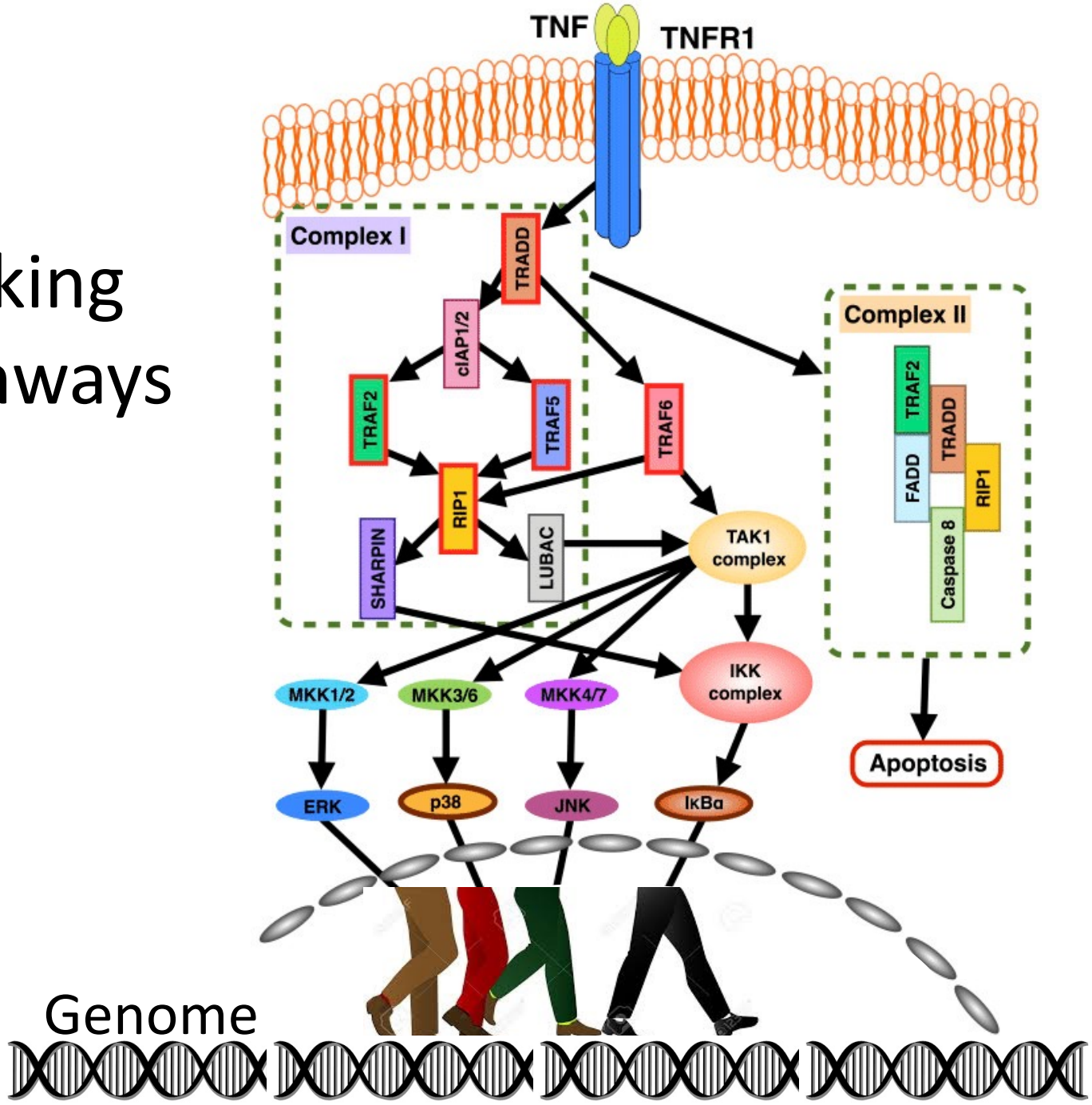
Disease



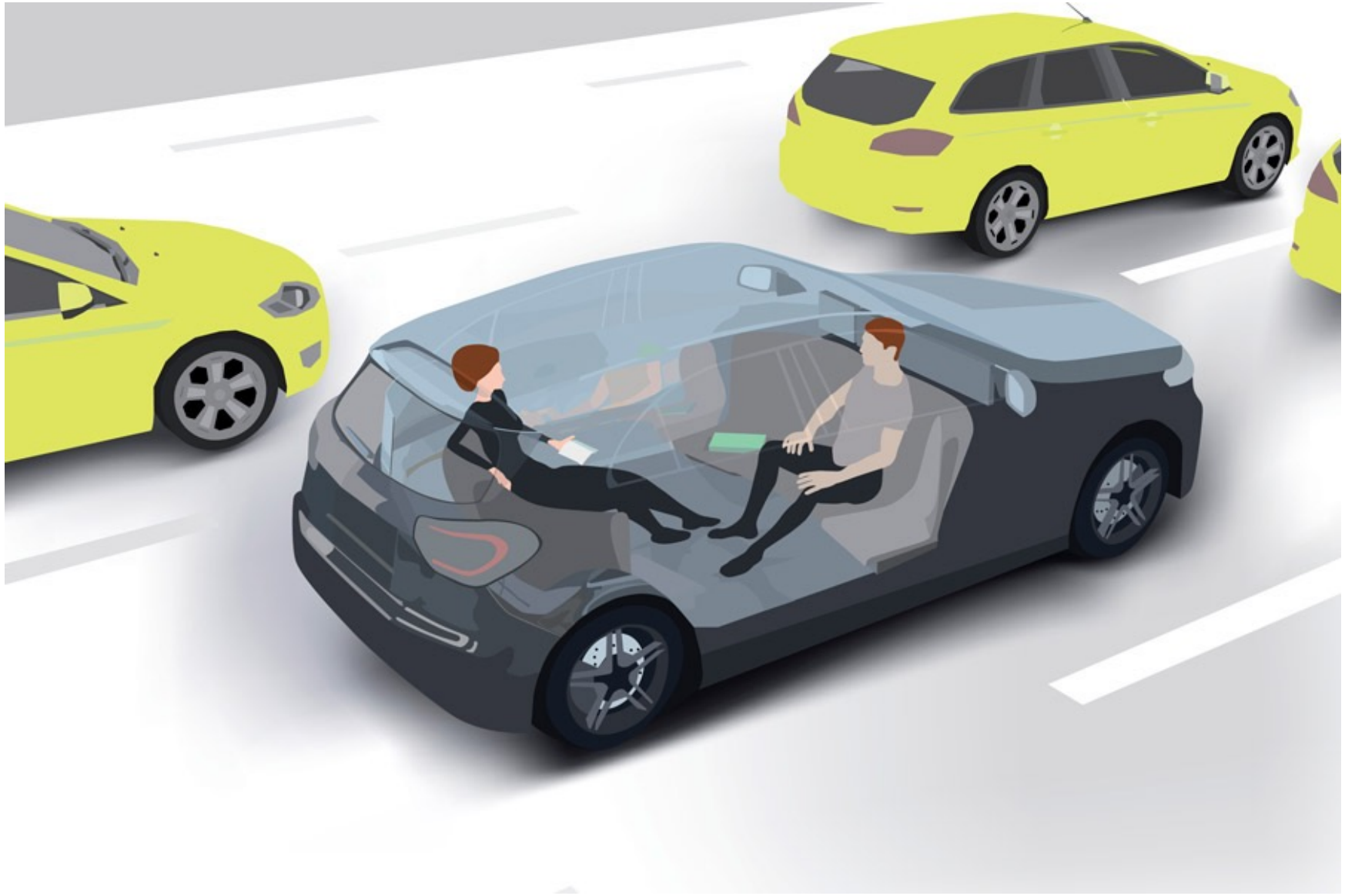
Walking pathways



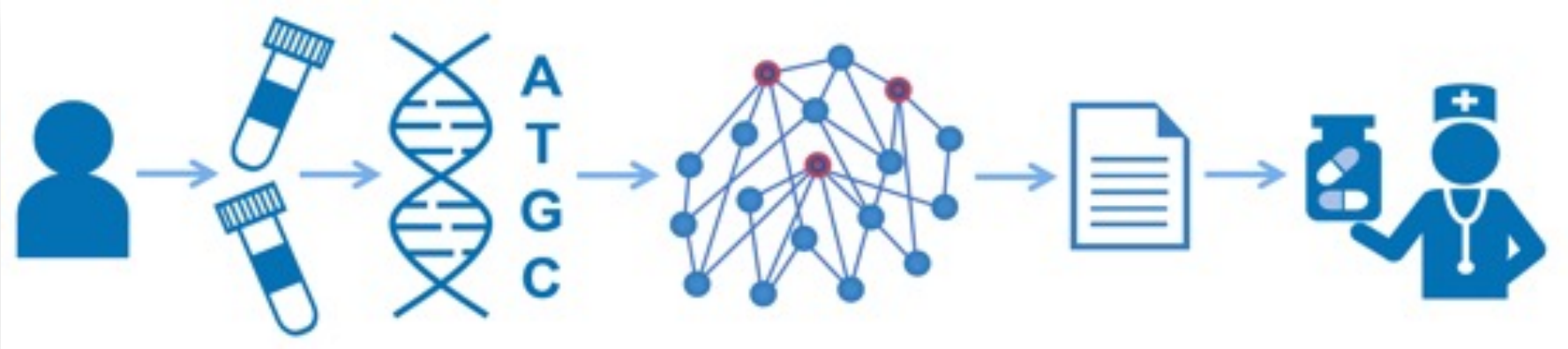
Walking pathways

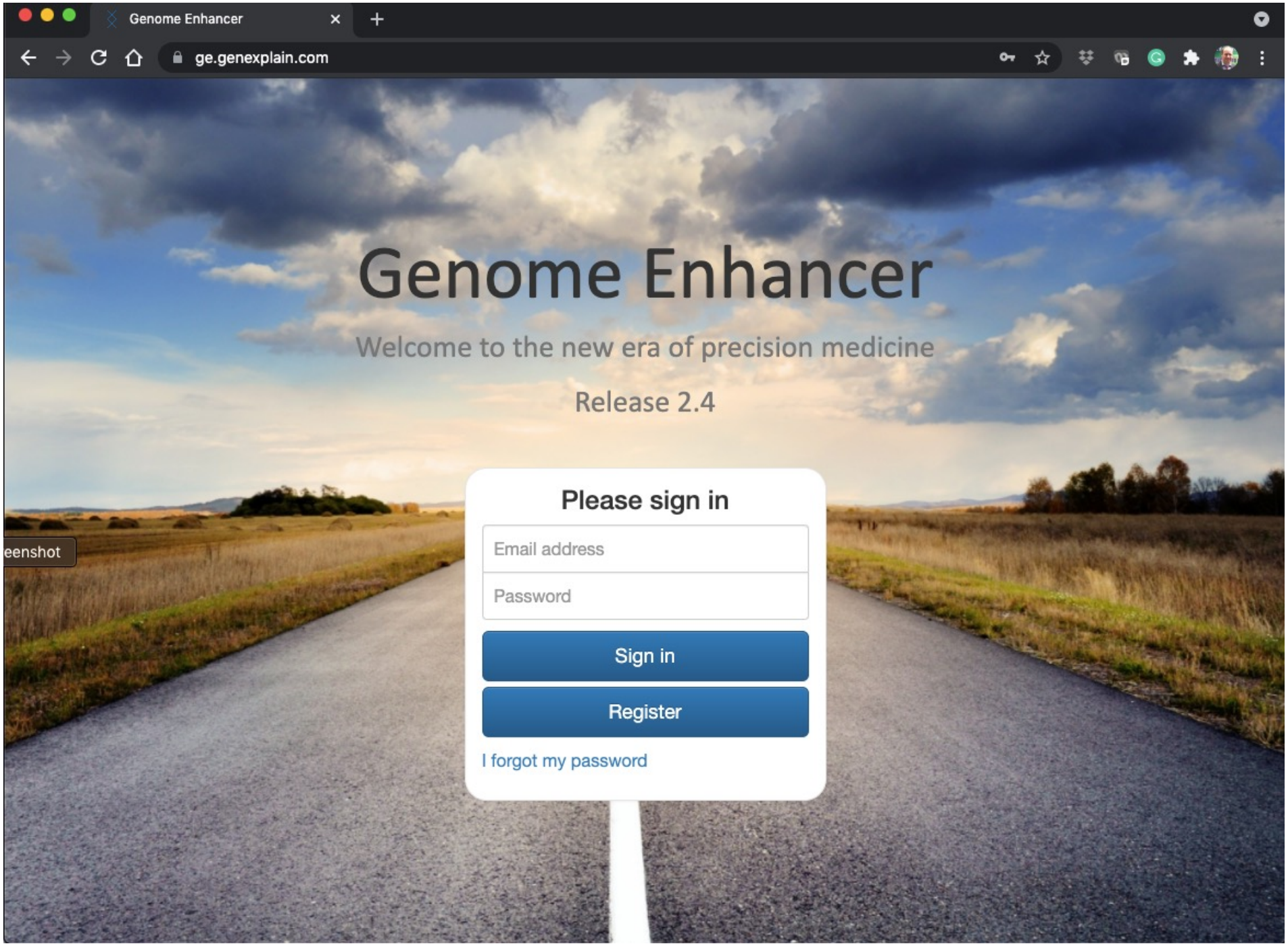


We would like AI to run the full data analysis completely automatic…



Genome Enhancer



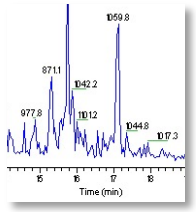

Genome Enhancer
ge.genexplain.com
Genome Enhancer
Welcome to the new era of precision medicine
Release 2.4
Please sign in
Email address
Password
Sign in
Register
I forgot my password

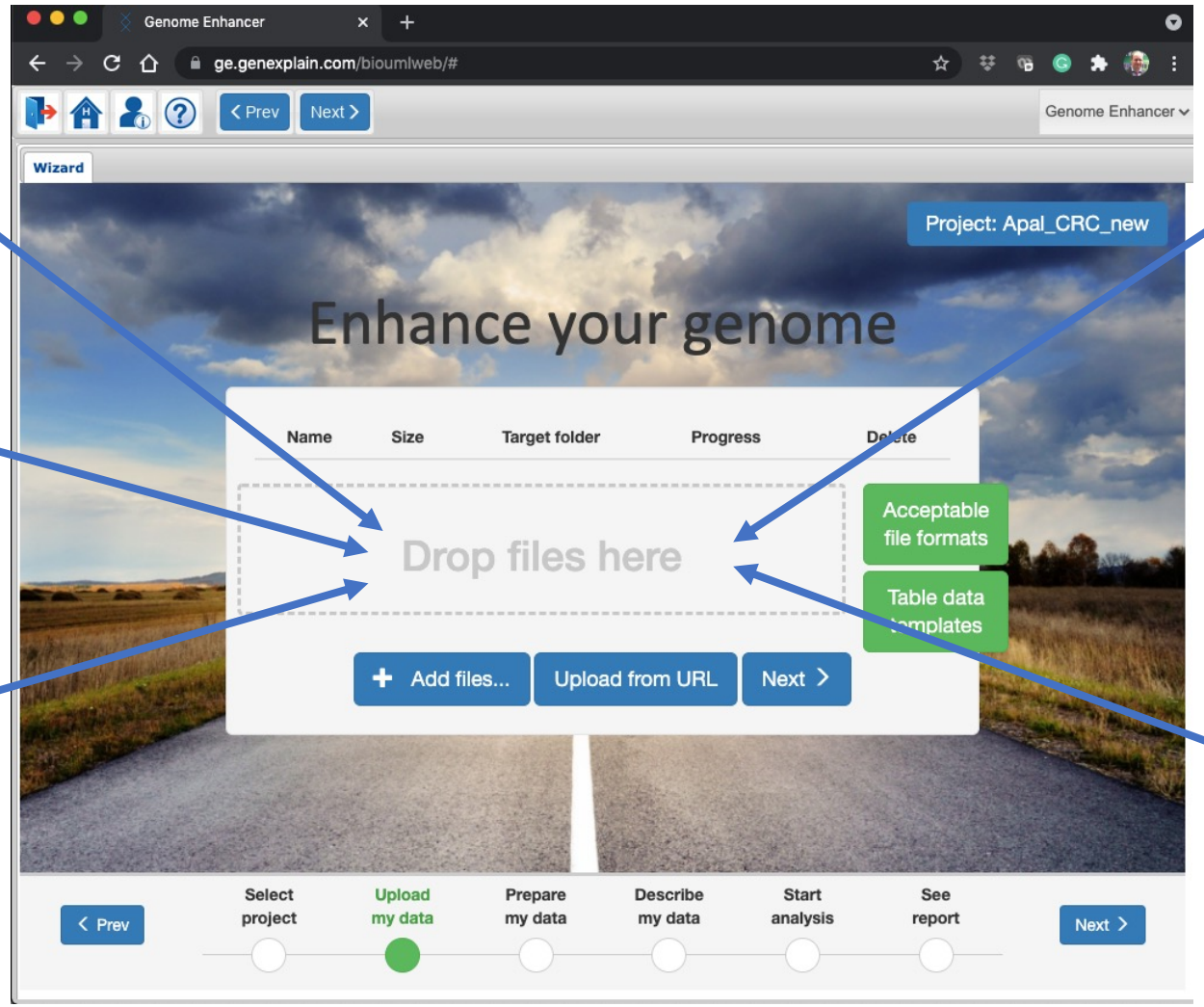
Multi-omics data input

Transcriptomics

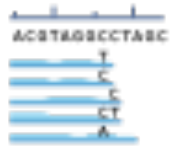
Epigenomics

Proteomics

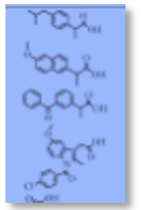




Genomics



Metabolomics



Series GSE145804	Query DataSets for GSE145804
Status	Public on Feb 24, 2020
Title	α-Synuclein Translocates To The Nucleus To Activate Retinoic Acid- Dependent Gene Transcription
Organism	Homo sapiens
Experiment type	Expression profiling by high throughput sequencing
Summary	α-Synuclein (α-Syn) is a protein implicated in the pathogenesis of Parkinson's disease (PD). It is primarily cytosolic and reversibly interacts with cell membranes. α-Syn also occurs in the nucleus, however, the mechanisms involved in its nuclear localization are poorly understood. We analyzed alterations in gene expression following induced α-Syn expression in SH-SY5Y cells. Analysis for upstream regulators pointed