KEGG NETWORK
Database of disease-related network variants
疾患に関連したネットワークバリアントのデータベース

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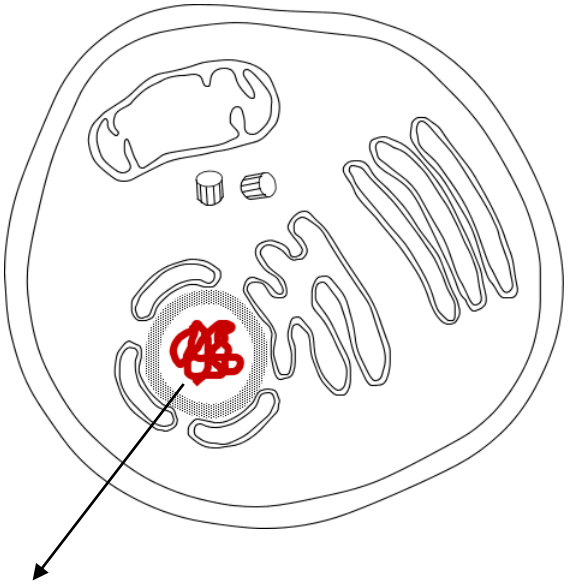
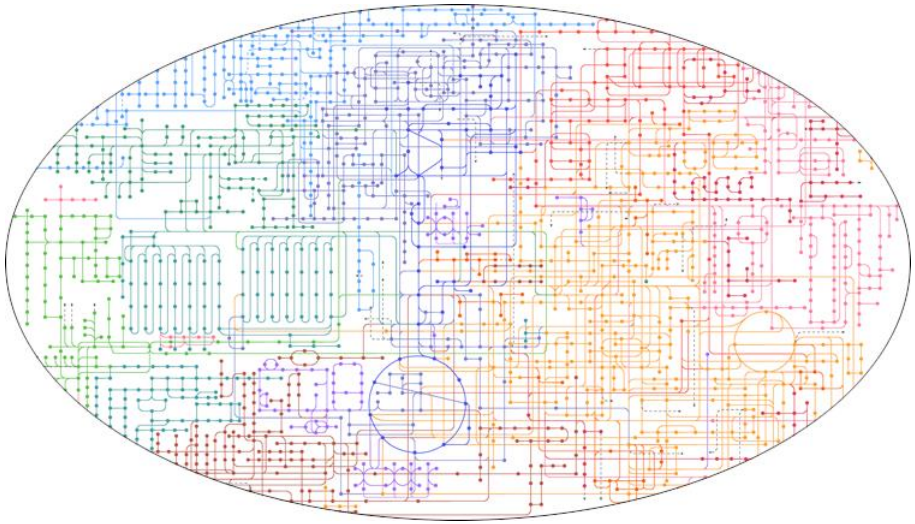
What Is KEGG?

