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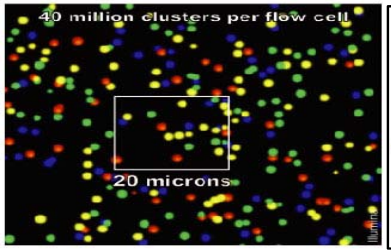
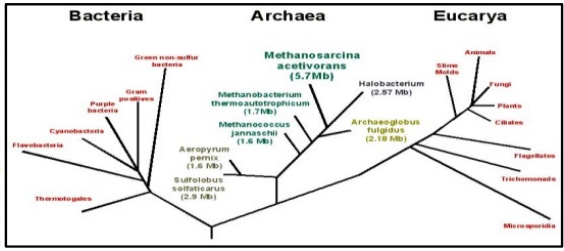


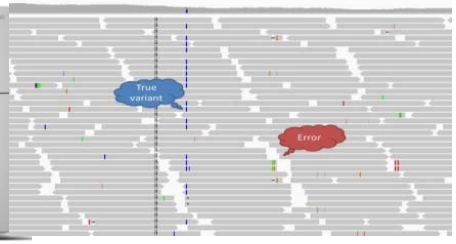


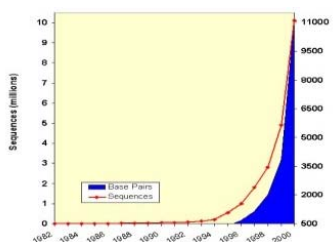
Ontology, and Identification of Molecular Pathways

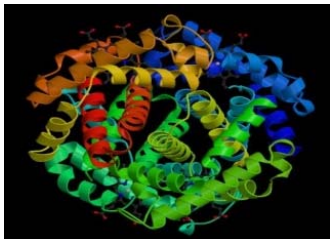
北京大学生物信息学中心 魏丽萍

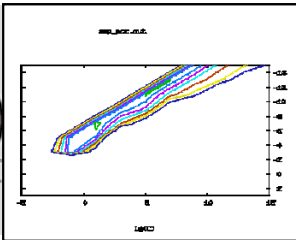
Liping Wei, Ph.D.

Center for Bioinformatics, Peking University









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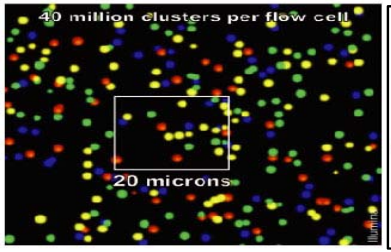

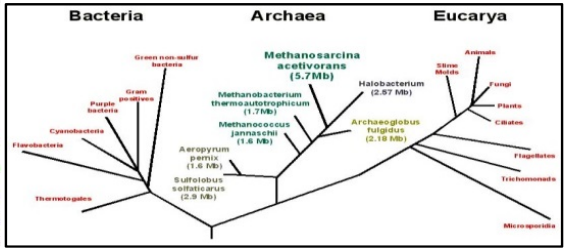

Unit 5:

An Application: Common Molecular Pathways Underlying Addiction

北京大学生物信息学中心 魏丽萍

Liping Wei, Ph.D.

