バイオサイエンスデータベースセンター統合化推進プログラム
「ゲノム・疾患・医薬品のネットワークデータベース」

ネットワークによる
ゲノム・疾患・医薬品の統合

京都大学化学研究所

金久　實

2018年10月5日　トーゴーの日シンポジウム

KEGG: Kyoto Encyclopedia of Genes and Genomes

Basic understanding
of biological systems

Practical applications
for use in society

- Cellular organisms
  - Eukaryotes
    - Animals
      - *Homo sapiens*
        - Variant groups
        - .....
    - Plants
    - Fungi
    - Protists
  - Prokaryotes
    - Bacteria
    - Archaea

Genome, Metagenome, Metabolome,
Transcriptome, Proteome

Personal genome
Pathogen genome

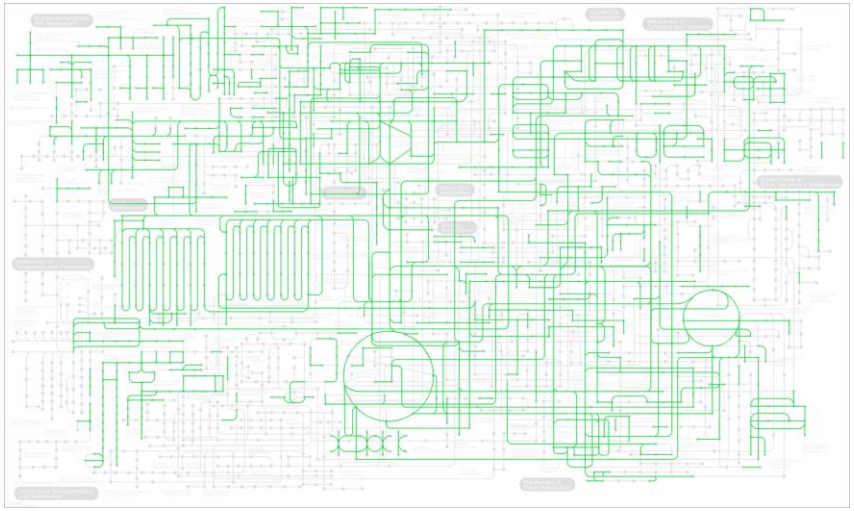
https://www.kegg.jp/

https://www.genome.jp/kegg/

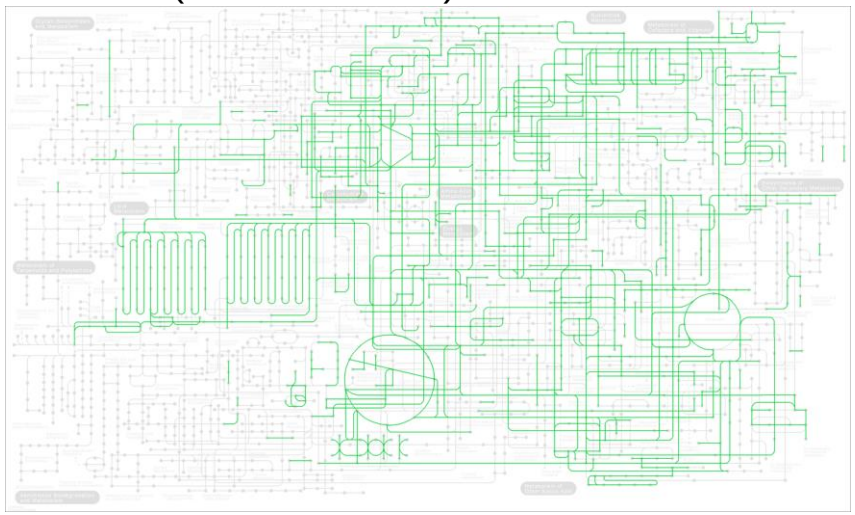
Blueprints of life

- Genetic blueprint – molecules (parts) encoded in the genome
- Chemical blueprint – molecular networks (wiring diagrams) encoded in the cell