1. **K**yoto **E**ncyclopedia of **G**enes and **G**enomes

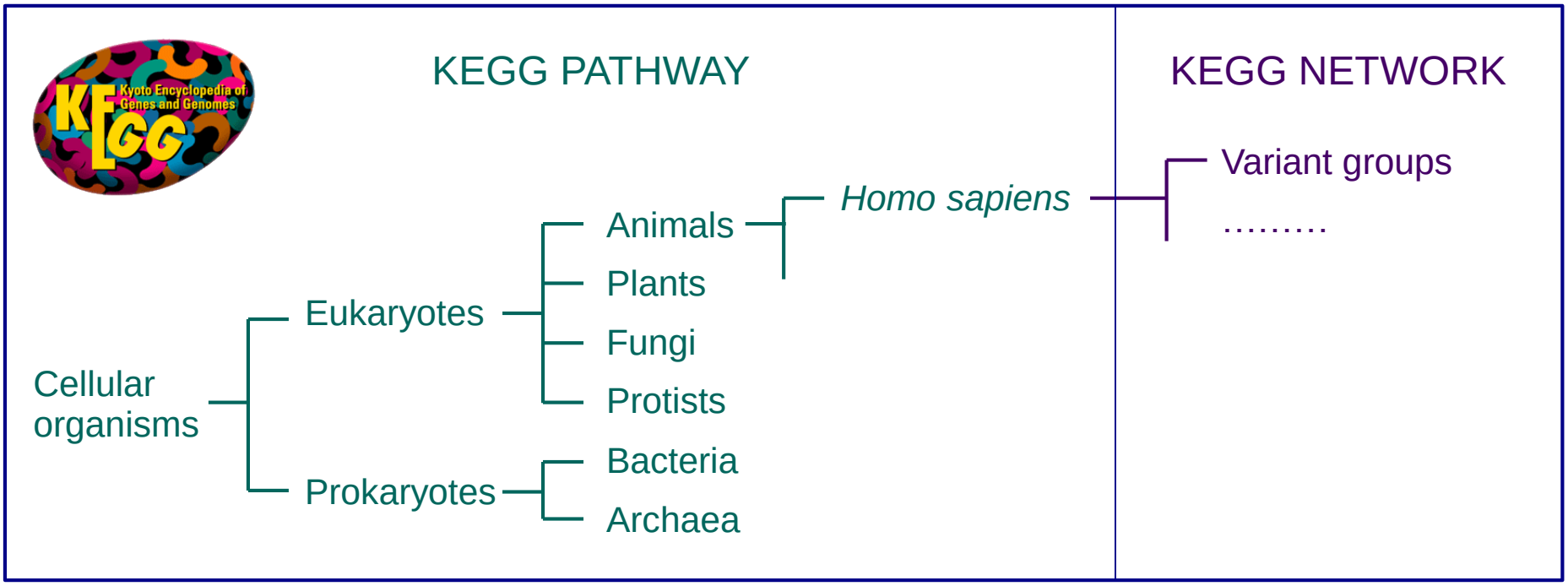
2. Genome vs. Cell
   Genetic blueprint of life — Chemical blueprint of life
   Molecular parts — Molecular networks

3. Cellular structure vs. Cellular function





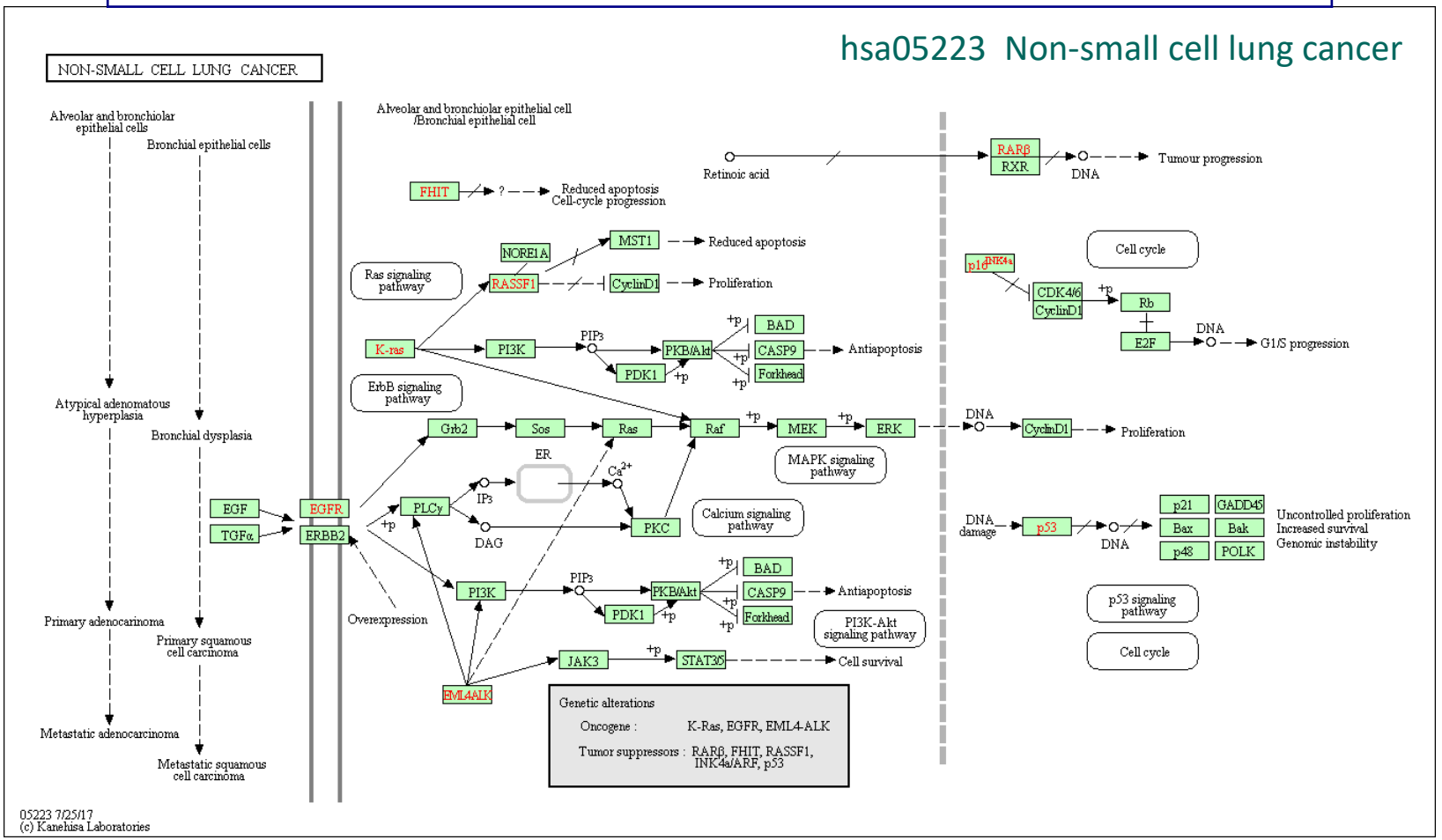
KEGG: Kyoto Encyclopedia of Genes and Genomes



