National Cancer Institute

Biobehavioral Influences on Cancer Biology

AN EMERGING OPPORTUNITY

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Gene-Social Environment Interactions in Cancer
A Bioinformatic Approach

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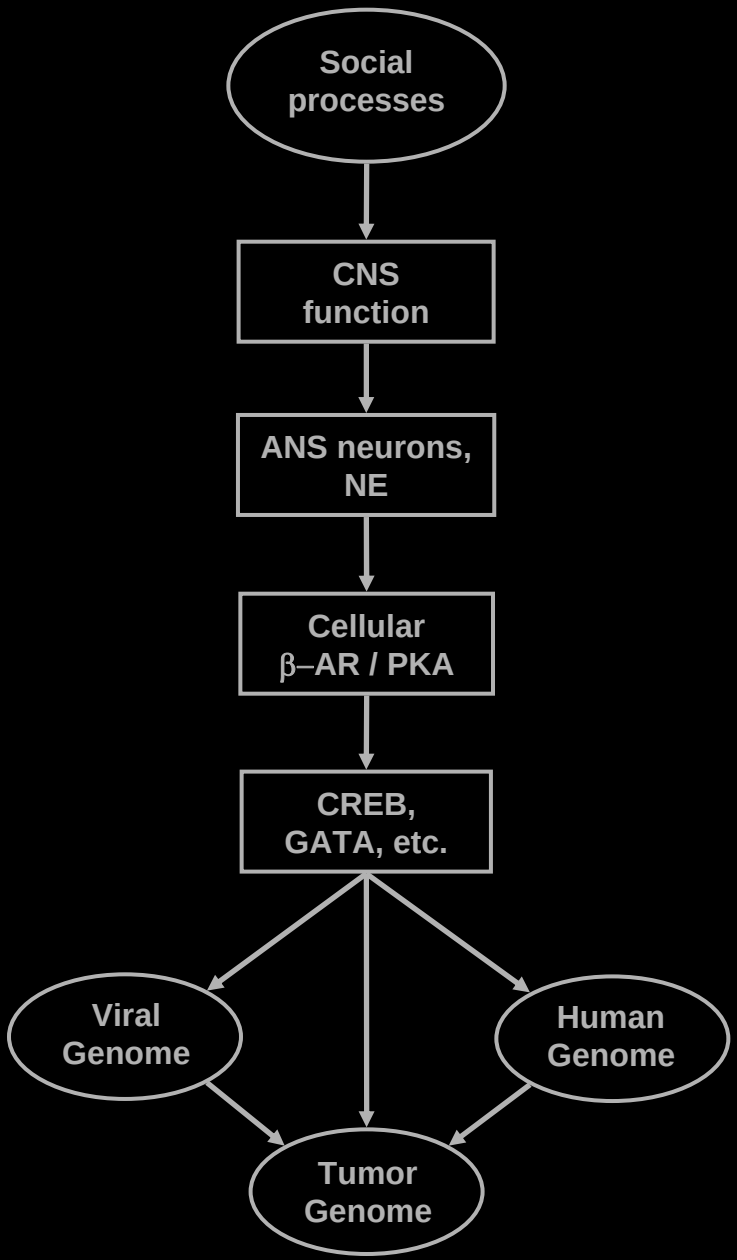
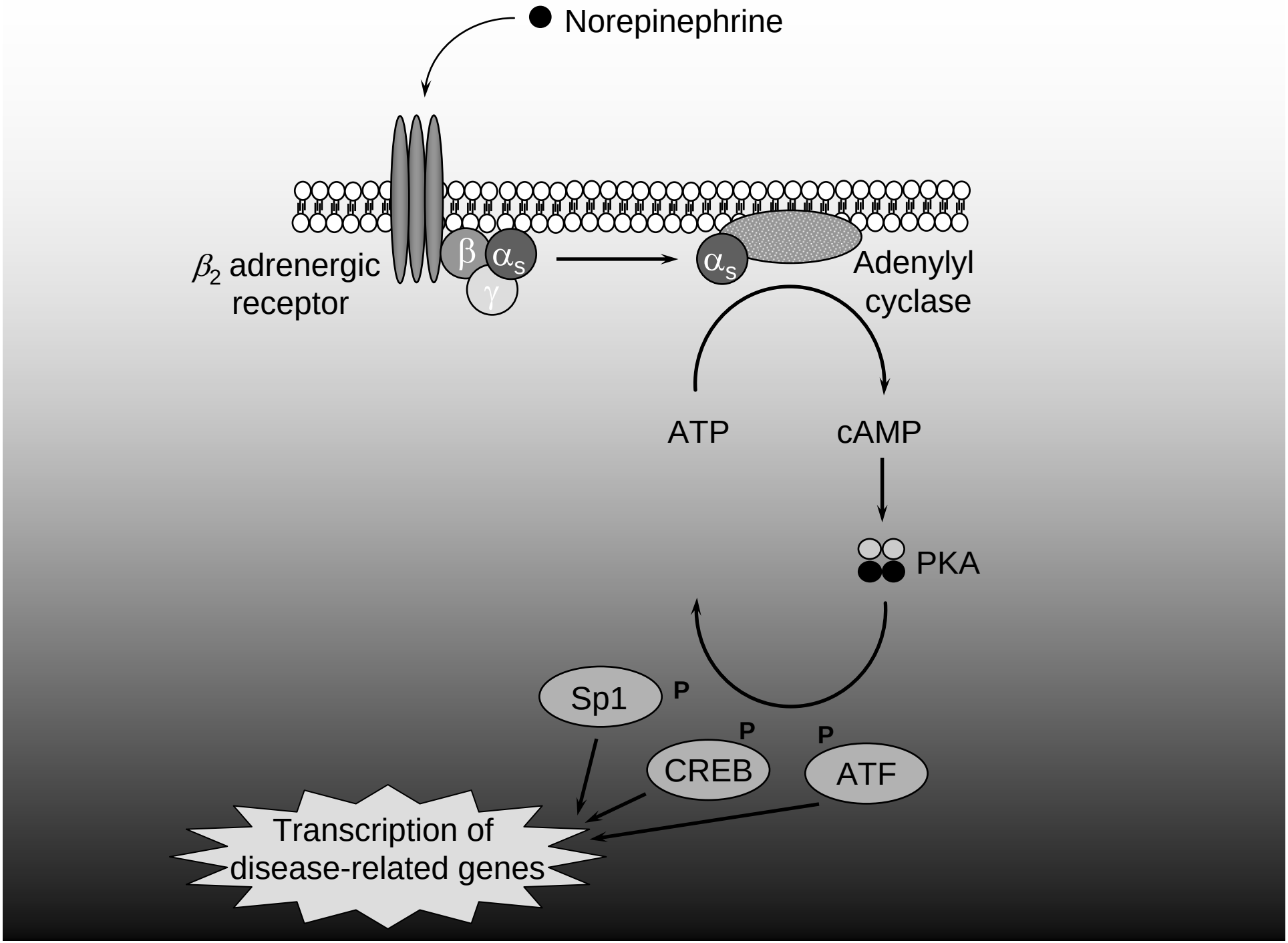
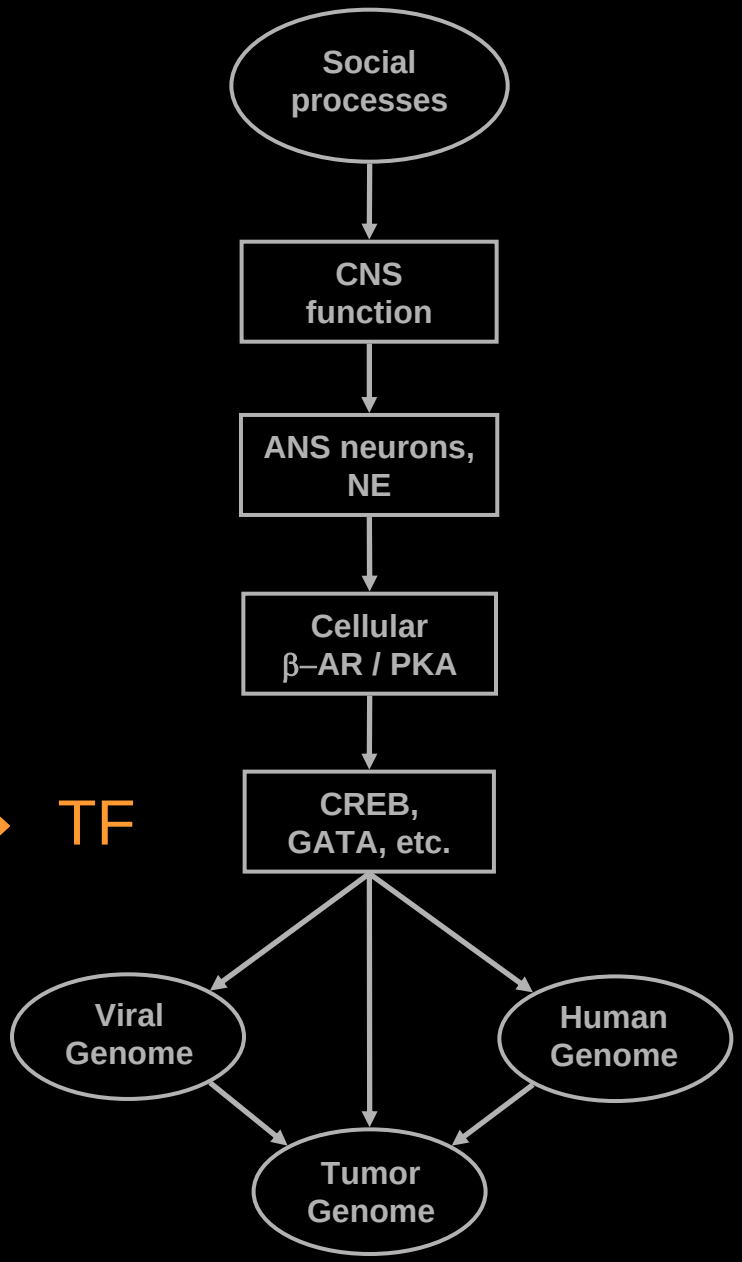
Biobehavioral regulation of gene expression in cancer