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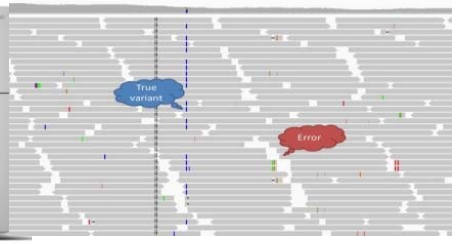
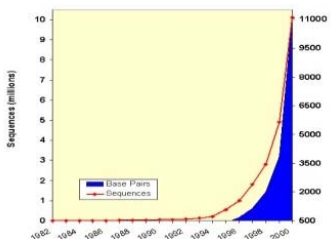
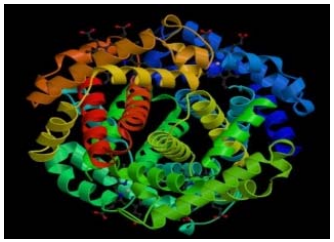
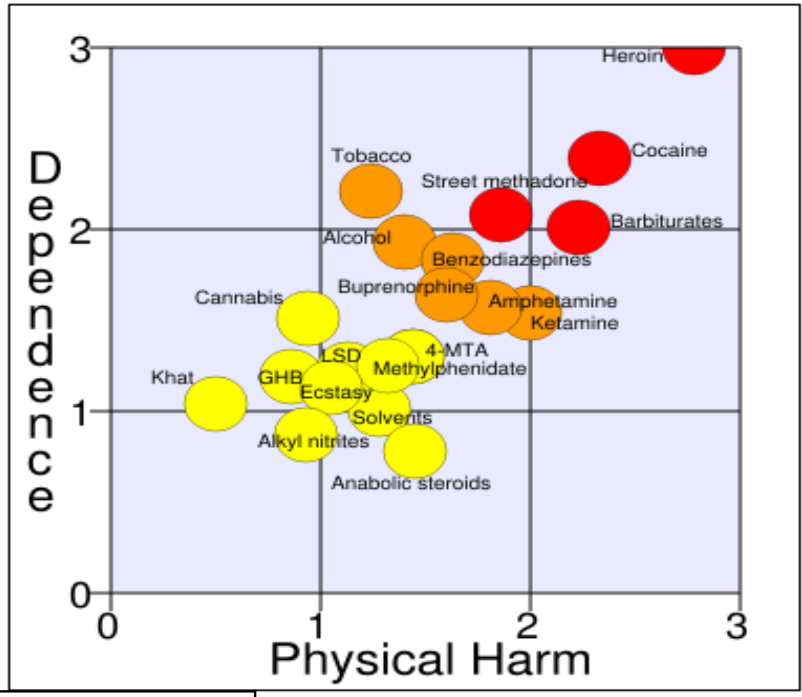






Addiction is a serious medical and social problem.



Nutt, *NEJM*, '07

Is there a common molecular pathway for addiction?

Eric J Nestler

Drugs of abuse have very different acute mechanisms of action but converge on the brain's reward pathways by producing a series of common functional effects after both acute and chronic administration. Some similar actions occur for natural rewards as well. Researchers are making progress in understanding the molecular and cellular basis of these common effects. A major goal for future research is to determine whether such common underpinnings of addiction can be exploited for the development of more effective treatments for a wide range of addictive disorders.

acute rewarding effects of all drug of abuse, and research over the past several decades has delineated how each drug, regardless of its distinct mechanism of action, converges on the VTA and NAc with common acute functional effects (**Fig. 1**). Each drug activates dopaminergic transmission in the NAc and many produce dopamine-like, yet dopamine-independent effects on the same NAc neurons, in many cases via indirect, circuit-level actions[1–8]. In addition, several drugs (see **Fig. 1** legend) seem to activate the brain's endogenous opioid and cannabinoid systems within the VTA-NAc pathway, as exemplified by reduced drug effects in cannabinoid and opioid receptor knockout mice, which further underscores shared acute mechanisms of drug action[1,8].