Purpose	Basic understanding of cellular functions and organism behaviors	Practical applications for use in society
Content	Generic databases that can be used for any cellular organisms	Human specific databases of health information
Main Identifiers	KOs (KEGG Orthology IDs)	Human gene IDs and variant IDs

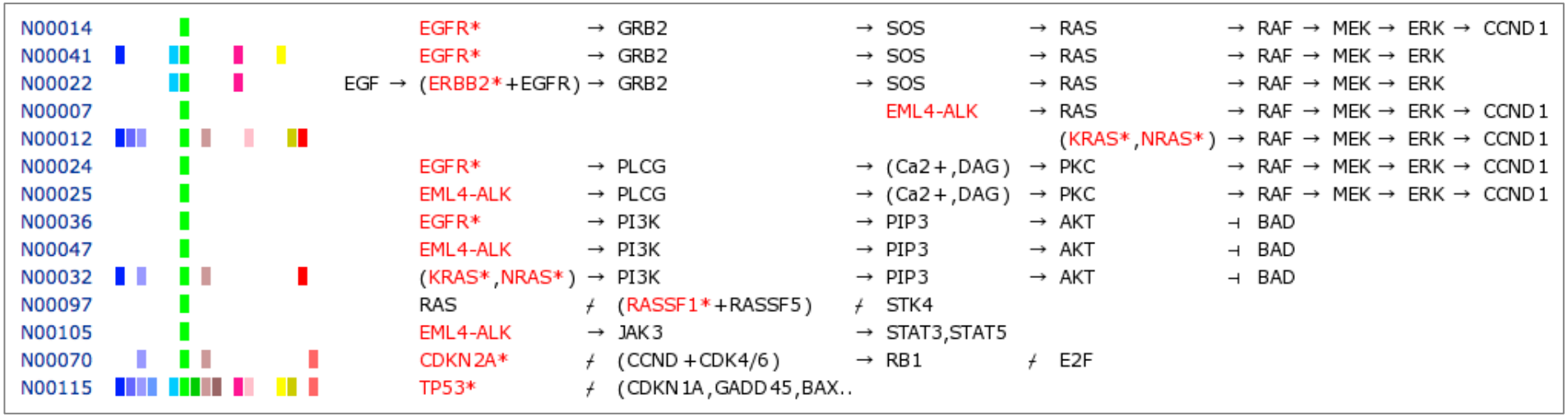
KEGG PATHWAY: Database of molecular networks