at alterations in transcription activity of retinoic acid receptors (RAR)s and additional nuclear receptors. We show that α-Syn binds RA and translocates to the nucleus to selectively enhance gene transcription. Nuclear translocation of α-Syn is regulated by calreticulin, in a leptomycin-B independent mechanism. Importantly, nuclear translocation of α-Syn following RA treatment enhances its toxicity in cultured neurons and the expression levels of PD-associated genes, among which are two familial PDassociated genes, ATPase cation transporting 13A2 (ATP13A2) and PTEN-induced kinase 1 (PINK1). The results link a physiological role for α-Syn in the regulation of RAmediated gene transcription and its toxicity in the synucleinopathies.
Overall design	SH-SY5Y cells induced to express α-Syn (with 1 µg/ml doxycycline) and treated for 16 hours in DMEM supplemented with 0.1% serum and RA (5 µM). Cells were collected and analyzed following 72 hours from induction of α-Syn expression. Control samples included an identical set up but without induced α-Syn expression.
Contributor(s)	Davidi D, Schechter M, Abd ElHadi S, Matatov A, Nathanson L, Sharon R
Citation missing	*Has this study been published? Please login to update or notify GEO.*
Submission date	Feb 24, 2020
Last update date	Feb 25, 2020
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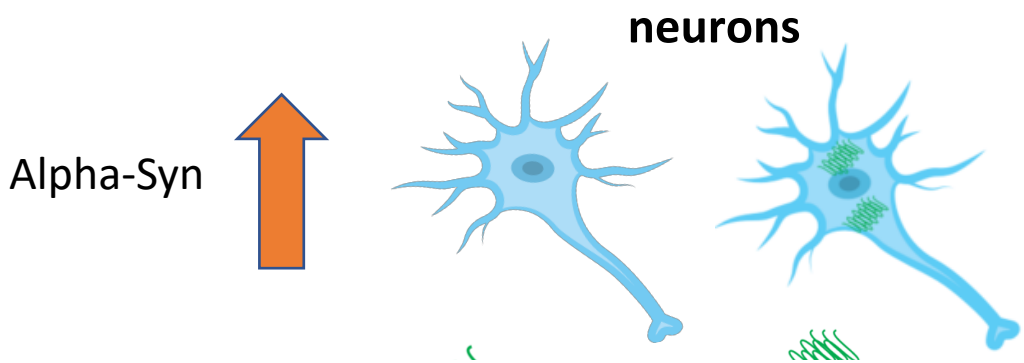
State/province	Florida
ZIP/Postal code	33314