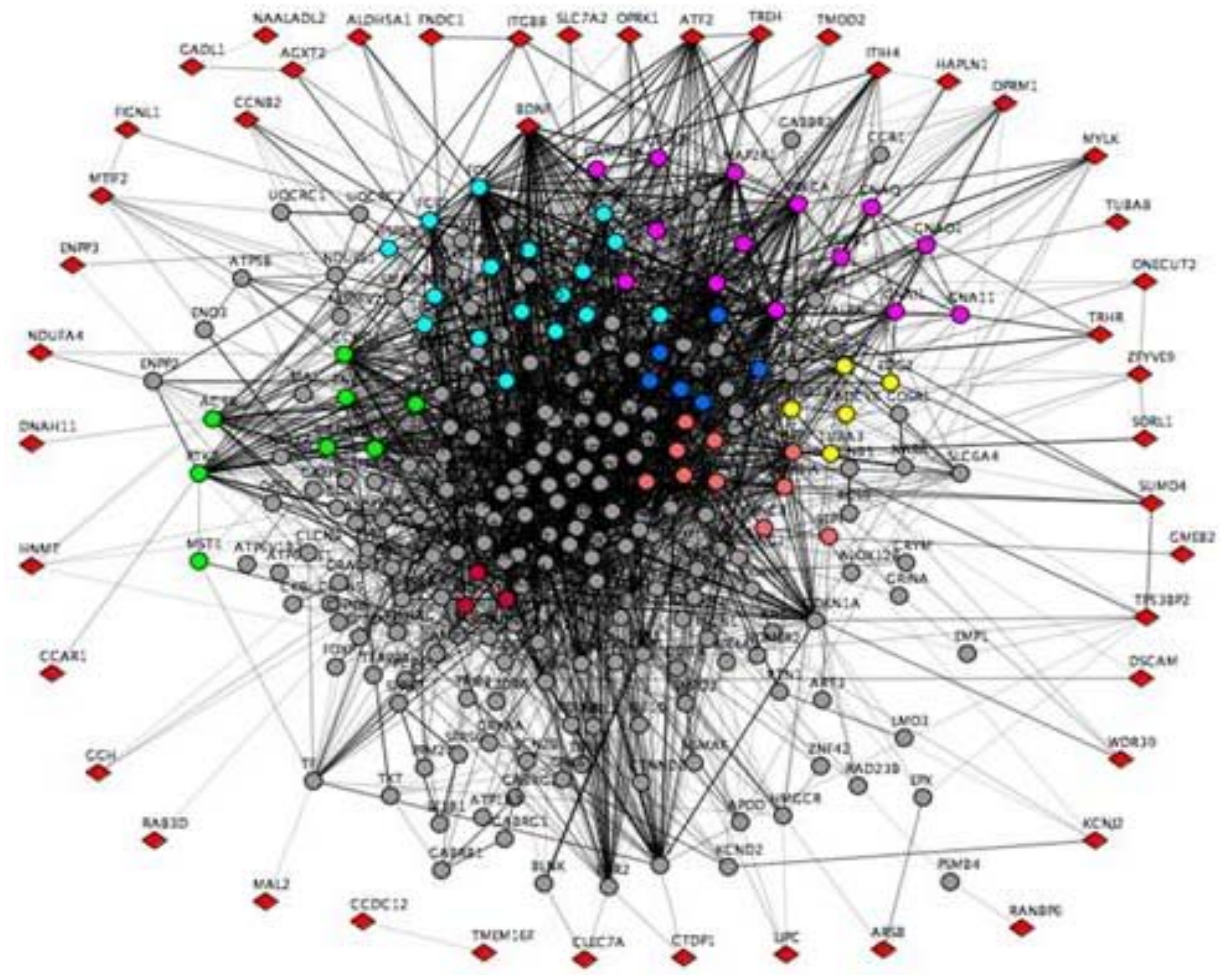
Nestler,
Nat Neurosci, '05

Which genes are related to addiction?

Evidence Origin	Evidence Type	Gene Count	Evidence Count
Genetics Strategies			**553**
Genetic Linkage	**Addiction-vulnerable peak regions**		**119**
Population Association	**Addiction-vulnerable points/clusters**		**174**
Animal QTL	**Addiction-vulnerable Regions**		**260**
Molecular Biology Strategies		**1221**	**1790**
Single gene strategies	**Genes implicated in addiction**	**185**	**299**
Microarray	**Genes encoding significantly differentially expressed mRNAs**	**949**	**1297**
Proteomics	**Genes encoding significantly differentially expressed proteins**	**119**	**170**
OMIM	**Database annotations**	**24**	**24**

Li, ’08, PLos Comp Biol

Genetic and molecular biological technologies often detect different parts of the same pathways/networks