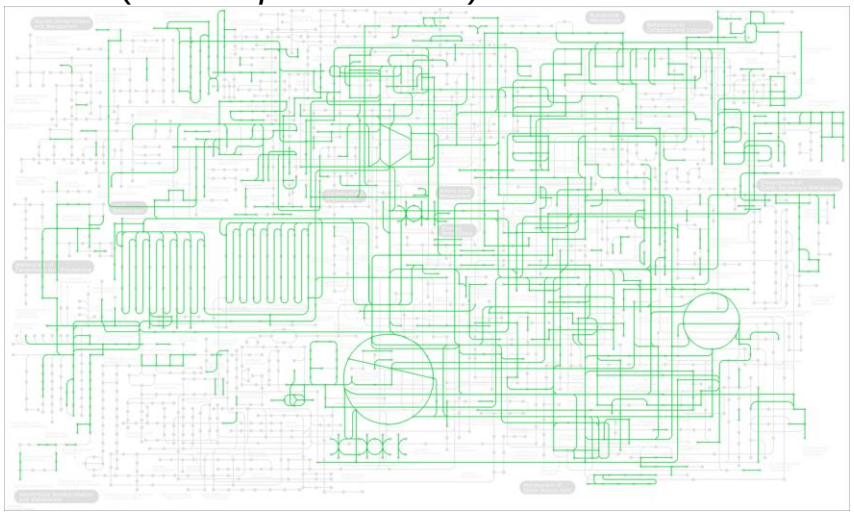
Animal (*Homo sapiens*)



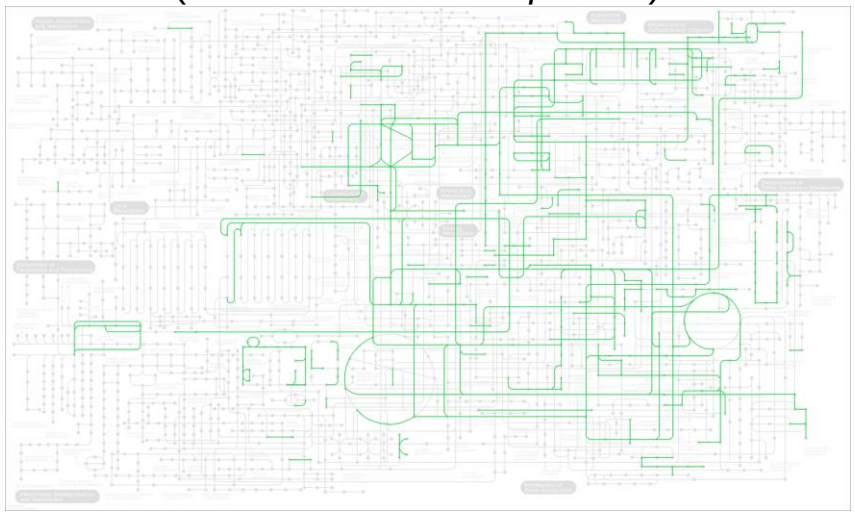
Bacteria (*Escherichia coli*)



Plant (*Arabidopsis thaliana*)