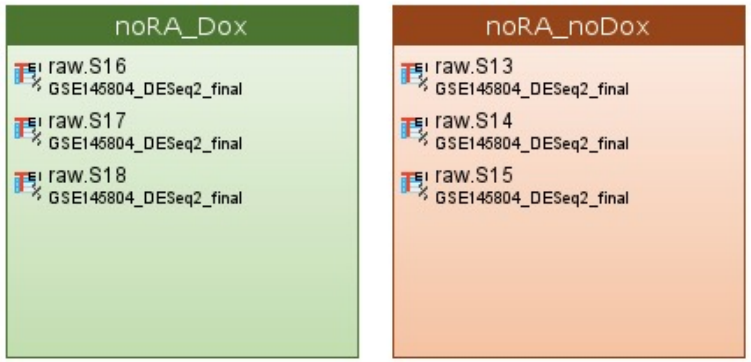


2. Data

For this study the following experimental data was used:

Table 1. Experimental datasets used in the study

File name	Data type
GSE145804_DESeq2_final.csv/GSE145804_DESeq2_final	Transcriptomics



detected 8084 upregulated genes (LogFC>0) out of which 578 genes were found as significantly upregulated (p-value<0.1) and 8862 downregulated genes (LogFC<0) out of which 726 genes were significantly downregulated (p-value<0.1). See tables below for the top significantly up- and downregulated genes. Below we call **target genes** the full list of up- and downregulated genes revealed in our analysis (see tables in Supplementary section).

*Table 2. Top ten significant **up-regulated** genes in noRA_Dox vs. noRA_noDox.*

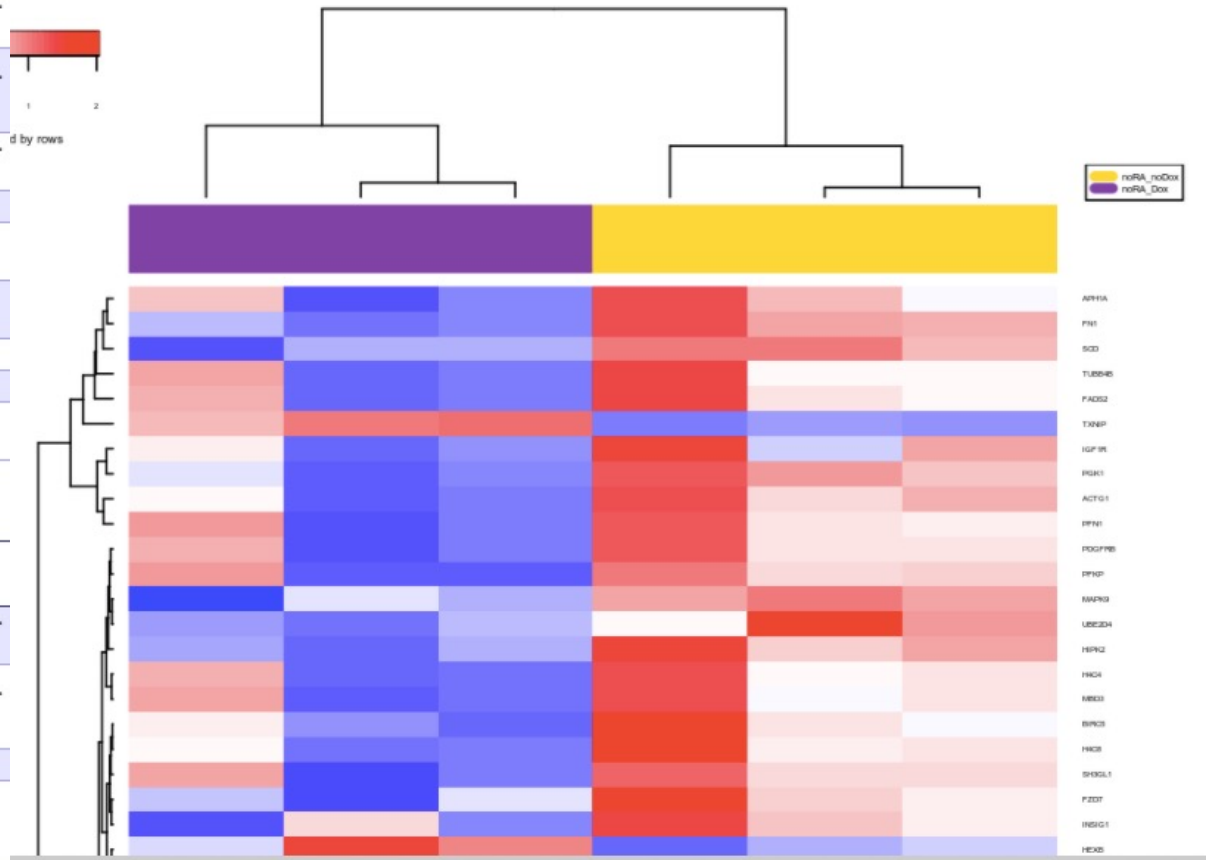
See full table →

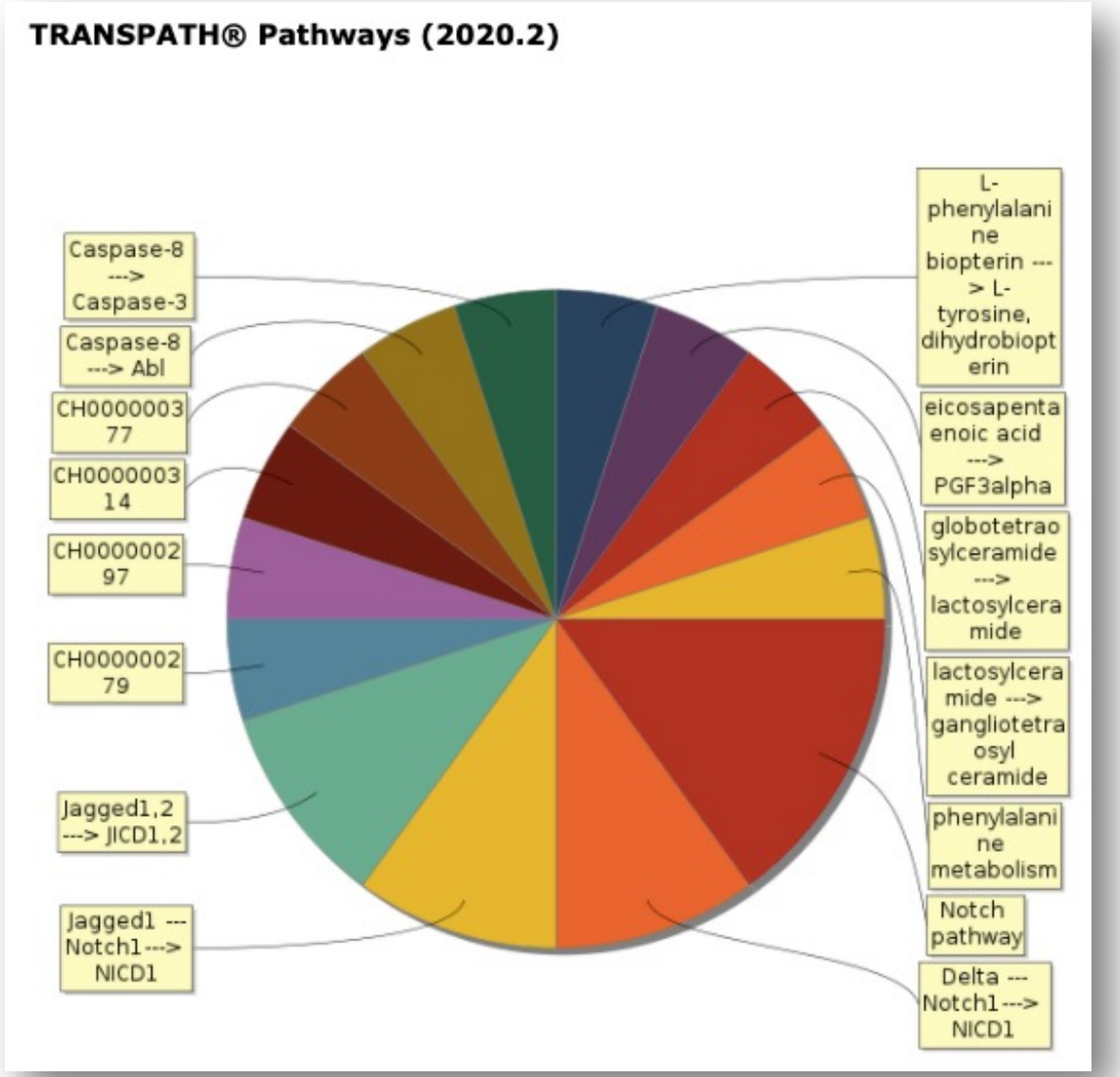
ID	Gene symbol	Gene description	logFC	logCPM	PValue	FDR
ENSG00000145335	SNCA	synuclein alpha	4.38	10.36	2.71E-88	4.59E-84
ENSG00000118785	SPP1	secreted phosphoprotein 1	2.98	-0.28	6.23E-7	2.11E-3
ENSG00000169282	KCNAB1	potassium voltage-gated channel subfamily A member regulatory beta subunit 1	2.91	0.49	1.32E-7	5.61E-4
ENSG00000162692	VCAM1	vascular cell adhesion molecule 1	2.67	-4.05E-2	1.1E-5	2.34E-2
ENSG00000237280	AL136982.3	novel transcript	2.15	0.2	1.42E-4	0.16
ENSG00000214892	USP8P1	ubiquitin specific peptidase 8 pseudogene 1	1.81	0.19	4.4E-3	0.83
ENSG00000224837	GCSHP5	glycine cleavage system protein H pseudogene 5	1.72	-0.1	1.84E-3	0.6
ENSG00000243300	null	null	1.65	0.44	2.8E-3	0.68
ENSG00000229474	PATL2	PAT1 homolog 2	1.53	-0.14	7.97E-3	0.98
ENSG00000236813	BTF3P8	basic transcription factor 3 pseudogene 8	1.53	-0.48	9.95E-3	0.98