MAPK signaling pathway
Neuroactive ligand-receptor interaction
Calcium signaling pathway
TGF-beta signaling pathway
Cytokines
Huntington's disease
Glycerolipid metabolism
Starch and sucrose metabolism
Alanine and aspartate metabolism
Nicotinate and nicotinamide metabolism
Glycine, serine and threonine metabolism

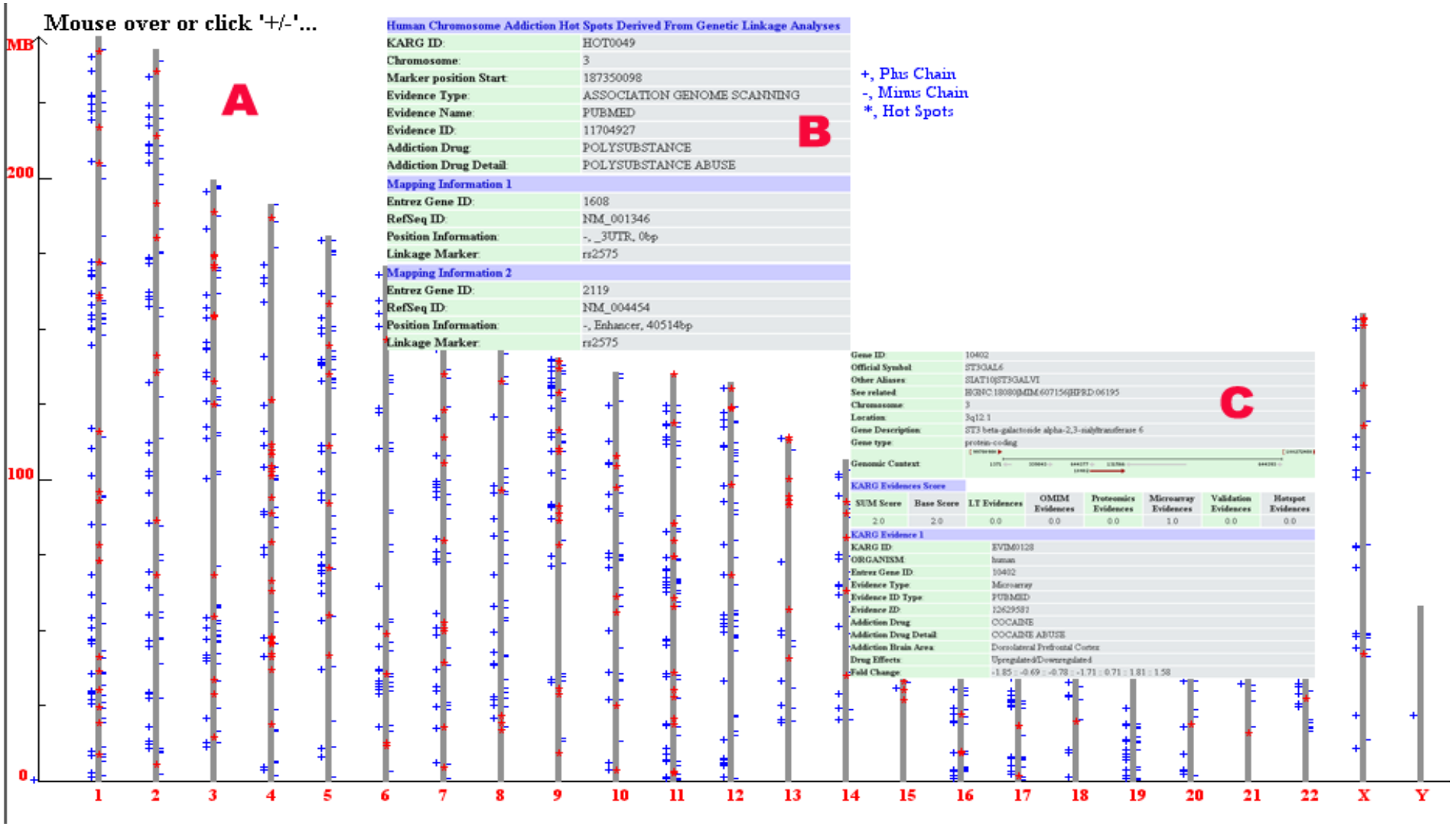
Genes related to addiction

Evidence Origin	Evidence Type	Gene Count	Evidence Count
Genetics Strategies			**553**
Single gene strategies	**Genes implicated in addiction**	**185**	**299**
Microarray	**Genes encoding significantly differentially expressed mRNAs**	**949**	**1297**
Proteomics	**Genes encoding significantly differentially expressed proteins**	**119**	**170**
OMIM	**Database annotations**	**24**	**24**

1500 human genes were related to addiction

Among them 396 had two or more pieces of evidence

Li, ’08, PLos Comp Biol



Human Chromosome Addiction Hot Spots Derived From Genetic Linkage Analyses	
KARG ID:	HOT0049
Chromosome:	3
Marker position Start:	187350098
Evidence Type:	ASSOCIATION GENOME SCANNING
Evidence Name:	PUBMED
Evidence ID:	11704927
Addiction Drug:	POLYSUBSTANCE
Addiction Drug Detail:	POLYSUBSTANCE ABUSE
Mapping Information 1	
Entrez Gene ID:	1608
RefSeq ID:	NM_001346
Position Information:	-, _3UTR, 0bp
Linkage Marker:	rs2575
Mapping Information 2	
Entrez Gene ID:	2119
RefSeq ID:	NM_004454
Position Information:	-, Enhancer, 40514bp
Linkage Marker:	rs2575

Gene ID:	10402
Official Symbol:	ST3GAL6
Other Aliases:	SIAT10|ST3GALVI
See related:	HGNC:18080|MIM:607156|HPRD:06195
Chromosome:	3
Location:	3q12.1
Gene Description:	ST3 beta-galactoside alpha-2,3-sialyltransferase 6
Gene type:	protein-coding
Genomic Context:	