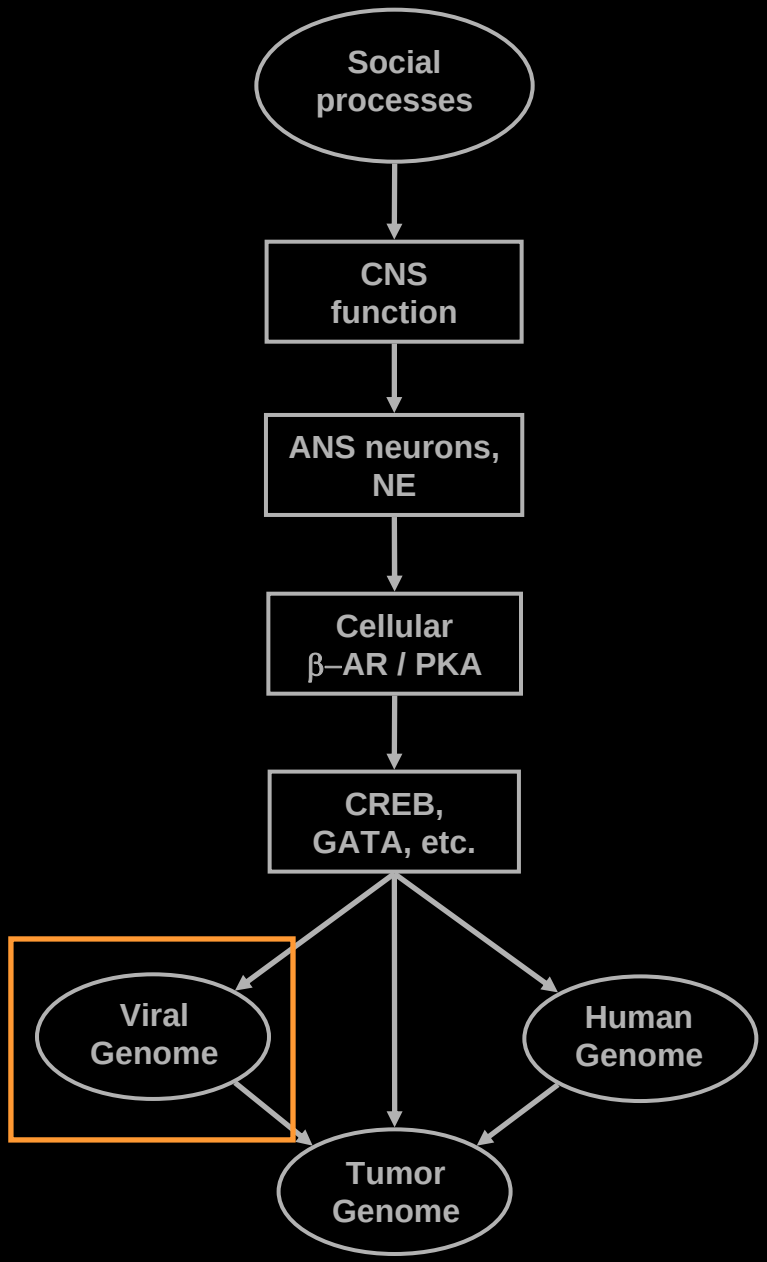
1. How do social factors regulate gene expression?
2. Are these “social signal transduction” pathways active in clinical cancer?
3. Do they shape the evolution of the tumor genome?
4. What are the prospects for protective intervention?


Social processes
CNS function
ANS neurons, NE
Cellular β–AR / PKA
CREB, GATA, etc.
Viral Genome
Human Genome
Tumor Genome


Norepinephrine
β_2 adrenergic receptor
β
α_s
γ
α_s
Adenylyl cyclase
ATP
cAMP
PKA
Sp1
P
CREB
P
ATF
P
Transcription of disease-related genes