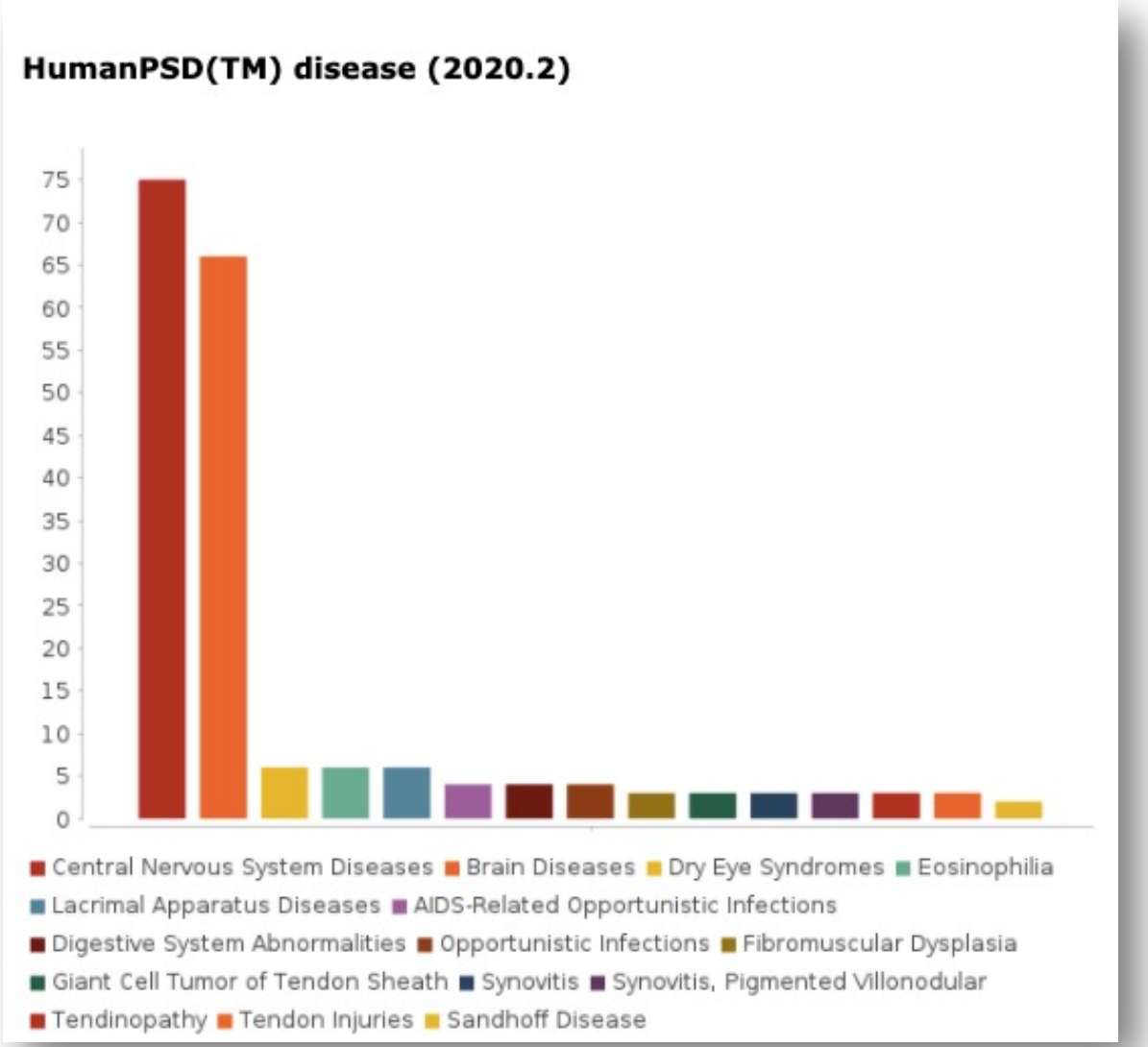
*Table 3. Top ten significant **down-regulated** genes in noRA_Dox vs. noRA_noDox.*

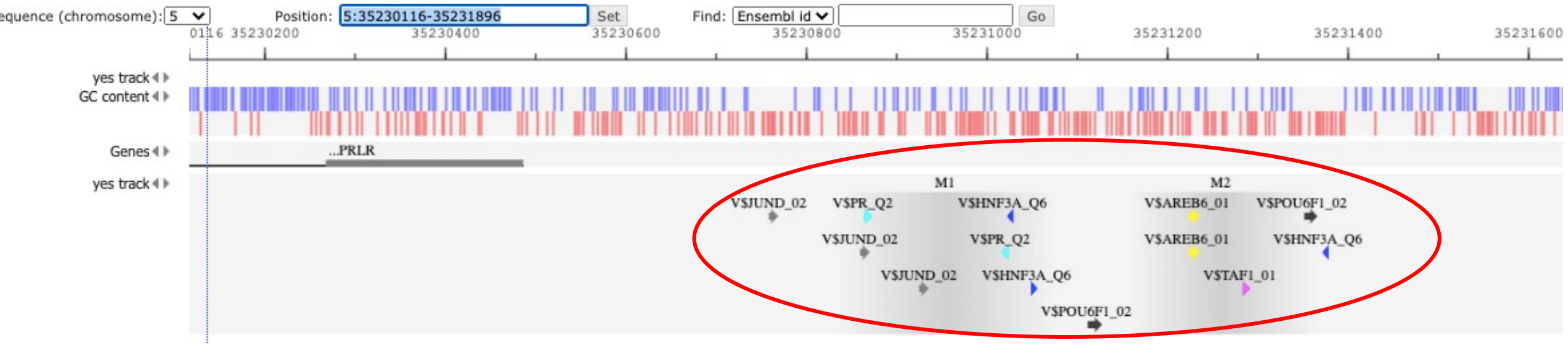
See full table →

ID	Gene symbol	Gene description	logFC	logCPM	PValue	FDR
ENSG00000186081	KRT5	keratin 5	-10.36	2.57	9.35E-7	2.64E-3
ENSG00000257594	GALNT4	polypeptide N-acetylgalactosaminyltransferase 4	-2.37	1.39E-2	4.31E-5	6.08E-2
ENSG00000167244	IGF2	insulin like growth factor 2	-2.13	-0.49	1.23E-3	0.47
ENSG00000255115	AP002812.4	family with sequence similarity 162, member A (FAM162A) pseudogene	-1.97	-0.38	2.22E-3	0.61
ENSG00000134955	SLC37A2	solute carrier family 37 member	-1.9	-0.42	9.67E-3	0.98

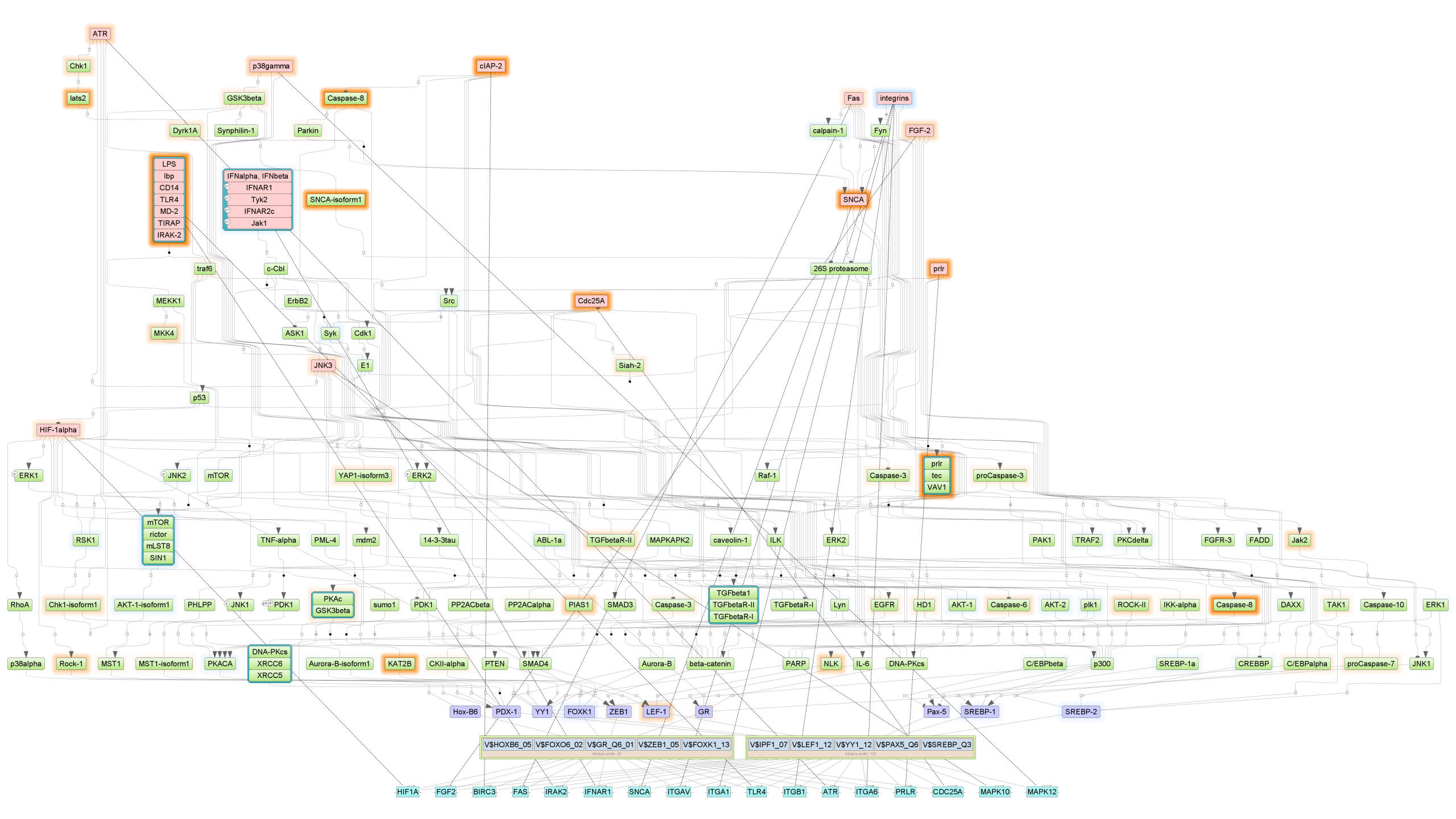



TRANSPATH® Pathways (2020.2)
Caspase-8 ---> Caspase-3
Caspase-8 ---> Abl
CH0000003 77
CH0000003 14
CH0000002 97
CH0000002 79
Jagged1,2 ---> JICD1,2
Jagged1 --- Notch1---> NICD1
L-phenylalani ne biopterin ---> L-tyrosine, dihydrobiopt erin
eicosapenta enoic acid ---> PGF3alpha
globotetrao sylceramide ---> lactosylcera mide
lactosylcera mide ---> gangliotetra osyl ceramide
phenylalani ne metabolism
Notch pathway
Delta --- Notch1---> NICD1