KARG Evidences Score

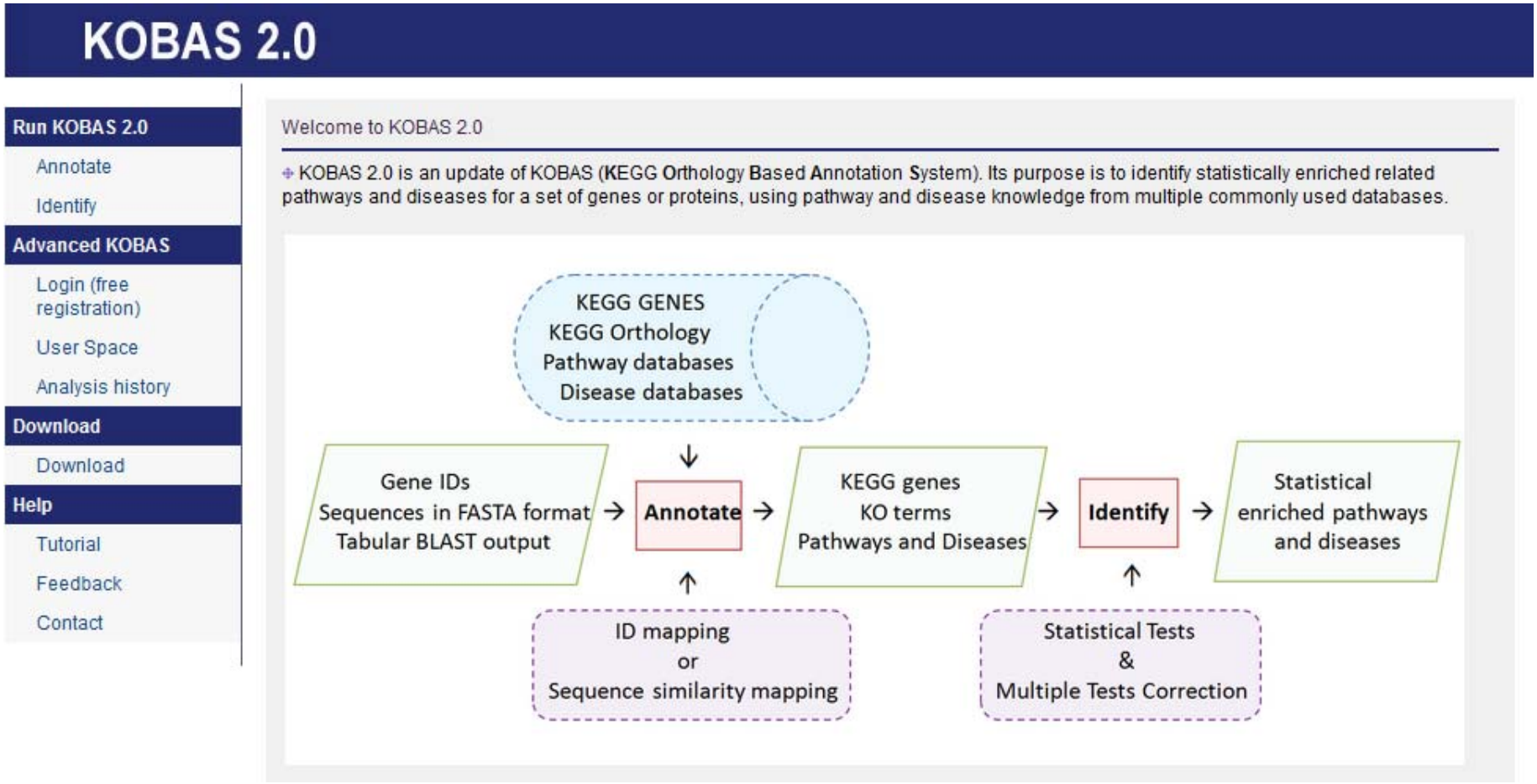
SUM Score	Base Score	LT Evidences	OMIM Evidences	Proteomics Evidences	Microarray Evidences	Validation Evidences	Hotspot Evidences
2.0	2.0	0.0	0.0	0.0	1.0	0.0	0.0

KARG Evidence 1	
KARG ID:	EVIM0128
ORGANISM:	human
Entrez Gene ID:	10402
Evidence Type:	Microarray
Evidence ID Type:	PUBMED
Evidence ID:	12629581
Addiction Drug:	COCAINE
Addiction Drug Detail:	COCAINE ABUSE
Addiction Brain Area:	Dorsolateral Prefrontal Cortex
Drug Effects:	Upregulated|Downregulated
Fold Change:	-1.85 : -0.69 : -0.78 : -1.71 : 0.71 : 1.81 : 1.58

Given the set of 396 addiction genes,

- **Which pathways are involved?**
- **Which pathways are statistically significantly represented?**

KOBAS web server (http://kobas.cbi.pku.edu.cn)



(Wu *et al*, Nucleic Acids Research, '06; Xie *et al*, Nucleic Acids Research, '12)

18 Statistically Enriched Pathways

Pathways	*P*-Value	*Q*-Value
Long-term depression	2.1E-07	1.1E-05
Gap junction	1.5E-07	1.1E-05
Long-term potentiation	3.5E-06	7.2E-05
Neuroactive ligand-receptor interaction	2.1E-06	7.2E-05
MAPK signaling pathway	3.1E-06	7.2E-05
GnRH signaling pathway	8.5E-06	1.5E-04
Calcium signaling pathway	4.8E-04	7.0E-03
Colorectal cancer	6.5E-04	8.3E-03
Pores ion channels	2.1E-03	0.02
VEGF signaling pathway	3.2E-03	0.03
Glycolysis /Gluconeogenesis	3.8E-03	0.03
Protein folding and associated processing	3.8E-03	0.03
Focal adhesion	4.4E-03	0.03
Insulin signaling pathway	4.9E-03	0.03
Parkinson's disease	6.3E-03	0.04
Fc epsilon RI signaling pathway	6.9E-03	0.04
Type II diabetes mellitus	7.7E-03	0.05
Progesterone-mediated oocyte maturation	9.1E-03	0.05

Li, *et al*,
PLos Comp Biol, ’08

Are there common pathways underlying addiction to different substances?