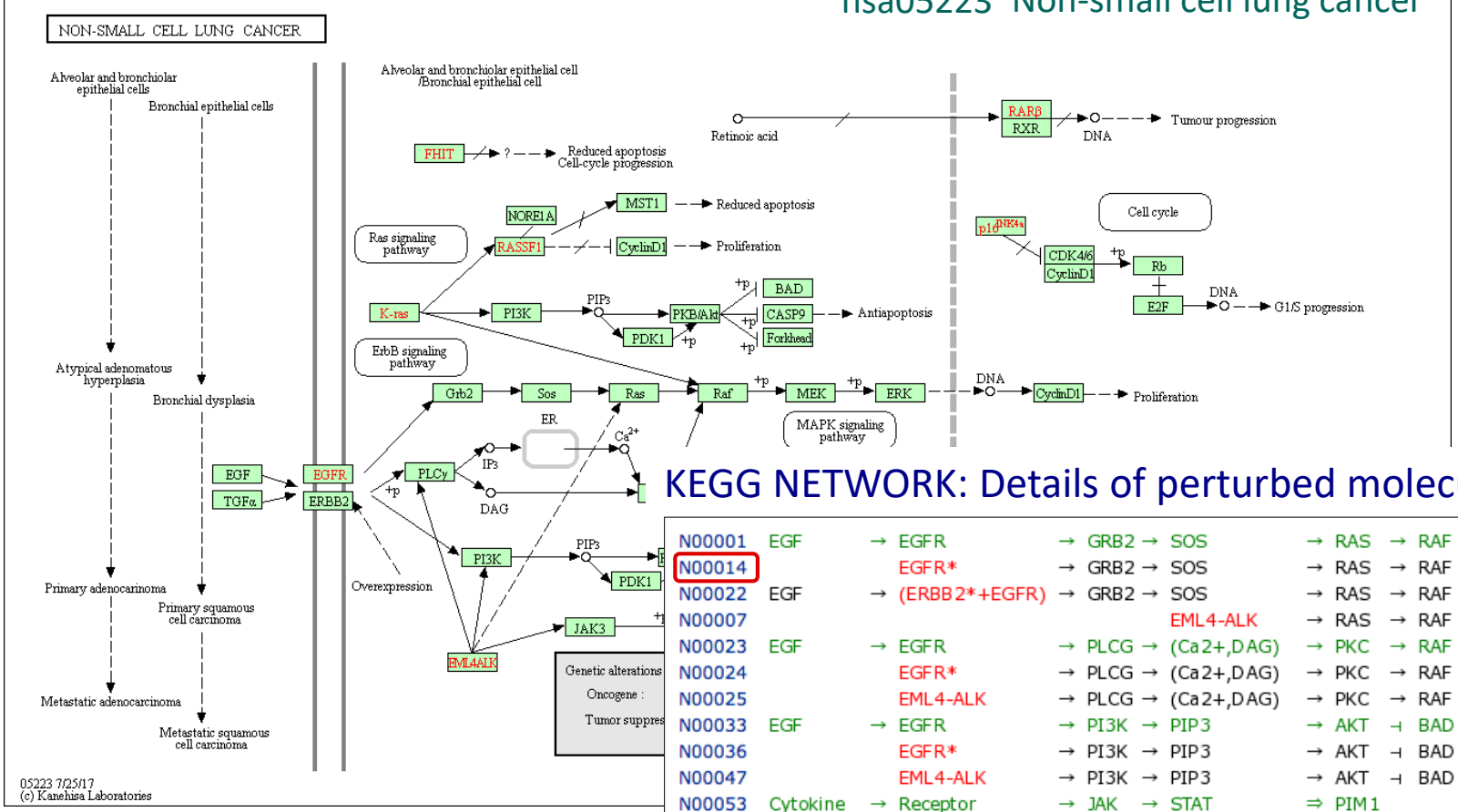
Archaea (*Methanococcus maripaludis*)



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

hsa05223 Non-small cell lung cancer



KEGG NETWORK: Details of perturbed molecular networks

N00001	EGF	→	EGFR	→	GRB2	→	SOS	→	RAS	→	RAF	→	MEK	→ ERK → CCND1
N00014			EGFR*	→	GRB2	→	SOS	→	RAS	→	RAF	→	MEK	→ ERK → CCND1
N00022	EGF	→	(ERBB2*+EGFR)	→	GRB2	→	SOS	→	RAS	→	RAF	→	MEK	→ ERK
N00007							EML4-ALK	→	RAS	→	RAF	→	MEK	→ ERK → CCND1
N00023	EGF	→	EGFR	→	PLCG	→	(Ca2+,DAG)	→	PKC	→	RAF	→	MEK	→ ERK → CCND1
N00024			EGFR*	→	PLCG	→	(Ca2+,DAG)	→	PKC	→	RAF	→	MEK	→ ERK → CCND1
N00025			EML4-ALK	→	PLCG	→	(Ca2+,DAG)	→	PKC	→	RAF	→	MEK	→ ERK → CCND1
N00033	EGF	→	EGFR	→	PI3K	→	PIP3	→	AKT	⊣	BAD			
N00036			EGFR*	→	PI3K	→	PIP3	→	AKT	⊣	BAD			
N00047			EML4-ALK	→	PI3K	→	PIP3	→	AKT	⊣	BAD			
N00053	Cytokine	→	Receptor	→	JAK	→	STAT	⇒	PIM1					
N00105			EML4-ALK	→	JAK3	→	STAT3,STAT5							