HumanPSD(TM) disease (2020.2)
75
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
Central Nervous System Diseases
Brain Diseases
Dry Eye Syndromes
Eosinophilia
Lacrimal Apparatus Diseases
AIDS-Related Opportunistic Infections
Digestive System Abnormalities
Opportunistic Infections
Fibromuscular Dysplasia
Giant Cell Tumor of Tendon Sheath
Synovitis
Synovitis, Pigmented Villonodular
Tendinopathy
Tendon Injuries
Sandhoff Disease


equence (chromosome): 5
Position: 5:35230116-35231896
Set
Find: Ensembl id
Go
35230200
35230400
35230600
35230800
35231000
35231200
35231400
35231600
yes track
GC content
Genes
..PRLR
yes track
M1
M2
V$JUND_02
V$PR_Q2
V$HNF3A_Q6
V$AREB6_01
V$POU6F1_02
V$JUND_02
V$PR_Q2
V$AREB6_01
V$HNF3A_Q6
V$JUND_02
V$HNF3A_Q6
V$TAF1_01
V$POU6F1_02


Module 1
V$IPF1_07
0.82; N=2
V$LEF1_12
0.82; N=3
V$YY1_12
0.79; N=3
V$PAX5_Q6
0.98; N=3
V$SREBP_Q3
0.85; N=2
Module width: 126
Module 2
V$HOXB6_05
0.98; N=3
V$FOXO6_02
1.00; N=1
V$GR_Q6_01
0.99; N=2
V$ZEB1_05
0.99; N=2
V$FOXK1_13
0.89; N=2
Module width: 49


ATR
Chk1
p38gamma
cIAP-2
lats2
GSK3beta
Caspase-8
Fas
integrins
Dyrk1A
Synphilin-1
Parkin
calpain-1
Fyn
FGF-2
LPS
lbp
CD14
TLR4
MD-2
TIRAP
IRAK-2
IFNalpha, IFNbeta
IFNAR1
Tyk2
IFNAR2c
Jak1
SNCA-isoform1
SNCA
traf6
c-Cbl
26S proteasome
prlr
MEKK1
ErbB2
Src
Cdc25A
MKK4
ASK1
Syk
Cdk1
JNK3
E1
Siah-2
p53
HIF-1alpha
ERK1
JNK2
mTOR
YAP1-isoform3
ERK2
Raf-1
Caspase-3
prlr
tec
VAV1
proCaspase-3
mTOR
rictor
mLST8
SIN1
RSK1
TNF-alpha
PML-4
mdm2
14-3-3tau
ABL-1a
TGFbetaR-II
MAPKAPK2
caveolin-1
ILK
ERK2
PAK1
TRAF2
PKCdelta
FGFR-3
FADD
Jak2
RhoA
Chk1-isoform1
AKT-1-isoform1
PHLPP
JNK1
PDK1
PKAc
GSK3beta
sumo1
PDK1
PP2ACbeta
PP2ACalpha
PIAS1
SMAD3
Caspase-3
TGFbeta1
TGFbetaR-II
TGFbetaR-I
TGFbetaR-I
Lyn
EGFR
HD1
AKT-1
Caspase-6
AKT-2
plk1
ROCK-II
IKK-alpha
Caspase-8
DAXX
TAK1
Caspase-10
ERK1
p38alpha
Rock-1
MST1
MST1-isoform1
PKACA
DNA-PKcs
XRCC6
XRCC5
Aurora-B-isoform1
KAT2B
CKII-alpha
PTEN
SMAD4
Aurora-B
beta-catenin
PARP
NLK
IL-6
DNA-PKcs
C/EBPbeta
p300
SREBP-1a
CREBBP
C/EBPalpha
proCaspase-7
JNK1
Hox-B6
PDX-1
YY1
FOXK1
ZEB1
LEF-1
GR
Pax-5
SREBP-1
SREBP-2
V$HOXB6_05
V$FOXO6_02
V$GR_Q6_01
V$ZEB1_05
V$FOXK1_13
V$IPF1_07
V$LEF1_12
V$YY1_12
V$PAX5_Q6
V$SREBP_Q3
HIF1A
FGF2
BIRC3
FAS
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ITGA6
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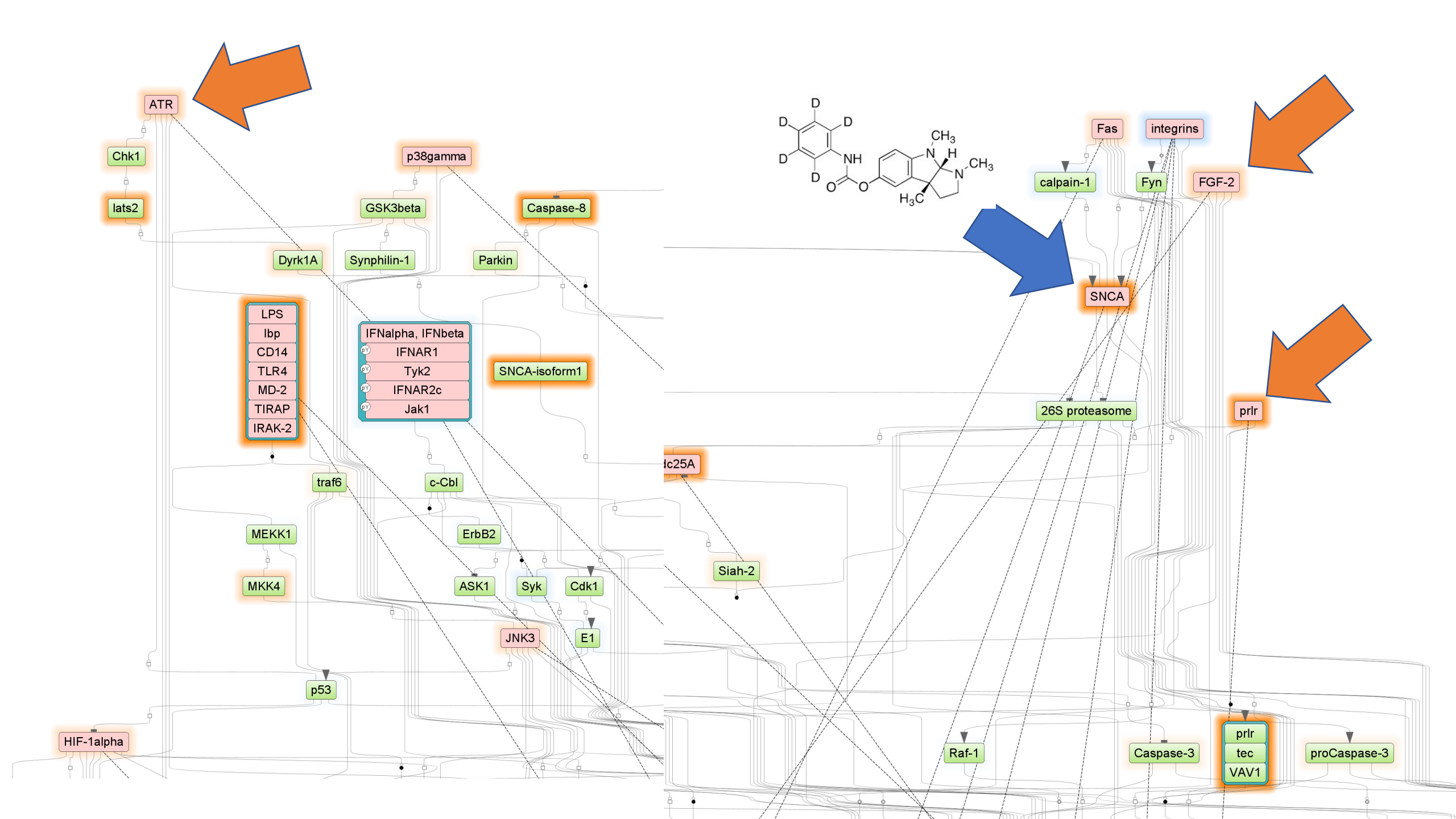
MAPK10
MAPK12


ATR
Chk1
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p38gamma
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Caspase-8
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Synphilin-1
Parkin
LPS
lbp
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MD-2
TIRAP
IRAK-2
IFNalpha, IFNbeta
IFNAR1
Tyk2
IFNAR2c
Jak1
SNCA-isoform1
traf6
c-Cbl
MEKK1
ErbB2
MKK4
ASK1
Syk
Cdk1
JNK3
E1
p53
HIF-1alpha
Fas
integrins
calpain-1
Fyn
FGF-2
SNCA
26S proteasome
prlr
Siah-2
Raf-1
Caspase-3
prlr
tec
VAV1
proCaspase-3

Drugs approved in clinical trials

Table 10. FDA approved drugs or drugs used in clinical trials for the studied pathology (most promising treatment candidates selected for the identified drug targets on the basis of literature curation in HumanPSD™ database)

See full table →

Name	Target names	Drug score	Disease activity score	Disease trial phase
Sirolimus	IKBKB, MAPK10, RPS6KA3, ROCK2, TGM2, MAPK12, DYRK1A...(more)	86	3	Phase 2: Parkinson Disease, Acute Disease, Acute Lung Injury, Adenocarcinoma, Adenocarcinoma of Lung...(more)
Caffeine	ATR, FGF2	64	6	Phase 3: Parkinson Disease, Alzheimer Disease, Apnea, Asymptomatic Diseases, Atrial Fibrillation, Br...(more)
Acetylsalicylic acid	IKBKB, FAS, FGF2	53	4	Phase 4: Parkinson Disease, Acute Coronary Syndrome, Aneurysm, Aneurysm, Dissecting, Angina Pectoris...(more)
Cholecalciferol	FAS	43	7	Phase 4: Parkinson Disease, Affect, Amenorrhea, Anemia, Anemia, Aplastic, Anemia, Sickle Cell, Arthr... (more)
Melatonin	PRLR	37	9	Phase 4: Parkinson Disease, Arteriosclerosis, Attention Deficit Disorder with Hyperactivity, Autism ... (more)

The ***Disease trial phase*** column reflects the maximum clinical trials phase in which the drug was studied for the analyzed pathology.