Collection of meta-data enables detailed analysis

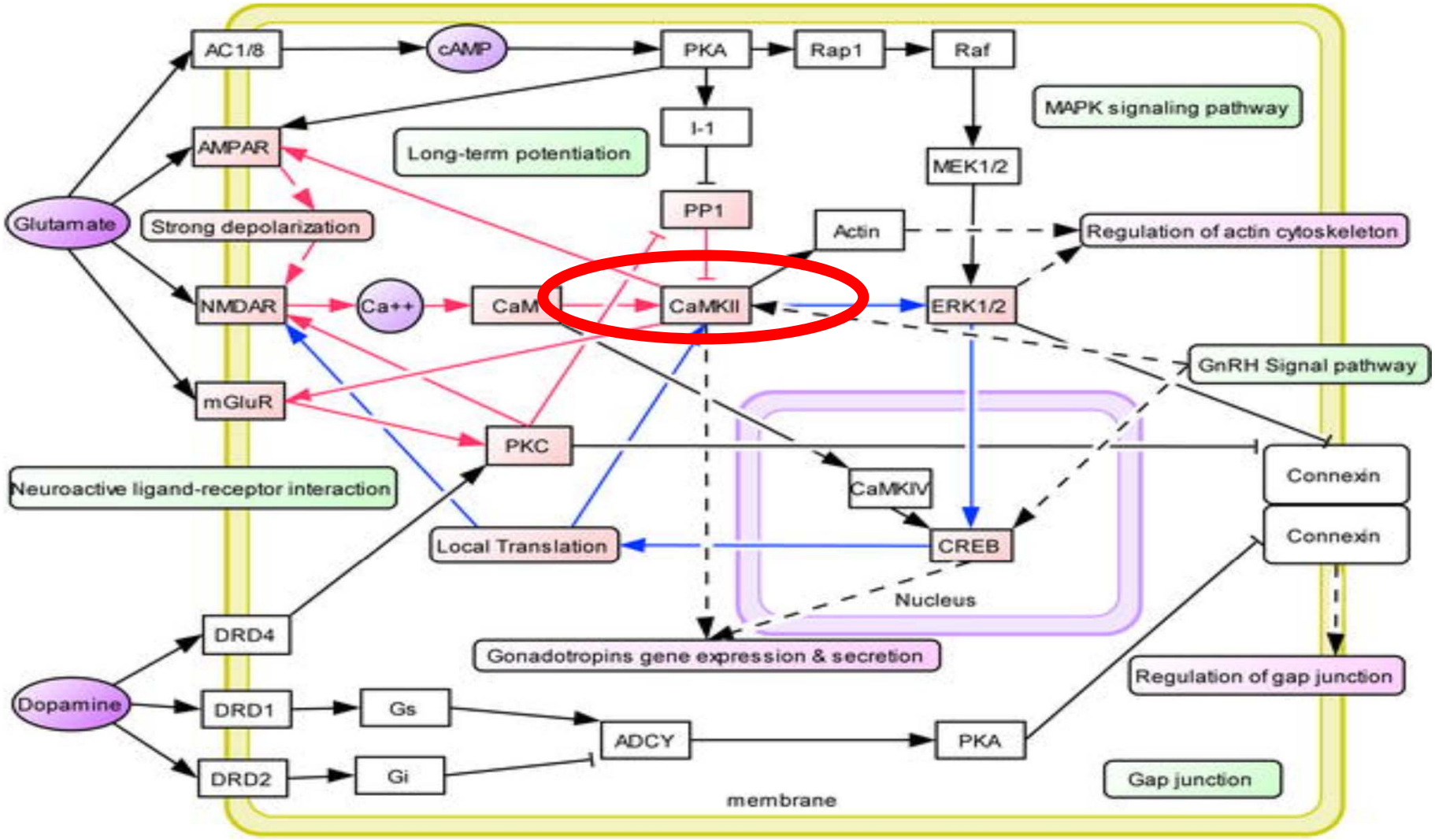
Entry Fields	Descriptions and Data Resources
Basic Information	**Basic information for this gene, including Gene ID, official symbol, aliases, links to OMIM, links to HPRD, chromosome and location, gene descriptions, gene type and genomic context. Data from NCBI ENTREZ GENE**
Evidence Summary	**A summary of evidence linking this gene to addiction**
KARG Evidence	**For each piece of evidence, KARG internal ID, organism, evidence ID and links, addictive drug types and addiction brain areas were annotated. For large-scale profiling evidence, differentially expressed effects and fold-changes were also included.**
Gene Ontology	**Gene Ontology annotations. Data from GO website**
Interaction information	**Protein interaction annotations. Data from BIND and HPRD**
Domain Information	**Protein domain annotations. Data from INTERPRO**