Network Element Entry

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 factor 1 6655 SOS2; SOS Ras/Rho guanine nucleotide exchange f 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 kin 673 BRAF; B-Raf proto-oncogene, serine/threonine kin 5894 RAF1; Raf-1 proto-oncogene, serine/threonine k 5604 MAP2K1; mitogen-activated protein kinase kinase 5605 MAP2K2; mitogen-activated protein kinase kinase 5594 MAPK1; mitogen-activated protein kinase 1 5595 MAPK3; mitogen-activated protein kinase 3 595 CCND1; cyclin D1
Variant	1956v2 EGFR mutation 1956v3 First generation TKI-resistant EGFR mutation
Reference	PMID:12379883
Authors	Osada H, Takahashi T.
Title	Genetic alterations of multiple tumor suppressors and 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 M
Title	Epidermal growth factor family of receptors in preneo 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

VARIANT: 1956v2

Help

Entry	1956v2 Variant
Name	EGFR mutation
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

KEGG NETWORK database
Collection of network elements + Network variation maps

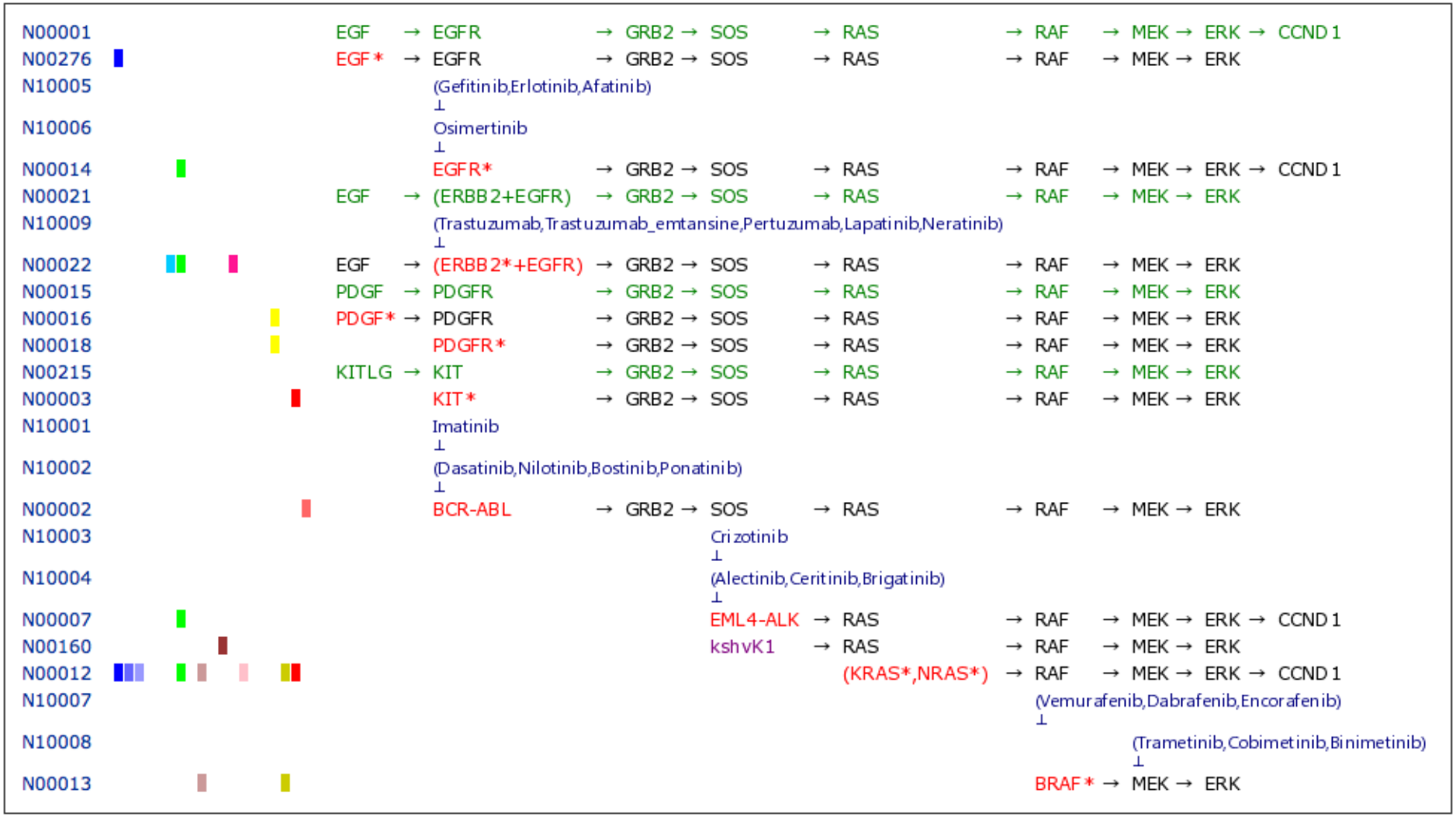
Nodes and edges of network elements

Node	Identifier	Coloring
Human reference gene/protein	hsa ID	None
Human gene variant	variant ID	Red
Viral or other pathogen gene/protein	K number	Purple
Metabolite and other chemical compound	C number	None
Drug	D number	Blue

Edge		Text	Symbol
Signaling network	Metabolic network		
Activation (single- or multi-step)	Enzymatic reaction	->	$\rightarrow$
Inhibition (single- or multi-step)		-|	$\dashv$
Complex formation	Substrate binding	--	—
Missing interaction	Missing reaction	//	$\not\rightarrow$
Expression (single-step)	Enhanced reaction	=>	$\Rightarrow$
Repression (single-step)		=|	$\Rightarrow\!\!\dashv$

Coloring of nodes and symbol representation of edges are used in network variation maps

KEGG NETWORK: Cancer Network



Cancer types

Reference network

Perturbations: gene variants, viral proteins, drugs

KEGG NETWORK: Virus Network (1)
Viral Oncoprotein

KSHV (Kaposi sarcoma-associated herpesvirus) K1 protein
in comparison with
EML4-ALK fusion gene in non-small cell lung cancer

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									