Repurposing drugs

Table 11. Repurposed drugs used in clinical trials for other pathologies (prospective drugs against the identified drug targets on the basis of literature curation in HumanPSD™ database)
See full table →

Name	Target names	Drug score	Maximum trial phase
1-(5-Tert-Butyl-2-P-Tolyl-2h-Pyrazol-3-Yl)-3-[4-(2-Morpholin-4-Yl-Ethoxy)-Naphthalen-1-Yl]-Urea	IKBKB, MAPK10, RPS6KA3, TEC, ROCK2, PRKCQ, TTK... (more)	94	N/A
Sorafenib	IKBKB, MAPK10, RPS6KA3, TEC, ROCK2, PRKCQ, TTK... (more)	94	Phase 4: Carcinoma, Carcinoma, Hepatocellular, Carcinoma, Renal Cell, Hand-Foot Syndrome, Liver Neop... (more)
seliciclib	IKBKB, MAPK10, RPS6KA3, TEC, ROCK2, PRKCQ, TTK... (more)	94	Phase 2: ACTH-Secreting Pituitary Adenoma, Adenoma, Carcinoma, Non-Small-Cell Lung, Cystic Fibrosis,... (more)
ruboxistaurin	IKBKB, MAPK10, RPS6KA3, TEC, ROCK2, PRKCQ, TTK... (more)	94	Phase 3: Diabetes Mellitus, Diabetes Mellitus, Type 1, Diabetes Mellitus, Type 2, Diabetic Neuropath...(more)
Tofacitinib	MAPK10, RPS6KA3, TEC, ROCK2, RIPK2, MERTK, LATS2... (more)	93	Phase 4: Alopecia, Alopecia Areata, Aortic Arch Syndromes, Arteritis, Arthritis, Arthritis, Psoriati...(more)

The ***Maximum trial phase*** column reflects the maximum clinical trials phase in which the drug was studied for any pathology.

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ANTI-PARKINSON'S ACTIVITY OF SORAFENIB IN 6-OHDA INDUCED RAT MODEL

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Keywords:

6-OHDA, Levodopa, Neuroprotective, Sorafenib

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ABSTRACT: Objective: Studies have shown that sorafenib an anti-cancer agent has a neuroprotective effect. This study evaluated the neuroprotective activity of sorafenib in 6-OHDA induced rat model of Parkinson's disease. **Methods:** 6-OHDA was injected into the forebrain bundle through the stereotaxic apparatus to induce fast and severe degeneration in dopaminergic neurons of substantianigra. The animals were divided into four groups. Group I- vehicle control, Group II- 6-OHDA induced, Group III- 6- OHDA + Levodopa (6 mg/kg), Group IV- 6-OHDA + sorafenib (10 mg/kg s.c). Treatment was given for 21 days after induction of 6-OHDA. The animals were subjected to behavioral parameters such as apomorphine-induced rotations, grip strength, catatonia and biochemical parameters such as total protein estimation, reduced glutathione, lipid peroxidase, calcium concentration in the brain. **Results:** Sorafenib significantly decreased the apomorphine-induced rotations as well as catatonia and significantly increased ($p<0.001$) the grip strength when compared to 6-OHDA. In biochemical estimation total protein and glutathione is increased ($p<0.001$). Both lipid peroxidase and calcium level have been decreased significantly ($p<0.001$) when compared to 6. OHDA. **Conclusion:** In the present study, antiparkinson's effect of an LRRK2 inhibitor, sorafenib was evaluated in the 6-OHDA lesioned rat model. Behavioral and biochemical parameters were carried out. The parameters revealed that the LRRK2 inhibitor, sorafenib has shown significant antiparkinson's activity. The estimated parameters altered the normal behavior of the animal and the drug treatment protected the diseased brain of rat.

INTRODUCTION: Parkinson's disease (PD) is a progressive neurodegenerative disorder caused by PD is the second most common neurodegenerative disease after Alzheimer's disease affecting

Seliciclib

From Wikipedia, the free encyclopedia

Seliciclib (**roscovitine** or **CYC202**) is an experimental drug candidate in the family of pharmacological cyclin-dependent kinase (CDK) inhibitors that preferentially inhibit multiple enzyme targets including CDK2, CDK7 and CDK9, which alter the growth phase or state within the cell cycle of treated cells. Seliciclib is being developed by Cyclacel.This is a phase II, dose ranging, multicenter, randomized, double-blind, placebo-controlled study.

The aim of this study is to assess the safety of increasing doses of roscovitine administered orally for 4 cycles of 4 consecutive days (treatment "on") separated by a 3 days treatment free period (treatment "off") in adult CF subjects with Cystic Fibrosis carrying 2 Cystic Fibrosis causing mutations with at least one F508del-CFTR mutation and chronically infected with Pseudomonas aeruginosa.

This study involved 36 Cystic Fibrosis patients: 24 treated and 12 controls.[1]

Seliciclib is being researched for the treatment of non-small cell lung cancer (NSCLC), Cushing's disease, leukemia, HIV infection, Parkinson's disease, herpes simplex infection, cystic fibrosis[2] and the mechanisms of chronic inflammation disorders.

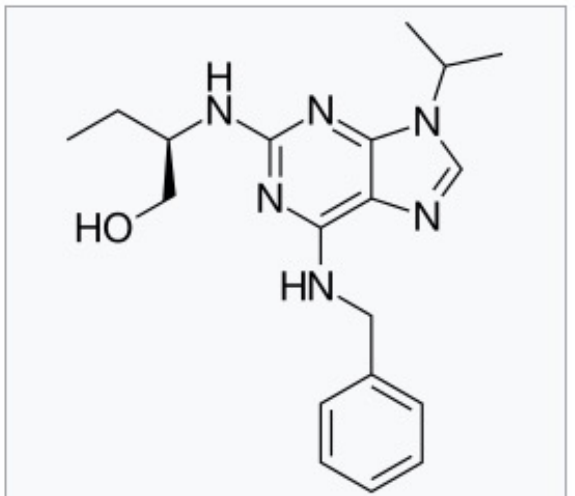
Seliciclib is a 2,6,9-substituted purine analog. Its structure in complex with CDK2 was determined in 1996.[3] Seliciclib inhibits CDK2/E, CDK2/A, CDK7 and CDK9.[4]

Uses [edit]

This section needs to be **updated**. Please help update this article to reflect recent events or newly available information. *(January 2014)*

Seliciclib has been found to produce apoptosis in treated cancerous cells of non-small cell lung cancer (NSCLC) and other

Seliciclib

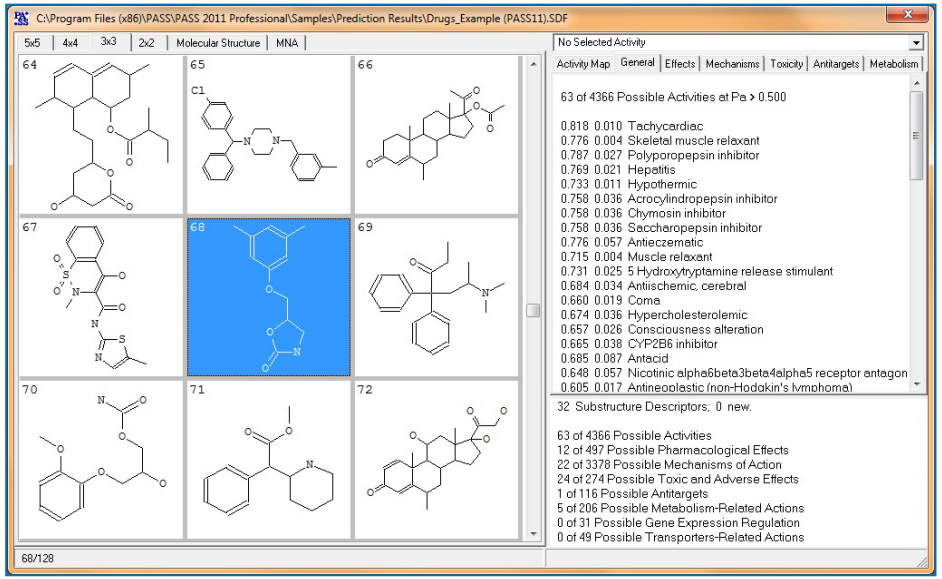


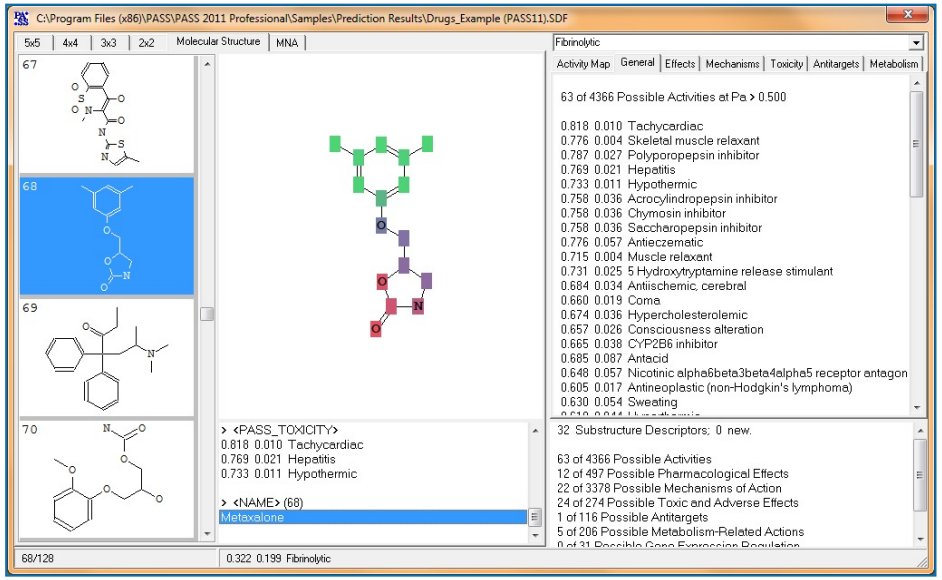
Names	
Preferred IUPAC name	(2*R*)-2-{[6-(Benzylamino)-9-(propan-2-yl)-9*H*-purin-2-yl]amino}butan-1-ol
Other names	Roscovitine; CYC202
Identifiers	
CAS Number	186692-46-6 ✓
3D model (JSmol)	Interactive image
ChEMBL	ChEMBL14762 ✗