psychology ➜ TF

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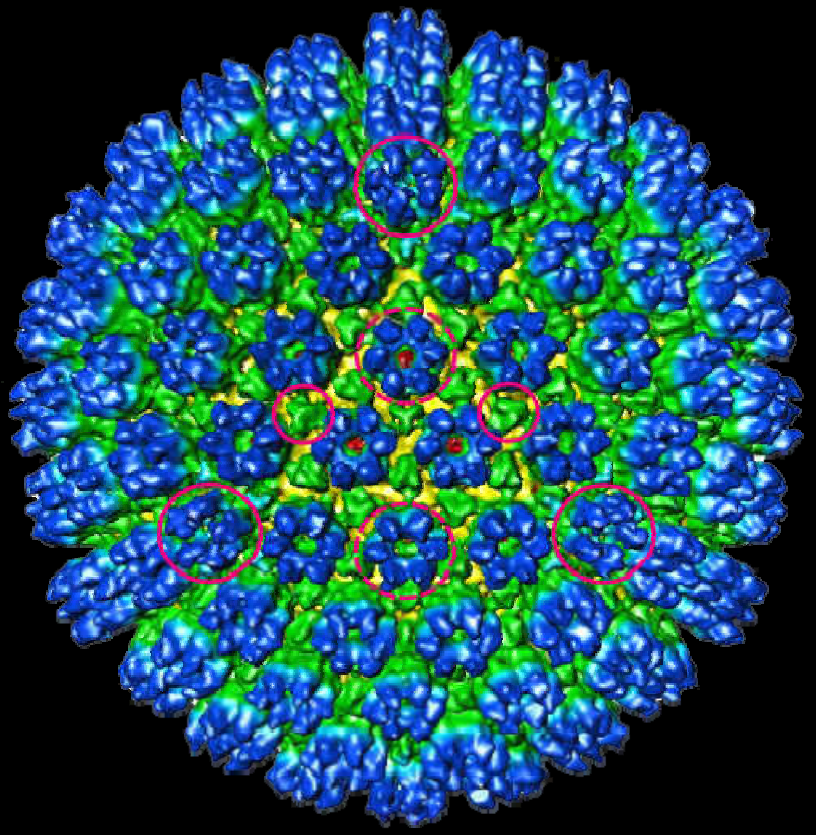
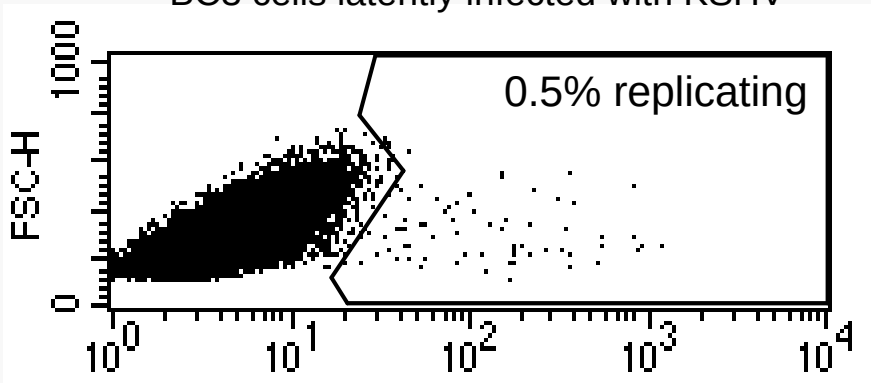
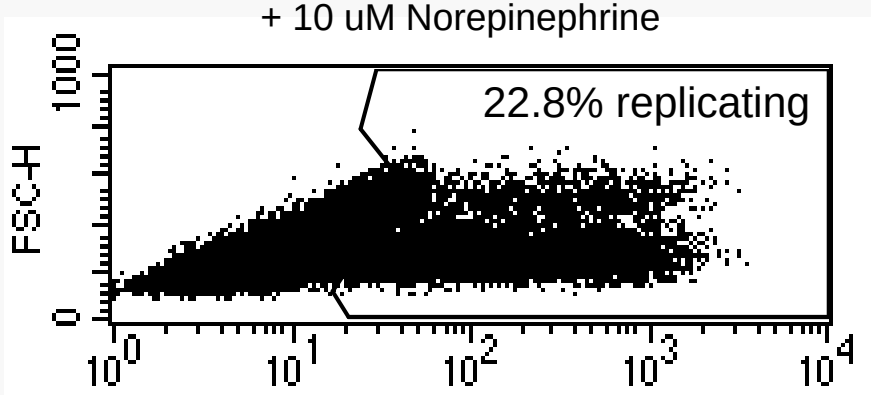
KSHV / HHV-8



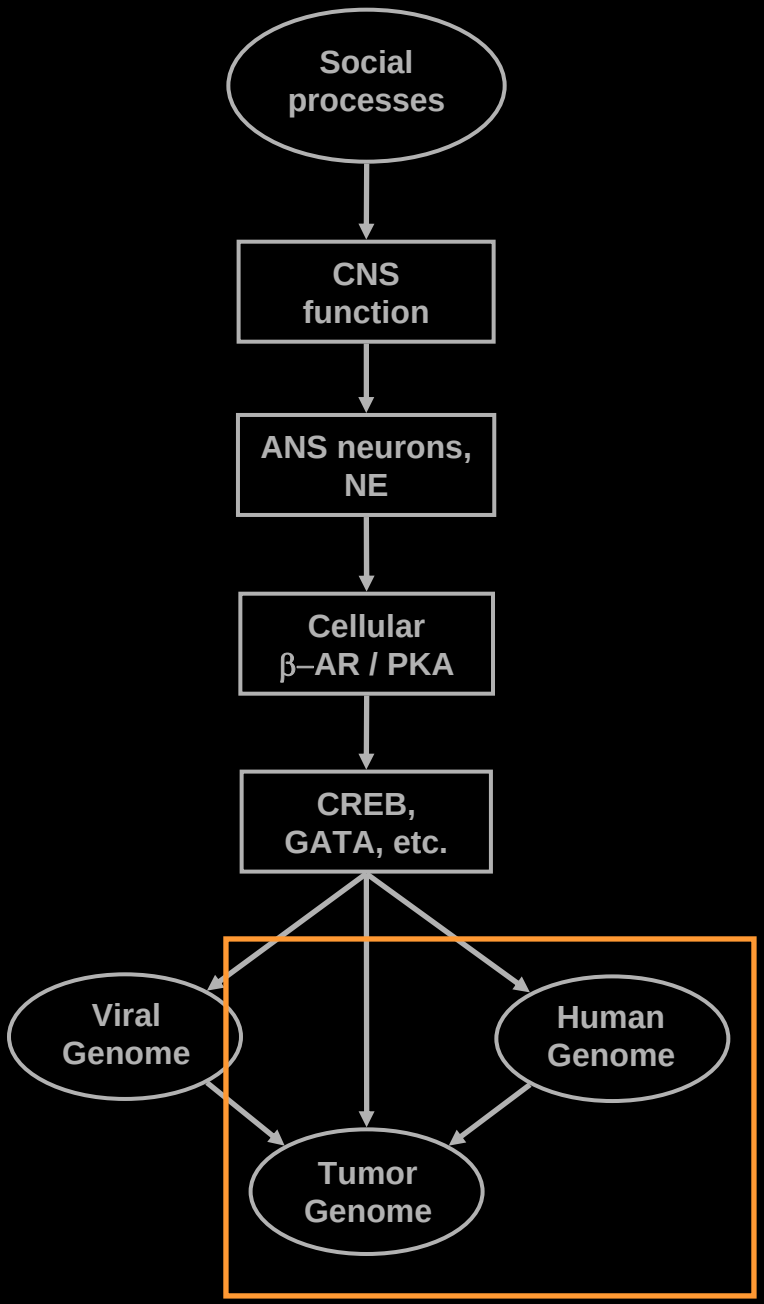
BC3 cells latently infected with KSHV



+ 10 uM Norepinephrine



Chang et al. (2005) Journal of Virology, 79, 13538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Answer: Neuroendocrine activation of cellular signal-transduction pathways**.**