KEGG NETWORK: Virus Network (2)
Viral Mimicry

Chemokines and chemokine receptors

KSHV vCCL1, vCCL2, vCCL3
KSHV vGPCR

N00401		CXCL12	→	CXCR4	→	GNAQ	→	(PLCB,PLCG..	→	IP3	→	Ca2+	→	CALM	−	CN	→	NFAT	
N00432		hivEnv	→	(CXCR4,CCR..	→	GNAQ	→	PLCG	→	IP3	→	Ca2+	→	CALM	−	CN	→	NFAT	
N00402				hcmvUS28	→	GNAQ	→	PLCB	→	IP3	→	Ca2+	→	CALM	−	CN	→	NFAT	⇒ (CXCL8,PTG..
N00407				hcmvUL33	→	(GNAQ,GNA1..	→	PLCB											
N00410		DA	→	DRD1	→	GNAS	→	ADCY5	→	cAMP	→	PKA	→	CREB					
N00411				hcmvUL33	→	GNAS	→	ADCY	→	cAMP	→	PKA	→	CREB					
N00403		CX3CL1	→	CX3CR1	→	GNAI	⊣	ADCY	→	cAMP	→	PKA							
N00404				hcmvUS28	→	(GNAI,GNAO..	⊣	ADCY	→	cAMP	→	PKA							
N00412				hcmvUL33	→	(GNAI,GNAO..	⊣	ADCY	→	cAMP	→	PKA	→	CREB					
N00430		CXCL12	→	CXCR4	→	GNAI	→	PI3K	→	PIP3	→	AKT	⊣	BAD					
N00431		hivEnv	→	(CXCR4,CCR..	→	GNAI	→	PI3K	→	PIP3	→	AKT	⊣	BAD					
N00405		CXCL12	→	CXCR4	→	GNA12/13	→	(ARHGEF12,..	→	RHOA	→	ROCK1/2							
N00406		(CCL2,CCL3..	→	hcmvUS28	→	GNA12/13	→	(ARHGEF12,..	→	RHOA	→	ROCK1/2	→	CTNNB1					
N00408		LPA	→	LPAR	→	GNB/G	→	RHOA											
N00409				hcmvUL33	→	GNB/G	→	RHOA	→	MAP2K6	→	p38	→	CREB					
N00152		CXCL8	→	CXCR2	→	GNB/G	→	RAS	→	RAF1	→	MEK	→	ERK					
N00157				kshvGPCR	→	GNB/G	→	RAS	→	RAF1	→	MEK	→	ERK	→	(HIF1A,FOS..	⇒	(VEGFA,PDG..	
N00433		CXCL12	→	CXCR4	→	GNB/G	→	RAC	→	PAK	→	LIMK1	→	CFL					
N00434		hivEnv	→	(CXCR4,CCR..	→	GNB/G	→	RAC	→	PAK	→	LIMK1	→	CFL					
N00399		CCL2	→	CCR2	→	GNB/G	→	PI3K	→	PIP3	→	AKT	→	IKK	→	NFKBIA	→	NFKB	
N00400				hcmvUS28	→	GNB/G	→	PI3K	→	PIP3	→	AKT	→	IKK	→	NFKBIA	→	NFKB	⇒ (IL6,CXCL8..
N00153		(CC,CXC)	→	(CCR,CXCR)	→	GNB/G	→	PI3Kgamma	→	PREX1	→	RAC1							
N00462		(kshvCCL1,..	→	(CCR3,CCR4..															
N00212		kshvCCL2	⊣	(CCR1,CCR5..															
N00178				kshvGPCR	→	GNB/G	→	PI3Kgamma	→	PREX1	→	RAC1	→	JNK	→	(NFKB1+REL..	⇒	(IL6,CXCL8..	
N00154		CXCL8	→	CXCR2	→	GNB/G	→	PI3Kgamma	→	PIP3	→	AKT	→	MTOR					
N00427		hcmvCXCL1	→	CXCR2															
N00158				kshvGPCR	→	GNB/G	→	PI3Kgamma	→	PIP3	→	AKT	→	MTOR					
N00413		CXCL12	→	CXCR4	→	GNB/G	→	PLCB	→	(Ca2+,DAG)	→	PKC	→	PTK2B	→	(PTK2+BCAR..			
N00414								hcmvUS27	→	Ca2+	→	PKC	→	PTK2B	→	(PTK2+BCAR..			
N00428		CCL5	→	CCR5	→	GNB/G	→	PLCB	→	(Ca2+,DAG)	→	PKC							
N00429	hcmvUL22A	⊣	CCL5																