Basic network	1. Metabolism
	2. Genetic information processing
	3. Environmental information processing
Cell-level network	4. Cellular processes
Organism-level network	5. Organismal systems
Perturbed network	6. Human diseases



KEGG NETWORK: Details of perturbed molecular networks

Network elements defined from KEGG pathway map for non-small cell lung cancer

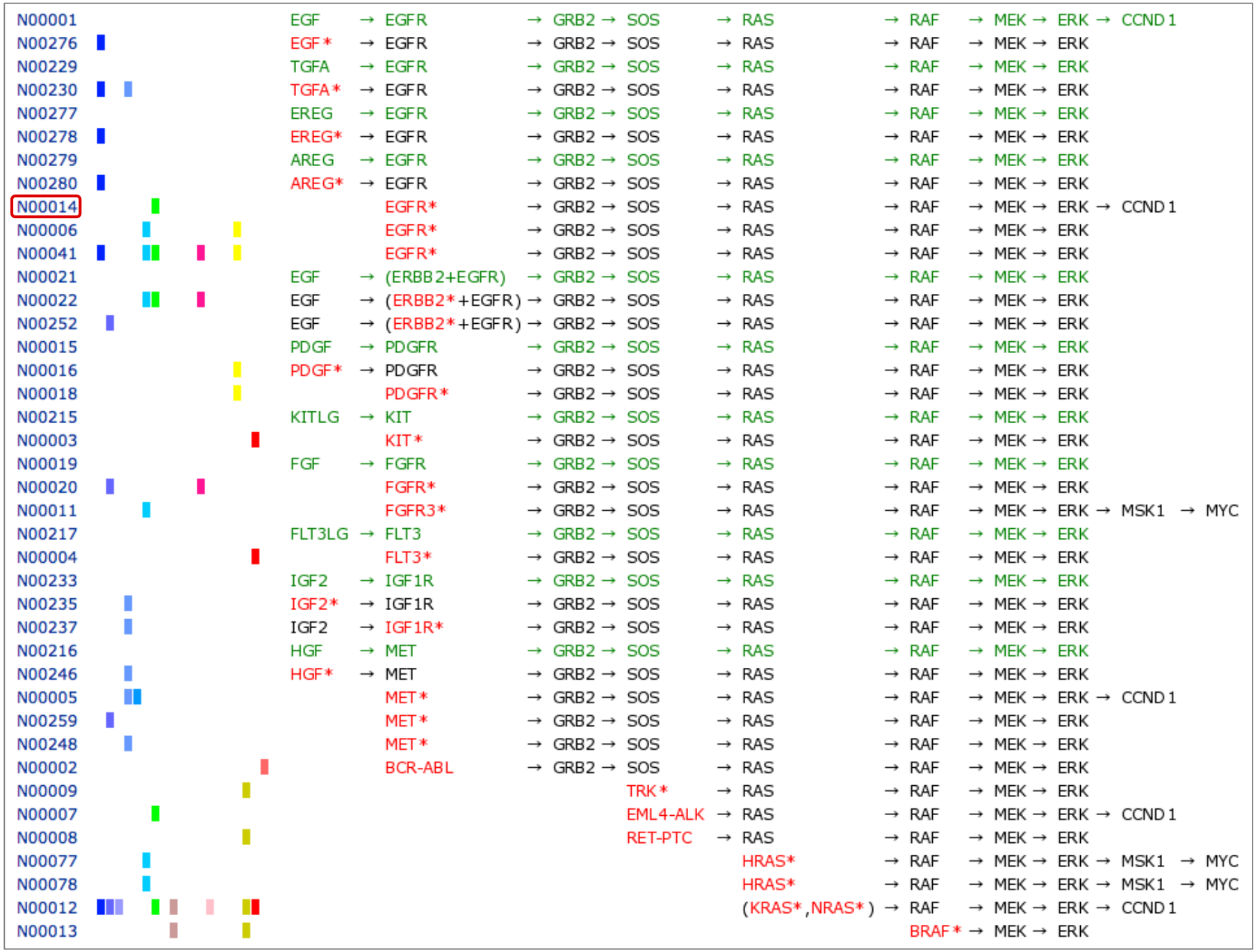


Cancer types

Node	Identifier	Coloring
Human reference gene	hsa ID	None
Human gene variant	variant ID	Red
Viral protein	K number	Purple
Chemical compound	C number	None
Drug	D number	Blue

Edge	Text	Symbol
Activation (single- or multi-step)	->	→
Inhibition (single- or multi-step)	-|	⊣
Complex formation	--	—
Missing interaction	//	⊬
Expression (single-step)	=>	⇒
Repression (single-step)	=|	⇥

Network variation map – Cancer network – MAPK (ERK) signaling



Network element entry – EGFR mutation-activated MAPK(ERK) signaling

KEGG **NETWORK: N00014**

Help

Entry	N00014 Network
Name	Mutation-activated EGFR to RAS-ERK signaling pathway
Definition	EGFR* -> GRB2 -> SOS -> RAS -> RAF -> MEK -> ERK -> CCND1
Expanded	(1956v2,1956v3) -> 2885 -> (6654,6655) -> (3265,3845,4893) -> (369,673, 5894) -> (5604,5605) -> (5594,5595) -> 595
Class	Cancer network; Signaling network; 06210 MAPK (ERK) signaling
Type	Variant
Pathway	hsa05223 Non-small cell lung cancer