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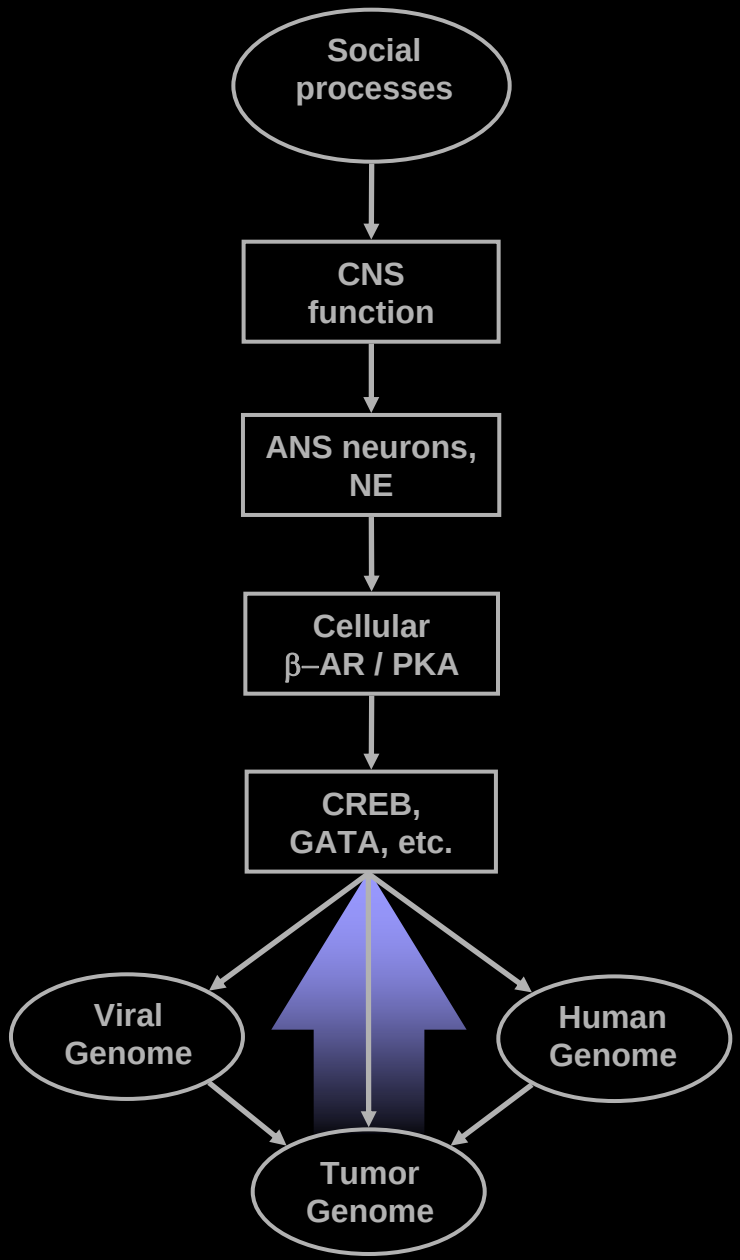
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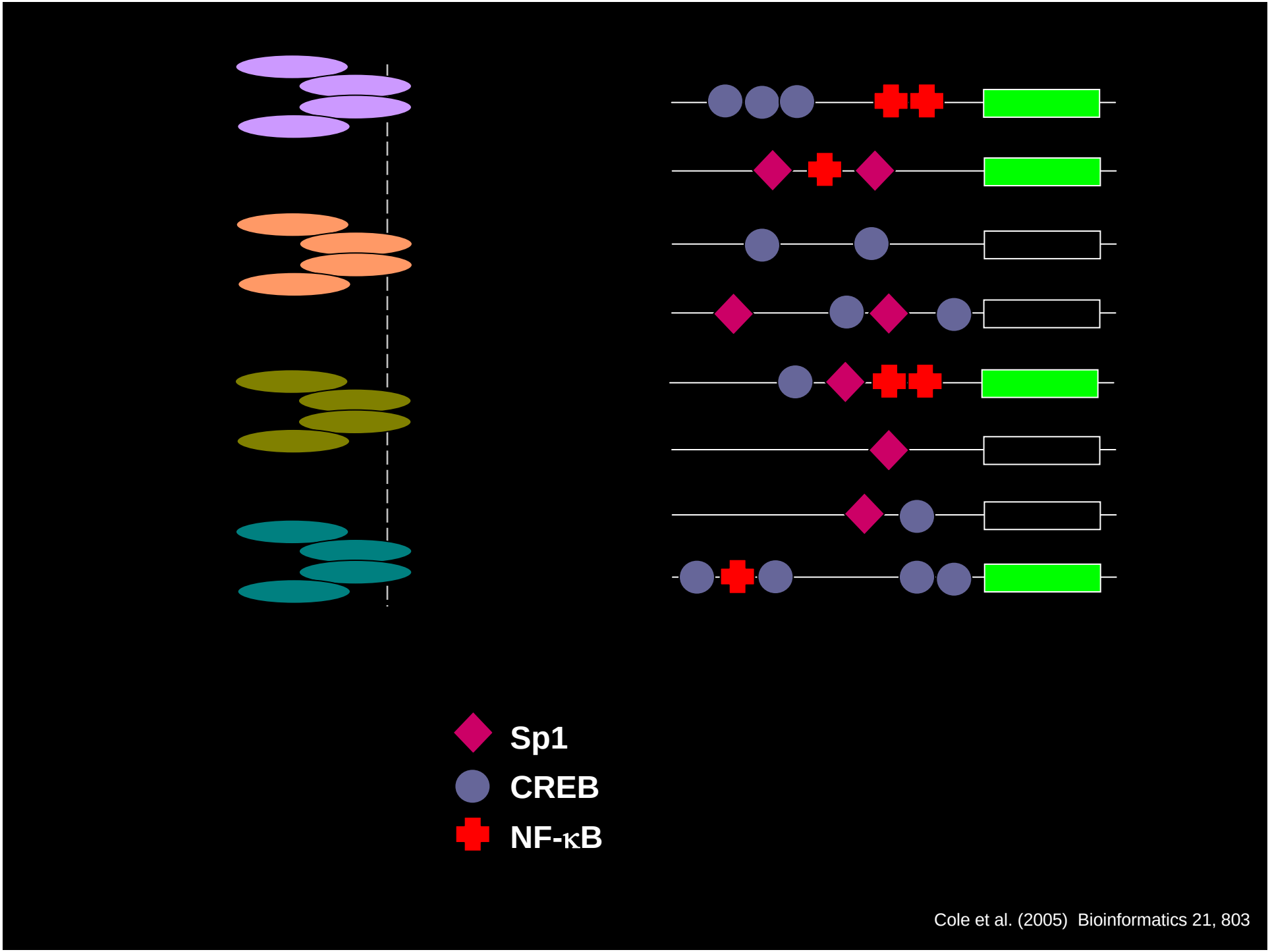
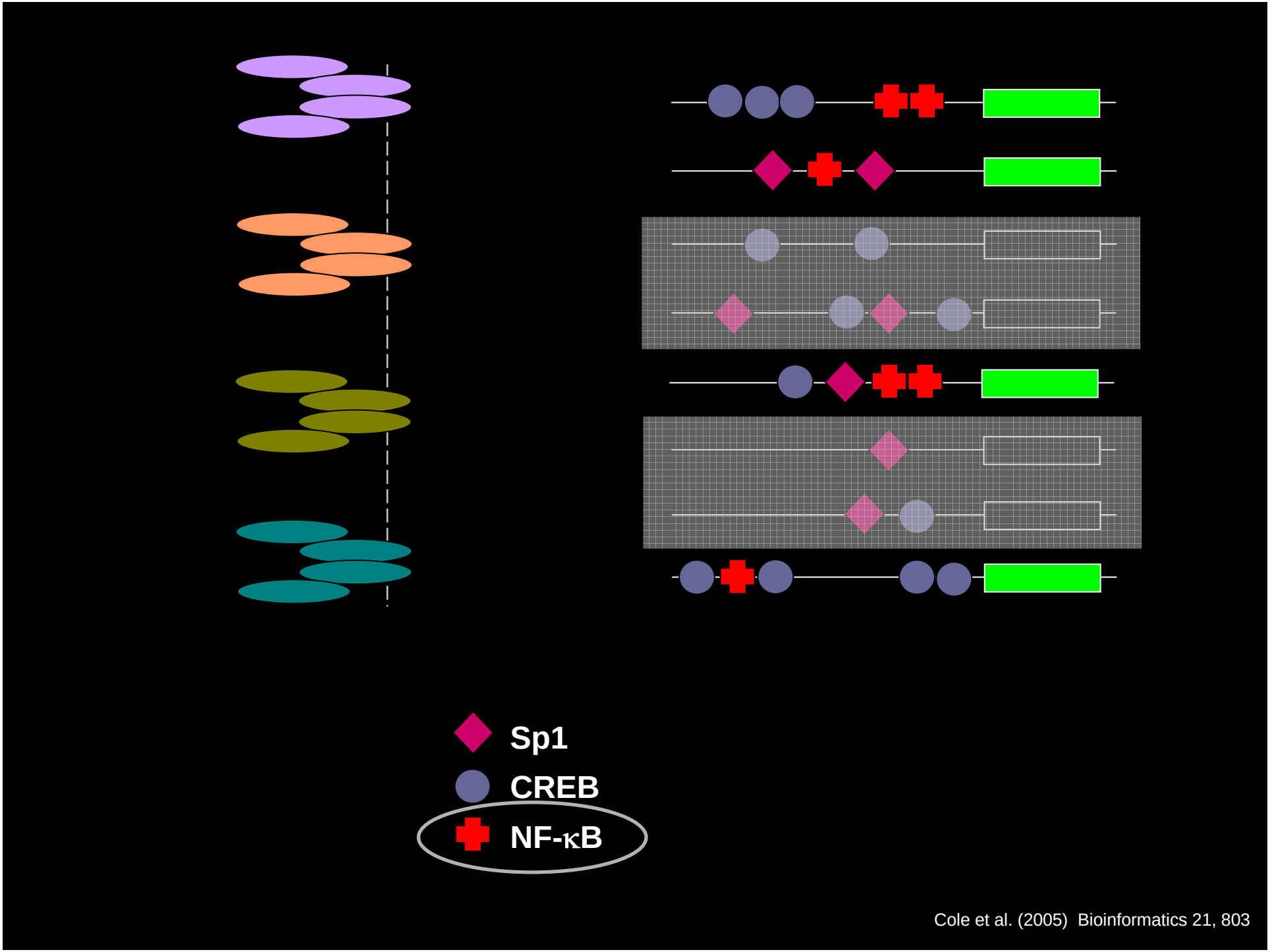