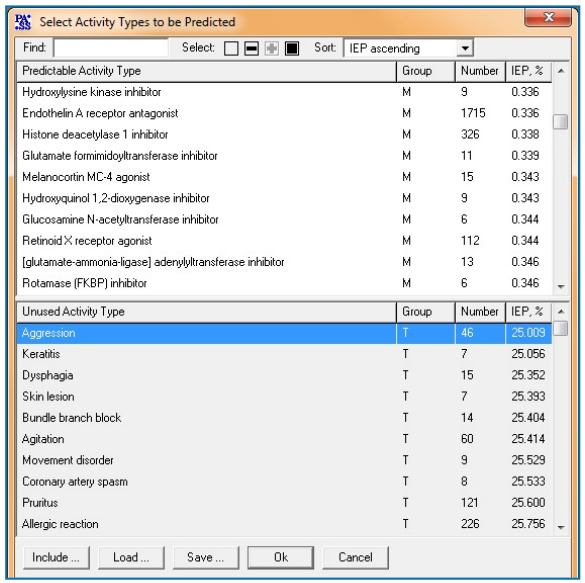
PASS

The acronym PASS stands for Prediction of Activity Spectra for Substances. PASS performs an instant prediction and computational evaluation of biological activity spectra for organic chemical compounds.

PASS results can be further interpreted via the PharmaExpert tool and combined with the structure-activity relationship models built in GUSAR.







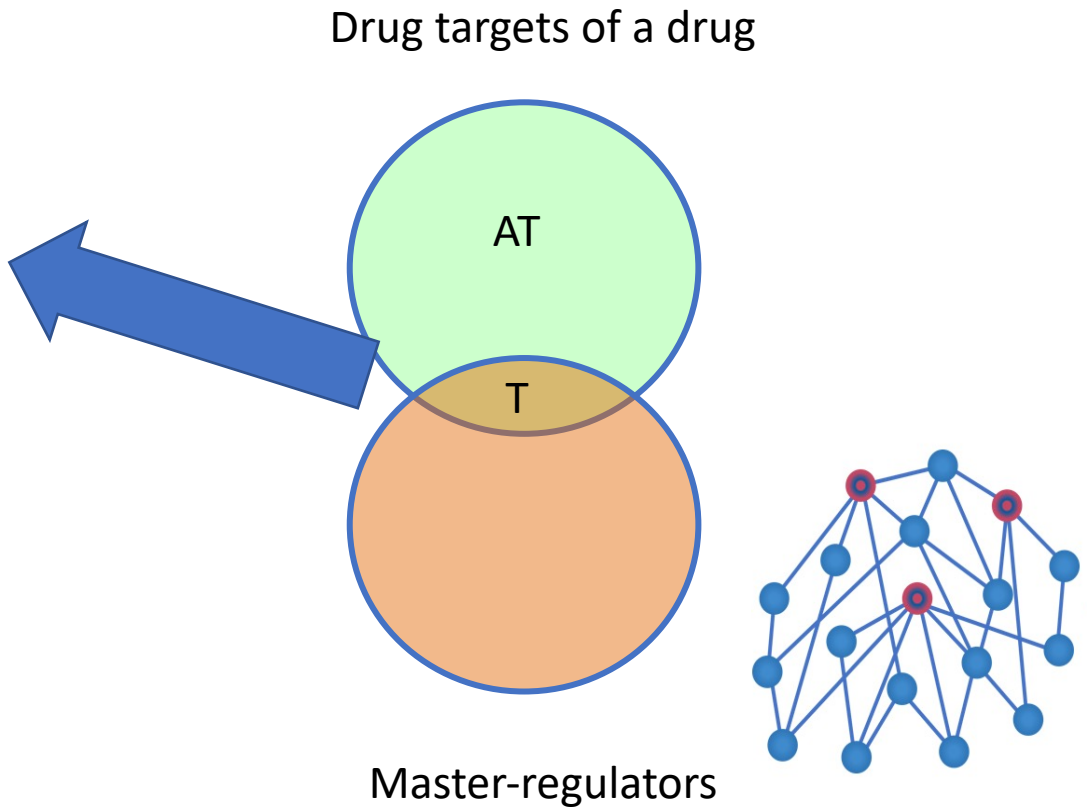
Target activity score

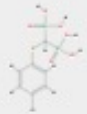
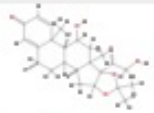
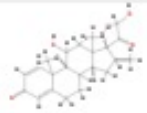
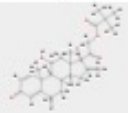
$$T\text{-}score(s) = \frac{|T|}{|T| + w(|AT| - |T|))} \sum_{m \in M(s)} \left(pa(m) \sum_{g \in G(m)} IAP(g) optWeight(g) \right),$$

M(s) is the set of activity-mechanisms for the given structure *s*

G(m) is the set of targets (converted to genes)

IAP(g) is the invariant accuracy of prediction



Name	Structure	Target names	Target activity score	Disease activity score	Disease activity rank	Drug score
Tacrolimus		PPM1M, PPM1B, IL7, PPM1G, GDNF, BDNF, PPM1D, NEK6, FLT1, IL1A, IL2RB, IL10	1.0298	0.996	1	96
Lipoic Acid		PTPRO, PTPN1, PTPRC, PTPN22, PTPRE, UBASH3B, PTPN14, DUSP4, PPM1M, PPM1B, CDC25A, DUSP2, DUSP5, ... (more)	1.44298	0.942	59	95
Tiludronate		IL7, PTPRO, PTPN1, IL1A, PTPRC, PTPN22, IL10, PTPRE, UBASH3B, PTPN14, DUSP4, PPM1M, PPM1B, CDC25A... (more)	1.41195	0.937	63	95
Fluocinolone Acetonide		IL7, TLR3, TLR4, HIF1A, IL1A, IL10, RELA	0.34081	0.993	2	93
Fluocinonide		IL7, TLR3, TLR4, HIF1A, IL1A, IL10, RELA	0.33469	0.992	3	93
Dexamethasone		IL7, TLR3, TLR4, HIF1A, IL1A, IL10, RELA	0.31757	0.987	9	92
Betamethasone		IL7, TLR3, TLR4, HIF1A, IL1A, IL10, RELA	0.31757	0.987	9	92
Diflorasone		IL7, TLR3, TLR4, HIF1A, IL1A, IL10, RELA	0.30191	0.992	3	92
Flumethasone Pivalate		IL7, TLR3, TLR4, HIF1A, IL1A, IL10, RELA	0.3033	0.988	8	92
		PTPRO, PTPN1				

Comparative Study > Int Immunopharmacol. 2004 Oct;4(10-11):1307-18.

doi: 10.1016/j.intimp.2004.05.006.

Dexamethasone protects against dopaminergic neurons damage in a mouse model of Parkinson's disease

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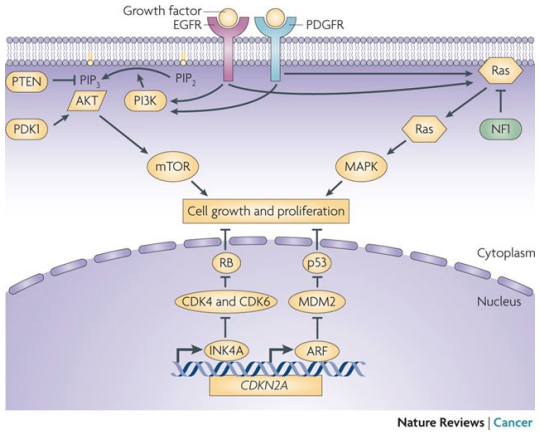
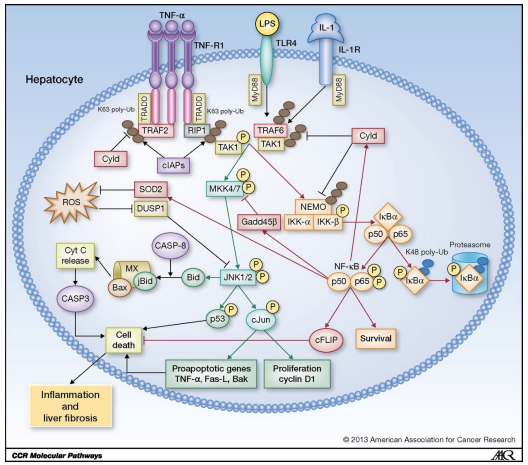
Affiliations + expand

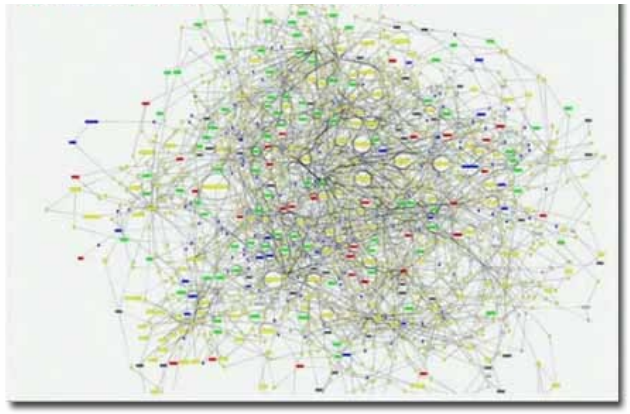
PMID: 15313429 DOI: 10.1016/j.intimp.2004.05.006