Disease	H00014 Non-small cell lung cancer
Gene	1956 EGFR; epidermal growth factor receptor 2885 GRB2; growth factor receptor bound protein 2 6654 SOS1; SOS Ras/Rac guanine nucleotide exchange 6655 SOS2; SOS Ras/Rho guanine nucleotide exchange 3265 HRAS; HRas proto-oncogene, GTPase 3845 KRAS; KRAS proto-oncogene, GTPase 4893 NRAS; NRAS proto-oncogene, GTPase 369 ARAF; A-Raf proto-oncogene, serine/threonine ki 673 BRAF; B-Raf proto-oncogene, serine/threonine ki 5894 RAF1; Raf-1 proto-oncogene, serine/threonine k 5604 MAP2K1; mitogen-activated protein kinase kinas 5605 MAP2K2; mitogen-activated protein kinase kinas 5594 MAPK1; mitogen-activated protein kinase 1 5595 MAPK3; mitogen-activated protein kinase 3 595 CCND1; cyclin D1
Variant	1956v2 EGFR mutation in non-small cell lung cancer 1956v3 First generation TKI-resistant EGFR mutation
Reference	PMID:12379883
Authors	Osada H, Takahashi T.
Title	Genetic alterations of multiple tumor suppressors an carcinogenesis and progression of lung cancer.
Journal	Oncogene 21:7421-34 (2002) DOI:10.1038/sj.onc.1205802
Reference	PMID:12867060
Authors	Hirsch FR, Scagliotti GV, Langer CJ, Varella-Garcia
Title	Epidermal growth factor family of receptors in prene cancer: perspectives for targeted therapies.
Journal	Lung Cancer 41 Suppl 1:S29-42 (2003) DOI:10.1016/S0169-5002(03)00137-5
LinkDB	All DBs