Cole et al. (2005) Bioinformatics 21, 803

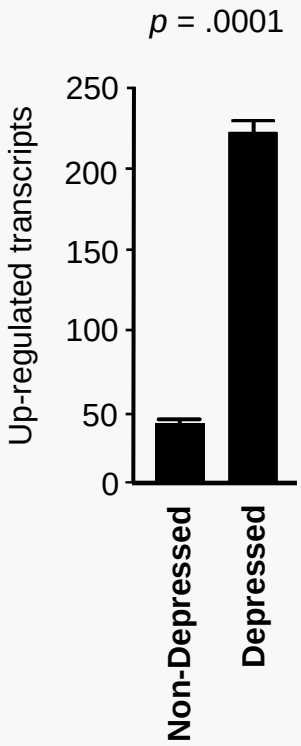


Cole et al. (2005) Bioinformatics 21, 803

Depression and ovarian carcinoma: functional genomics

- 10 primary ovarian epithelial carcinomas
  - 5 pt. with high social support and low depression
  - 5 pt. with low social support and high depression
  - matched on Grade, Stage, and histological subtype
- Global gene expression profiling
  - Affymetrix U133A high-density oligonucleotide arrays
  - simultaneous hybridization in UCLA / Jonsson Cancer Center DNA Microarray Core
  - low-level expression analysis by Robust Multi-array Averaging (RMA)
- Bioinformatics
  1. Identify differentially expressed genes (> 2-fold)
  2. Identify upstream transcription control pathways (www.telis.ucla.edu)

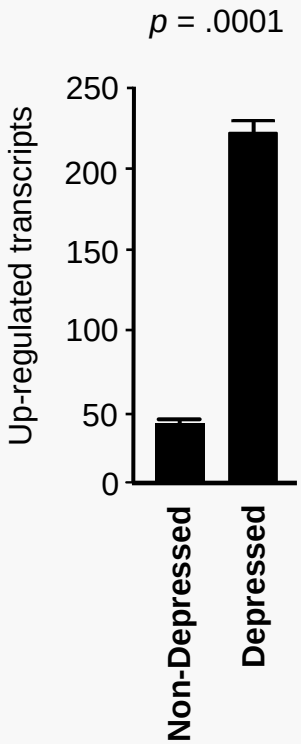
Depression and ovarian carcinoma: functional genomics



PPFIBP1
CST4
SQLE
EPS8L1
STX18
NDRG1
CST1
SMARCA4
EPB41L4B
UQCRH
DST
DPEP3
TEKT2
TACC2
NQO2
SFN
EFHC2
TBX2
ALCAM
SOX11
SRP68
MUC16
NR2E3
TBL1X
HIST1H1C
UNG2
VGLL1
SLC6A8
HOXA9
EPS8L1
KRT23
OVGP1
B7-H4
ASRGL1
ENDOG
HSPA1A
KIAA1641
HOXB6
VAV3
SLC3A1
PROM1
AMY2A

PLAT	FLJ10970	DCN	HLA-B	SPARC
ATF3	EGFL6	DUSP1	WFDC2	NALP1
CTGF	FXYD1	CSPG2	TM4SF1	PAPOLA
COL11A1	GAS1	FMOD	DUSP5	SMARCD3
SGNE1	LR8	SNX7	LTA4H	PSMD8
FOS	PNOC	HLA-DPA1	PLOD2	HLA-DQA1
CPVL	SERPING1	CYR61	PAPOLA	PITPNC1
ATP6V1B1	HLA-DRB1	HLA-DQB1	INHBA	FGFR3
CXCL12	HLA-DRA	SCPEP1	KIAA0657	SPARC
LYPDC1	C4A /// C4B	ARL1	XCL1 / XCL2	PLA2G7
HBA2	HBB	COL5A2	ECHDC3	SLC7A11
KLK11	OLFML3	KCTD14	GUCY1B3	CSPG2
UBD	HBA1	PRSS2	TRBC1	LSM4
COL11A1	JUN	WNT5B	GLT8D2	HLA-B
CP	PHYH	PRELP	ZFP36	PLEKHB1
C4A /// C4B	HLA-DRB1	SELENBP1	CALD1	GJA1
FOSB	HBA1	DUSP6	IGHM	NOL7
LUM	CSPG2	GMPR	TMEM14B	CDH11
LCRISP2	KIAA0657	FN1	CTSB	CST3
HLA-DRA	PFN2	PFKP	FXYD5	RPA3
ARL7	D4S234E	CCL2	IMP-3	KLF10
JUNB	SGCE	IGKC	PRSS21	TRBC1
CPE	HRASLS3	DUSP6	IGFBP2	EGR3
CGI-116	DUSP6	ANKRD6	CHPT1	RGC32
LOC440871	KNS2	PTGDS	TU3A	THY1
LOC492304	GPC4	TIMP3	PLXNC1	GALC
DKFZp564I1922	ARL7	BTG1	SH3BP5	INHBB
FXYD3	CECR1	DHRS8	FBLN5	POLD2
SEPP1	BBOX1	MYL9	NUP37	HLA-DPA1
POSTN	RARRES2	FN1	SPOCK	LOC388650
TM4SF1	TM4SF1	AKR1C3	HLA-B	PTGDS
HLA-DQA1	VCAM1	CSPG2	HLA-DMA	FBXO17
HBB	ID1	CXCL11	CYR61	JUND
EGR1	TU3A	POU2AF1	DCN	CKLFSF6
HBA1	ICAM2	BEXL1	HLA-DRB1	NRIP1
BTG2	RPL5	PYCARD	FLJ10159	PLOD2
NRCAM	KIAA0217	PIGV	COL5A1	IER3
SERPINE1	IGHD	MSRB2	C11orf9	LAMP2
HBA2	TRIB1	CXCL9	THBS2	PGA3
IGKC	ZDHHC4	ABAT	GATA6	LOC51315
IGLC2	PHLDA1	CACNA2D2	HCA112	
		COL3A1	MFAP2	