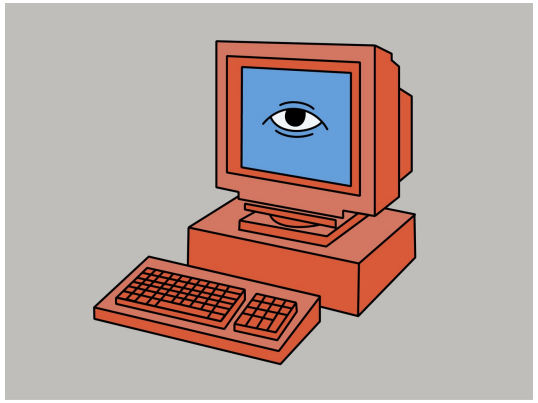
Abstract

The pathological process of neurodegeneration, which is observed in Alzheimer's (AD) and Parkinson's (PD) diseases and that follows any insult to the central nervous system, is accompanied by an inflammatory reaction, which is believed to contribute to the pathogenesis of the diseases. In accordance to this, the anti-inflammatory agents are suggested to be effective in slowing or inhibiting the degenerative process. In this study, we investigated the influence of dexamethasone (DXM) on the nigrostriatal dopaminergic neurons damage following administration









Drug targets

Drug targets

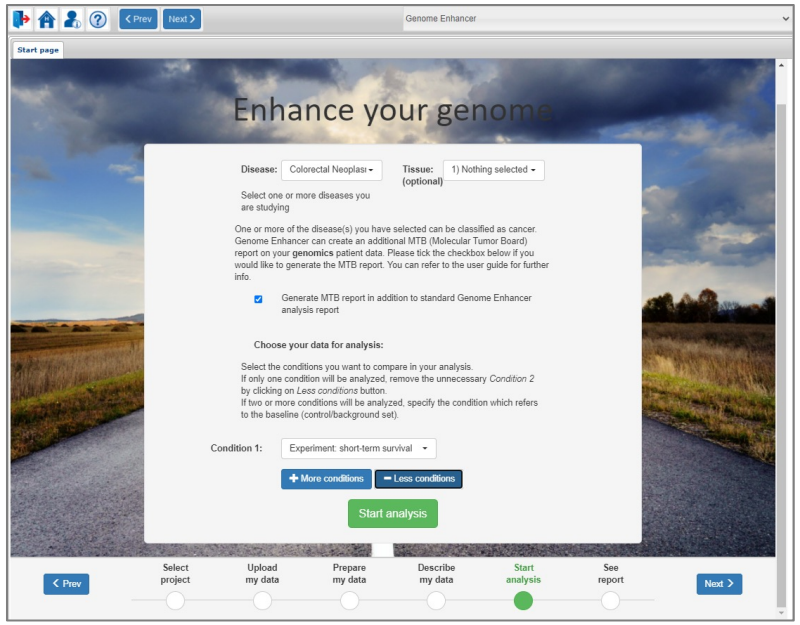
Drug targets

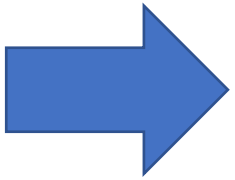
Robot-scientist

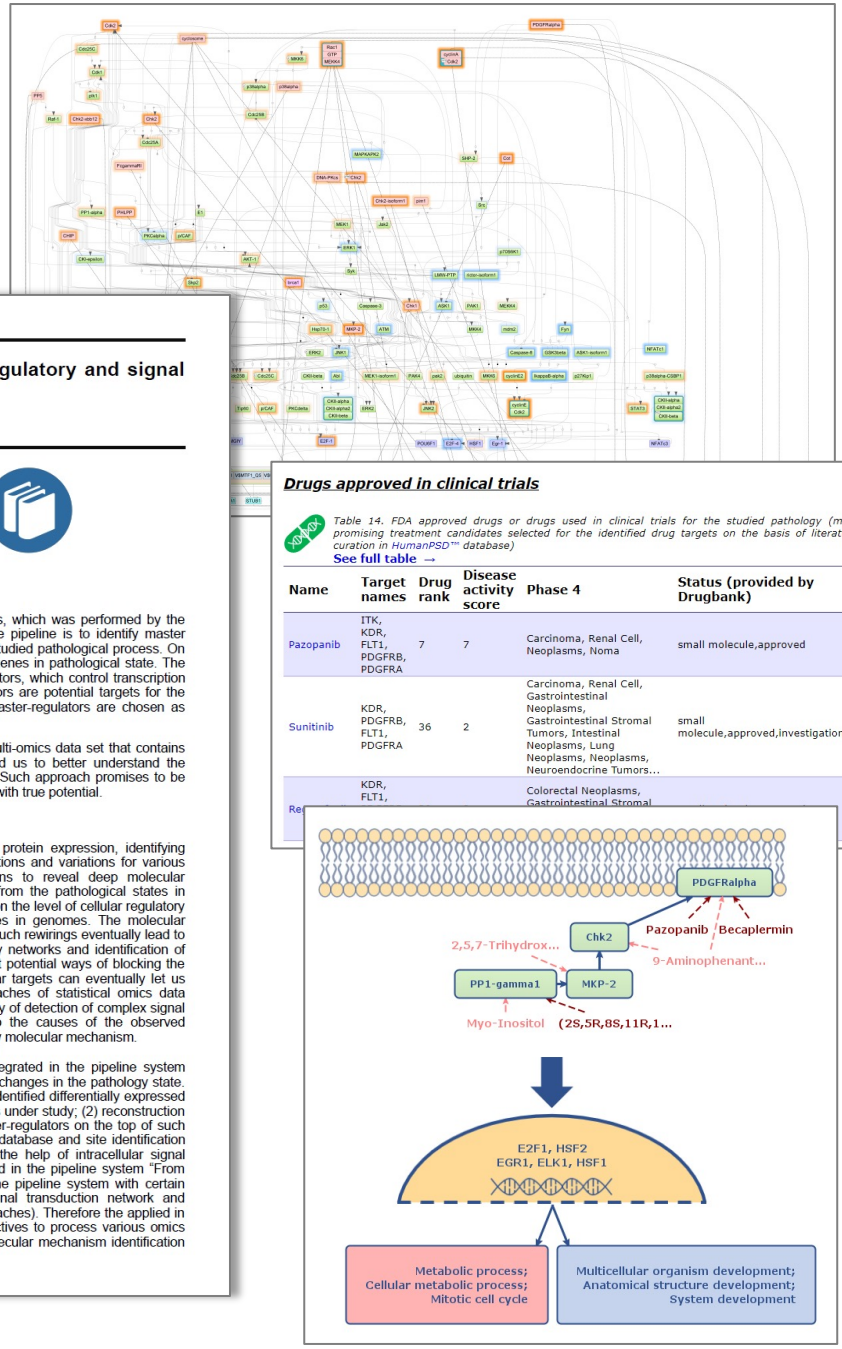
Genome Enhancer

Key result:

actionable drug targets and prospective treatments







Sequence and Pathway analysis

Identification of master-regulators in gene regulatory and signal transduction pathways.

Your name

Your organization

Data received on 01/06/2017; Run on 01/06/2017; Report generated on 01/06/2017

Summary

In this report we present the results of causal multi-omics data analysis, which was performed by the automatized pipeline system "From genome to target". The goal of the pipeline is to identify master regulators in gene regulatory networks as potential drug targets for the studied pathological process. On the first step of analysis we discover transcription factors that regulate genes in pathological state. The second step of analysis performs the search for so-called master-regulators, which control transcription factors that were found on the first step. The identified master-regulators are potential targets for the studied disease. After the druggability checkup, the most promising master-regulators are chosen as potential drug targets for the the analyzed pathology.

Here we applied the pipeline "From genome to target" for analysis of multi-omics data set that contains transcriptomics data in **carcinoma**. The results of this analysis helped us to better understand the molecular mechanisms of the studied pathological state of the disease. Such approach promises to be very effective for rapid and accurate identification of disease drug targets with true potential.

Introduction

Multiple "-omics" data are generated worldwide measuring gene and protein expression, identifying genetic and epigenetic changes and discovering disease causing mutations and variations for various pathological states of multiple organisms. Still the challenge remains to reveal deep molecular mechanisms underlying the various changes in omics data collected from the pathological states in comparison to the norm. The causal molecular mechanisms of diseases on the level of cellular regulatory networks can be described by specific pathological epigenetic changes in genomes. The molecular regulatory networks of cells are being rewired in disease conditions and such rewirings eventually lead to pathology progression. Reconstruction of the disease-specific regulatory networks and identification of potential master regulators of such networks can give us a clue on what potential ways of blocking the pathological regulatory cascades exist. Suppression of certain molecular targets can eventually let us stop the pathological process and cure the disease. Common approaches of statistical omics data analysis cannot reconstruct the cell regulatory networks due to the inability of detection of complex signal hierarchy. Thus such approaches provide only a very limited clue to the causes of the observed phenomena and actually do not lead to the understanding of the pathology molecular mechanism.

Unlike common approaches, the "upstream analysis" method [1-5], integrated in the pipeline system "From genome to target", performs causal interpretation of the observed changes in the pathology state. This approach comprises two major steps: (1) analysis of enhancers of identified differentially expressed genes (DEGs) to reveal transcription factors (TFs) involved in the process under study; (2) reconstruction of signaling pathways that activate these TFs and identification of master-regulators on the top of such pathways. The first step is done with the help of the TFs binding sites database and site identification algorithms - Match [6] and CMA [7]. The second step is done with the help of intracellular signal transduction database and special graph search algorithms implemented in the pipeline system "From genome to target". The upstream analysis approach is integrated in the pipeline system with certain improvements, such as dynamical simulation of the constructed signal transduction network and druggability check of the revealed targets (with the use of (Q)SAR approaches). Therefore the applied in this study pipeline system "From genome to target" opens new perspectives to process various omics data by complete automatization of such complex tasks as disease molecular mechanism identification and drug target selection.

Drugs approved in clinical trials

Table 14. FDA approved drugs or drugs used in clinical trials for the studied pathology (most promising treatment candidates selected for the identified drug targets on the basis of literature curation in HumanPSD™ database)

See full table →

Name	Target names	Drug rank	Disease activity score	Phase 4	Status (provided by Drugbank)
Pazopanib	ITK, KDR, FLT1, PDGFRB, PDGFRA	7	7	Carcinoma, Renal Cell, Neoplasms, Noma	small molecule,approved
Sunitinib	KDR, PDGFRB, FLT1, PDGFRA	36	2	Carcinoma, Renal Cell, Gastrointestinal Neoplasms, Gastrointestinal Stromal Tumors, Intestinal Neoplasms, Lung Neoplasms, Neoplasms, Neuroendocrine Tumors...	small molecule,approved,investigational
Re	KDR, FLT1,			Colorectal Neoplasms, Gastrointestinal Stromal	

Thank you!

Funding

EU

Russia