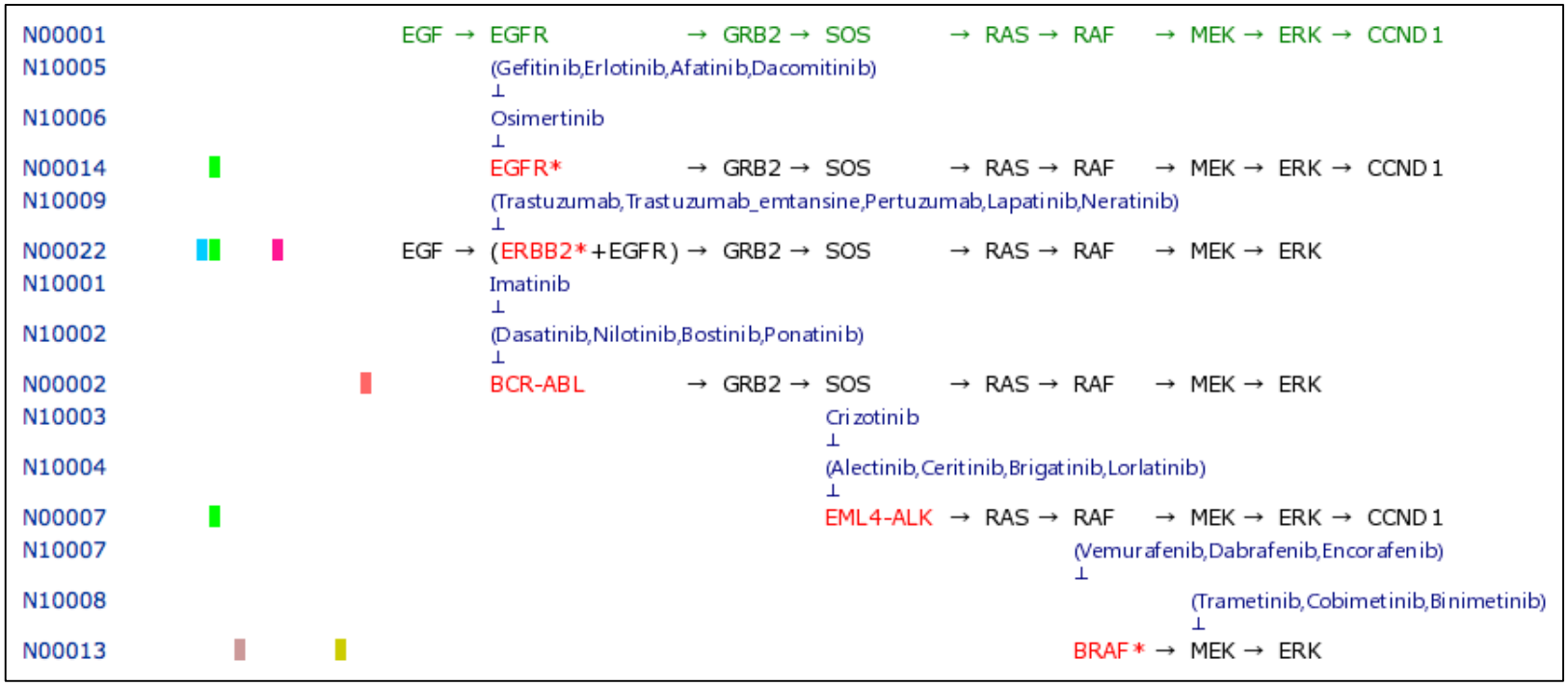
Variant entry - EGFR mutation in NSCLC

KEGG **VARIANT: 1956v2**

Help

Entry	1956v2 Variant
Name	EGFR mutation in non-small cell lung cancer
Gene	EGFR epidermal growth factor receptor [KO:K04361]
Organism	hsa_var Human gene variants (Homo sapiens)
Variation	exon 19 deletion
Variation	mutation L858R ClinVar: 16609 376282 376280 dbSNP: 121434568 1057519848 1057519847
Network	N00014 Mutation-activated EGFR to RAS-ERK signaling pathway N00024 Mutation-activated EGFR to PLCG-ERK signaling pathway N00036 Mutation-activated EGFR to PI3K signaling pathway N10005 First/second-generation tyrosine kinase inhibitor to EGFR mutation
Reference	PMID:21850578
Authors	Toyooka S, Mitsudomi T, Soh J, Aokage K, Yamane M, Oto T, Kiura K, Miyoshi S
Title	Molecular oncology of lung cancer.
Journal	Gen Thorac Cardiovasc Surg 59:527-37 (2011) DOI:10.1007/s11748-010-0743-3
Reference	PMID:28167215
Authors	Lee DH
Title	Treatments for EGFR-mutant non-small cell lung cancer (NSCLC): The road to a success, paved with failures.
Journal	Pharmacol Ther 174:1-21 (2017) DOI:10.1016/j.pharmthera.2017.02.001
LinkDB	All DBs