Depression and ovarian carcinoma: functional genomics



Transcription factors

PPFIBP1
CST4
SQLE
EPS8L1
STX18
NDRG1
CST1
SMARCA4
EPB41L4B
UQCRH
DST
DPEP3
TEKT2
TACC2
NQO2
SFN
EFHC2
TBX2
ALCAM
SOX11
SRP68
MUC16
NR2E3
TBL1X
HIST1H1C
UNG2
VGLL1
SLC6A8
HOXA9
EPS8L1
KRT23
OVGP1
B7-H4
ASRGL1
ENDOG
HSPA1A
KIAA1641
HOXB6
VAV3
SLC3A1
PROM1
AMY2A

PLAT
ATF3
CTGF
COL11A1
SGNE1
FOS
CPVL
ATP6V1B1
CXCL12
LYPDC1
HBA2
KLK11
UBD
COL11A1
CP
C4A /// C4B
FOSB
LUM
LCRISP2
HLA-DRA
ARL7
JUNB
CPE
CGI-116
LOC440871
LOC492304
DKFZp564I1922
FXYD3
SEPP1
POSTN
TM4SF1
HLA-DQA1
HBB
EGR1
HBA1
BTG2
NRCAM
SERPINE1
HBA2
IGKC
IGLC2

FLJ10970
EGFL6
FXYD1
GAS1
LR8
PNOC
SERPING1
HLA-DRB1
HLA-DRA
C4A /// C4B
HBB
OLFML3
HBA1
JUN
PHYH
HLA-DRB1
HBA1
CSPG2
KIAA0657
PFN2
D4S234E
SGCE
HRASLS3
DUSP6
KNS2
GPC4
ARL7
CECR1
BBOX1
RARRES2
TM4SF1
VCAM1
ID1
TU3A
ICAM2
RPL5
KIAA0217
IGHD
TRIB1
ZDHHC4
PHLDA1

DCN
DUSP1
CSPG2
FMOD
SNX7
HLA-DPA1
CYR61
HLA-DQB1
SCPEP1
ARL1
COL5A2
KCTD14
PRSS2
WNT5B
PRELP
SELENBP1
DUSP6
GMPR
FN1
PFKP
CCL2
IGKC
DUSP6
ANKRD6
PTGDS
TIMP3
BTG1
DHRS8
MYL9
FN1
AKR1C3
CSPG2
CXCL11
POU2AF1
BEXL1
PYCARD
PIGV
MSRB2
CXCL9
ABAT
CACNA2D2
COL3A1

HLA-B
WFDC2
TM4SF1
DUSP5
LTA4H
PLOD2
PAPOLA
INHBA
KIAA0657
XCL1 / XCL2
ECHDC3
GUCY1B3
TRBC1
GLT8D2
ZFP36
CALD1
IGHM
TMEM14B
CTSB
FXYD5
IMP-3
PRSS21
IGFBP2
CHPT1
TU3A
PLXNC1
SH3BP5
FBLN5
NUP37
SPOCK
HLA-B
HLA-DMA
CYR61
DCN
HLA-DRB1
FLJ10159
COL5A1
C11orf9
THBS2
GATA6
HCA112
MFAP2

SPARC
NALP1
PAPOLA
SMARCD3
PSMD8
HLA-DQA1
PITPNC1
FGFR3
SPARC
PLA2G7
SLC7A11
CSPG2
LSM4
HLA-B
PLEKHB1
GJA1
NOL7
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PGA3
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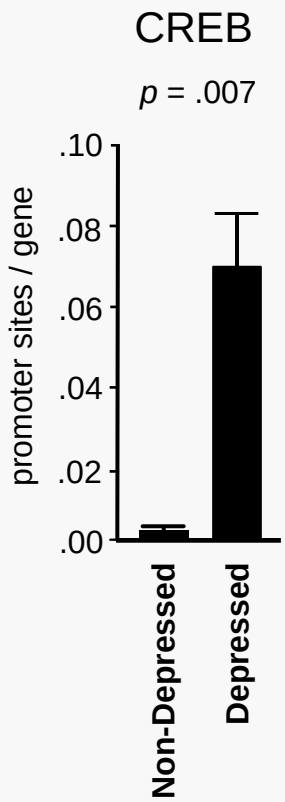
Depression and ovarian carcinoma: functional genomics



NE / β–AR signaling

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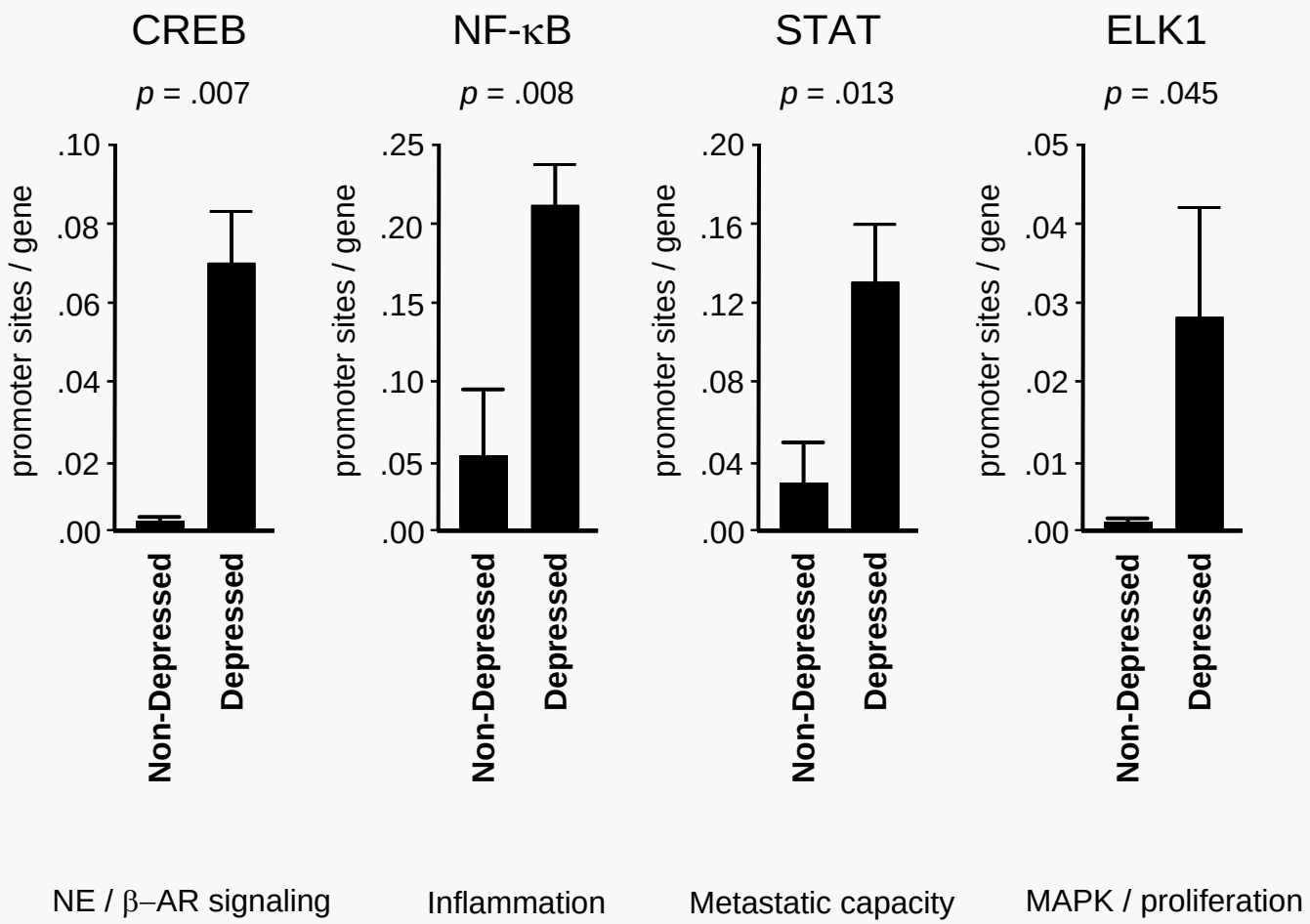