Entrez Gene ID	Official Symbol	Locations	Gene description	Cocaine	Alcohol	Opioids	Nicotine
12	SERPINA3	14q32.1	serpin peptidase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 3	Yes	Yes	Yes	Yes
18	ABAT	16p13.2	4-aminobutyrate aminotransferase	Yes	Yes	-	Yes
88	ACTN2	1q42-q43	actinin, alpha 2	Yes	Yes	Yes	Yes
112	ADCY6	12q12-q13	adenylate cyclase 6	-	-	Yes	-
114	ADCY8	8q24	adenylate cyclase 8 (brain)	Yes	Yes	Yes	Yes
143	PARP4	13q11	poly (ADP-ribose) polymerase family, member 4	-	Yes	-	-
213	ALB	4q11-q13	albumin	Yes	-	Yes	-
230	ALDOC	17cen-q12	aldolase C, fructose-bisphosphate	-	Yes	Yes	-
231	AKR1B1	7q35	aldo-keto reductase family 1, member B1 (aldose reductase)	Yes	Yes	Yes	Yes
242	ALOX12B	17p13.1	arachidonate 12-lipoxygenase, 12R type	-	Yes	-	-

Common Pathways

Addictive Drugs	Cocaine	Alcohol	Opioids	Nicotine
Neuroactive ligand-receptor interaction				
P-Value	5.39E-05	3.24E-02	2.68E-03	7.79E-03
Q-Value	1.8E-04	0.05	0.01	0.04
Long-term potentiation				
P-Value	3.21E-08	8.28E-03	1.05E-02	8.84E-03
Q-Value	2.8E-07	0.03	0.03	0.04
GnRH signaling pathway				
P-Value	2.84E-05	3.93E-04	4.67E-03	1.72E-02
Q-Value	1.2E-04	3.6E-03	0.02	0.05
MAPK signaling pathway				
P-Value	1.28E-04	2.97E-04	7.34E-05	1.10E-02
Q-Value	3.7E-04	3.6E-03	5.2E-04	0.04
Gap junctions				
P-Value	1.03E-08	2.11E-03	3.30E-03	5.85E-03
Q-Value	2.8E-07	0.01	0.01	0.03

Li, *et al*, PLos Comp Biol, ’08



Li, *et al*, PLos Comp Biol, ’08

Summary

To facilitate communication and computation,

- **store data in database whenever possible;**
- **define an ontology for the data;**
- **collect meta-data together with data.**

To discover higher level patterns in a set of genes or gene products,,

- **identify the most significant pathways and functional categories**
- **perform statistical analysis such as in KOBAS**

生物信息学：导论与方法
Bioinformatics: Introduction and Methods

Ge Gao 高歌 & Liping Wei 魏丽萍
Center for Bioinformatics, Peking University