Drug targets involving gene variants



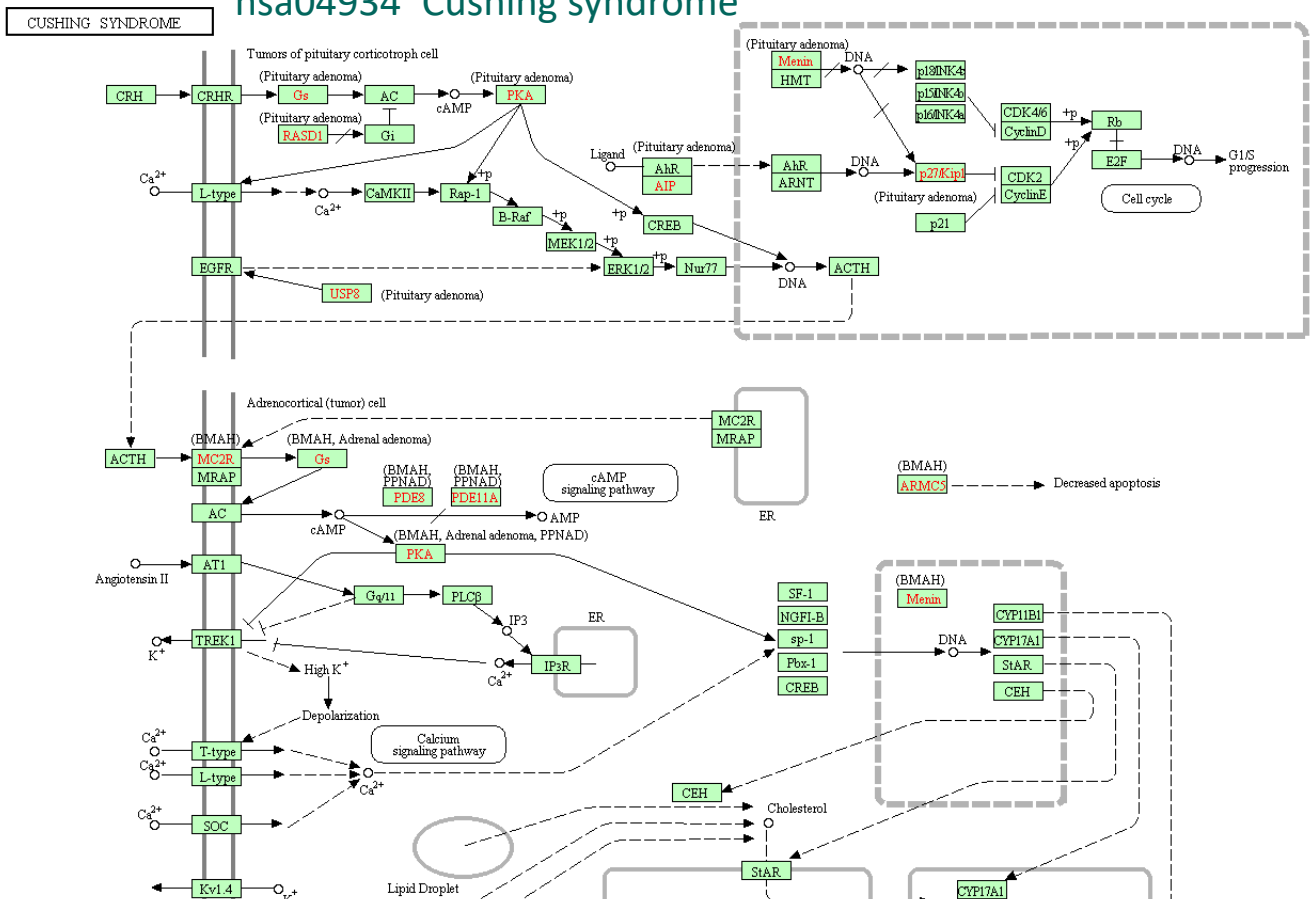
Similar perturbations caused by human gene variant and viral oncoprotein