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1. How do social factors regulate gene expression?
2. Are these “social signal transduction” pathways active in clinical cancer?
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4. What are the prospects for protective intervention?

Answer: Risk-related activation of the cAMP / PKA / CREB pathway in primary ovarian tumors

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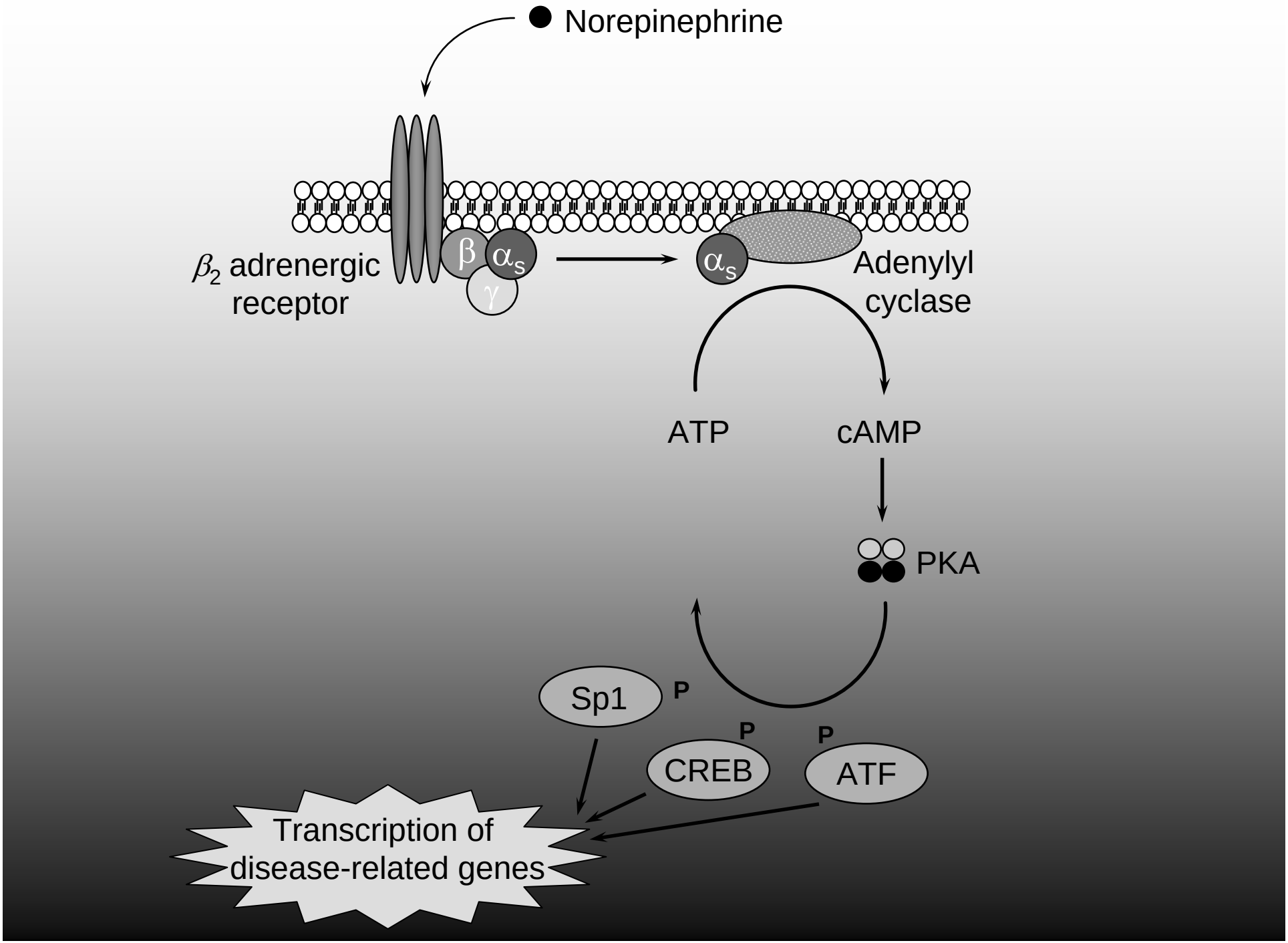
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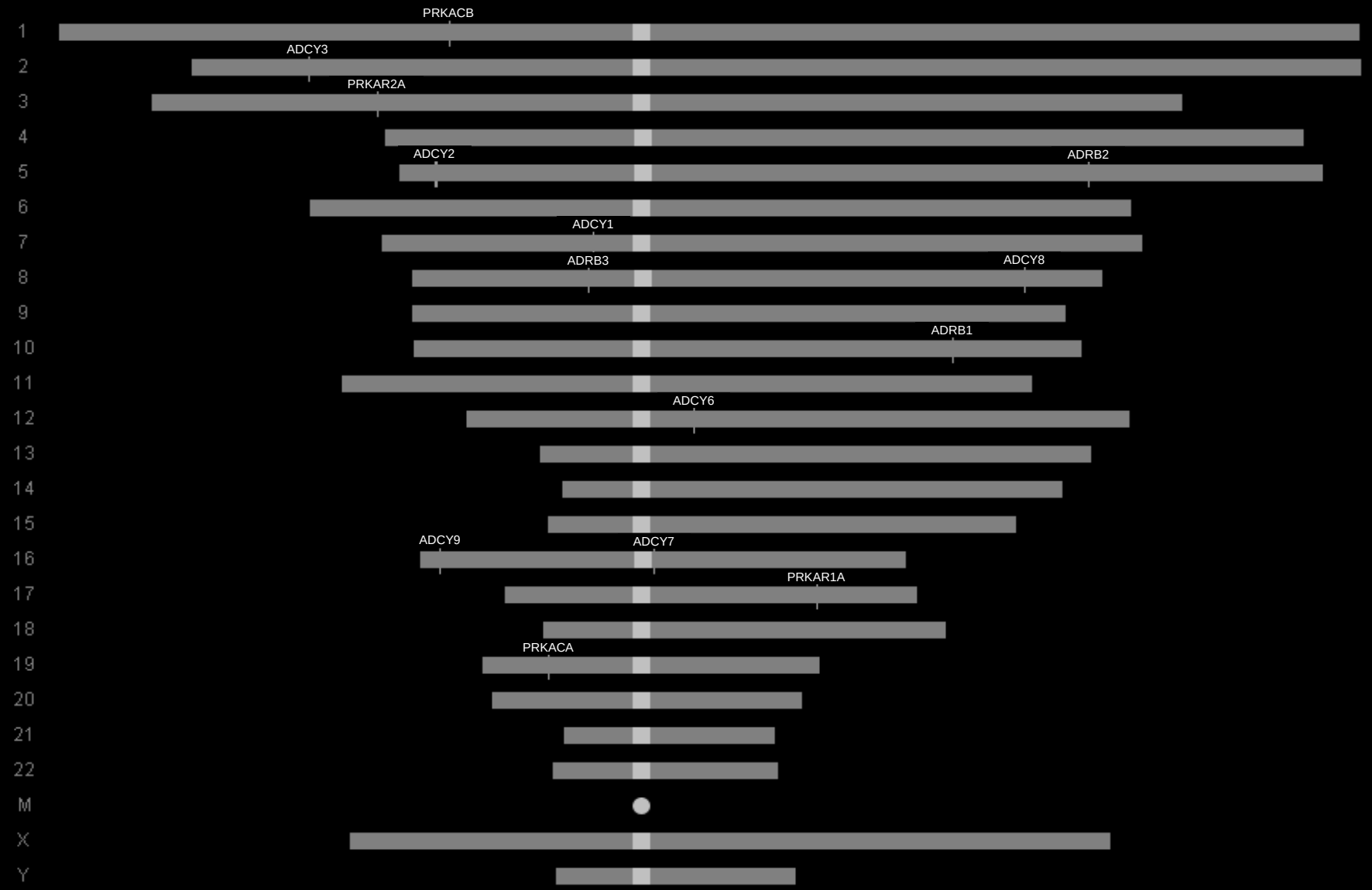
β-AR pathway genes: ovarian carcinoma