N00001	EGF	→	EGFR	→	GRB2	→	SOS	→	RAS	→	RAF	→	MEK	→	ERK	→	CCND1
N00007							EML4-ALK	→	RAS	→	RAF	→	MEK	→	ERK	→	CCND1
N00160							kshvK1	→	RAS	→	RAF	→	MEK	→	ERK		
N00023	EGF	→	EGFR	→	PLCG	→	(Ca2+,DAG)	→	PKC	→	RAF	→	MEK	→	ERK	→	CCND1
N00025			EML4-ALK	→	PLCG	→	(Ca2+,DAG)	→	PKC	→	RAF	→	MEK	→	ERK	→	CCND1
N00147	EGF	→	EGFR	→	PLCG	→	IP3	→	Ca2+	→	CALM	—	CN	→	NFAT		
N00180			kshvK1	→	PLCG2	→	IP3	→	Ca2+	→	CALM	—	CN	→	NFAT		
N00033	EGF	→	EGFR	→	PI3K	→	PIP3	→	AKT	⊣	BAD						
N00047			EML4-ALK	→	PI3K	→	PIP3	→	AKT	⊣	BAD						
N00159			kshvK1	→	PI3K	→	PIP3	→	AKT	→	MTOR						
N00053	Cytokine	→	Receptor	→	JAK	→	STAT	⇒	PIM1								
N00105			EML4-ALK	→	JAK3	→	STAT3,STAT5										

Endocrine network – CRH-ACTH-Cortisol network

N00324	CRH	→	CRHR	→	GNAS	→	ADCY	→	cAMP	→	PKA	→	CREB	→	ACTH
N00325			RASD1*	⊣	GNAI	⊣	ADCY	→	cAMP	→	PKA	→	CREB	→	ACTH
N00326					GNAS*	→	ADCY	→	cAMP	→	PKA	→	CREB	→	ACTH
N00327	CRH	→	CRHR	→	GNAS	→	ADCY	→	cAMP	→	(PRKAR1A*+PRKACA)	→	CREB	→	ACTH
N00318											EGFR	→	ERK1/2	→	ACTH
N00319									USP8*	→	EGFR	→	ERK1/2	→	ACTH
N00297	ACTH	→	(MC2R+MRAP)	→	GNAS	→	ADCY	→	cAMP	→	PKA	→	(NR5A1,NR4A1,SP1,P..	⇒	(STAR,CYP11B1)	→	Cortisol
N00321					GNAS*	→	ADCY	→	cAMP	→	PKA	→	(NR5A1,NR4A1,SP1,P..	⇒	(STAR,CYP11B1)	→	Cortisol
N00323							(PDE11A*,PDE8B*)	⊣	cAMP	→	(PRKAR1A+PRKACA)	→	(NR5A1,NR4A1,SP1,P..	⇒	(STAR,CYP11B1)	→	Cortisol
N00320											PRKACA*	→	(NR5A1,NR4A1,SP1,P..	⇒	(STAR,CYP11B1)	→	Cortisol
N00322											(PRKAR1A*+PRKACA)	→	(NR5A1,NR4A1,SP1,P..	⇒	(STAR,CYP11B1)	→	Cortisol

hsa04934 Cushing syndrome



ACTH dependent

ACTH independent PRKACA

Summary

KEGG NETWORK is a knowledge base of

Network–disease associations
- Cancers
- Endocrine and metabolic diseases
- Viral infections
- Bacterial infections
- Immune system diseases
- Nervous system diseases

Perturbants of cell signaling networks
- Human gene variants
- Drugs
- Viral proteins
- Bacterial effectors and toxins

Perturbants of metabolic networks
- Germline mutations
- Other variants

KEGG NETWORK may be used for

Basic understanding of disease mechanisms and
Practical applications in drug target discovery and precision medicine