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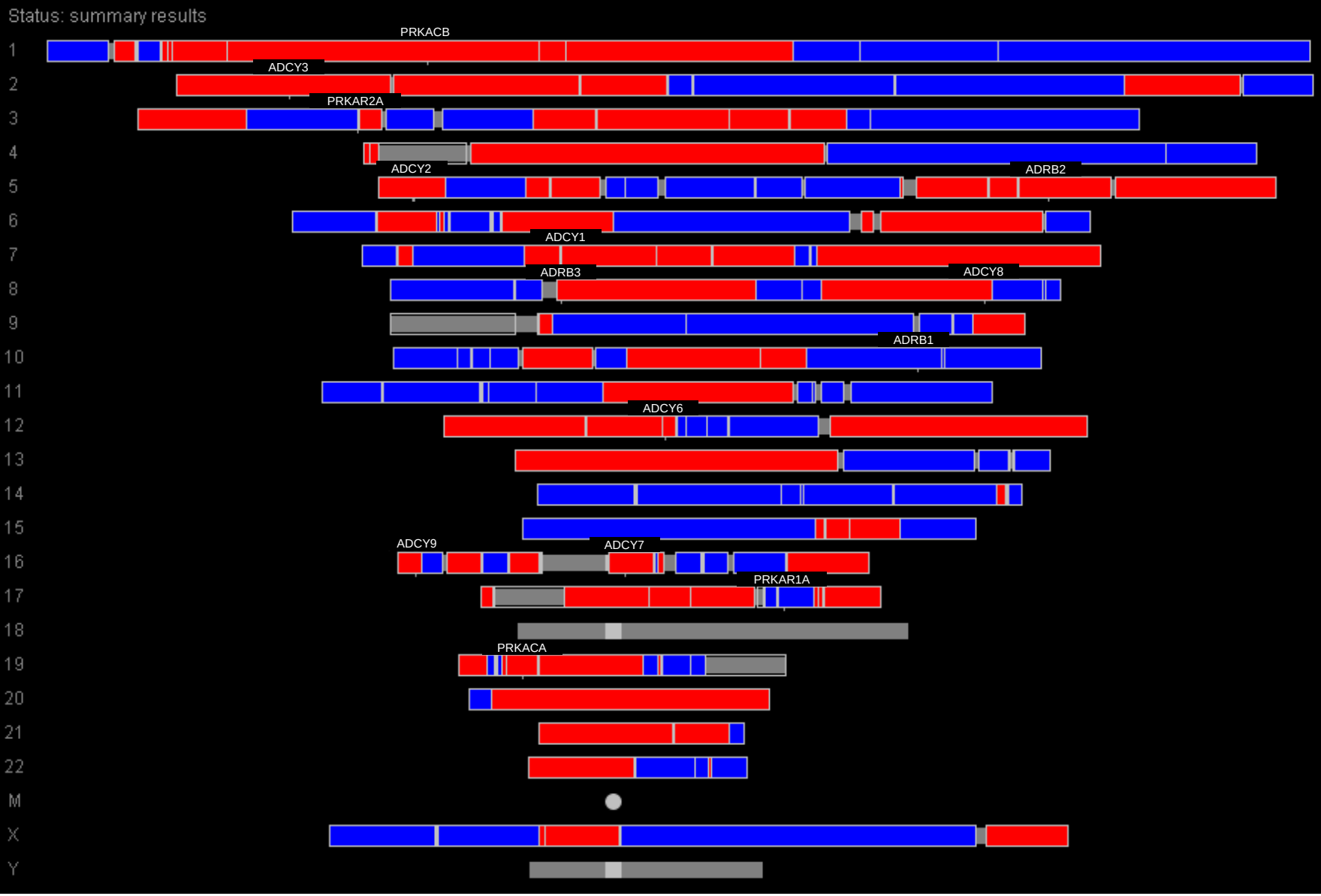

β-AR pathway genes: ovarian carcinoma

Gene	Functional relationship	Regional alteration	Consistency
ADRB1	+	-	-
ADRB2	+	+	+
ADRB3	+	+	+
ADCY1	+	+	+
ADCY2	+	+	+
ADCY3	+	+	+
ADCY6	+	+	+
ADCY7	+	+	+
ADCY8	+	+	+
ADCY9	+	+	+
PRKACA	+	+	+
PRKACB	+	+	+
PRKAR1A	-	-	+
PRKAR2A	-	-	+

◀ 13 / 14: Haplotype *p* = .00006

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Answer: Evidence of selection for β-AR / PKA genes in ovarian cancer

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Basic science: Pathway identification
- rational targeting of interventions (agent selection, personal risk profiling)
- genomic biomarkers for intervention impact

Translational opportunity: β-AR pathway
- β-blockade (safe, cheap, effective?)
- molecular manipulation (*ADRB2*, *ADCY*, transcription factors, stay upstream for leverage)

Support

NCI 1R01-CA116778
NCI 1R01-CA110793
NCI 1R01-CA109298
NIDCR 1R01-DE015970
NIDCR 1R03-DE016569
NIAID 1R01-AI52737
MacArthur Foundation
James Pendelton Trust
HopeLab Foundation