KEGG NETWORK: Endocrine Network

CRH-ACTH-Cortisol network

N00297	ACTH	→	(MC2R+MRAP)	→	GNAS	→	ADCY	→	cAMP	→	PKA	→	(NR5A1,NR4A1,SP1,P..	⇒	(STAR,CYP11B1)	→	Cortisol
N00299	ACTH	≠	(MC2R*+MRAP)	≠	GNAS												
N00300	ACTH	≠	(MC2R+MRAP*)	≠	GNAS												
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
N00298	ACTH	→	(MC2R+MRAP)	→	GNAS	→	ADCY	→	cAMP	→	PKA	→	(NR5A1,NR4A1,SP1,P..	⇒	CYP11B2*	→	Aldosterone
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		
N00306									NR0B1	⊣	NR5A1	⇒	(CYP11B1,CYP17A1)				
N00307									NR0B1*	≠	NR5A1	⇒	(CYP11B1,CYP17A1)				
N00308									NR0B1	⊣	NR5A1*	≠	(CYP11B1,CYP17A1)				
N00339	Cholesterol	−	CYP11A1	→	Pregnenolone	−	(HSD3B+CYP21A2+CYP..	→	Aldosterone								
N00338	Cholesterol	−	CYP11A1	→	Pregnenolone	−	(HSD3B+CYP17A1+CYP..	→	Cortisone	−	HSD11B	→	Cortisol				
N00309									(Cortisone+NADPH)	−	HSD11B	→	(Cortisol+NADP+)				
N00310									Cortisone	≠	HSD11B1*	≠	Cortisol				
N00311					NADP	−	H6PD	→	NADPH								
N00312					NADP	≠	H6PD*	≠	NADPH								
N00313											SERPINA6	−	Cortisol				
N00314											SERPINA6*	≠	Cortisol				

Cushing syndrome

視床下部　CRH (Corticotropin releasing hormone)

↓

下垂体　ACTH (Corticotropin)

↓

副腎　Cortisol

過剰分泌　ACTH 依存性

ACTH 非依存性　PRKACA

Sato Y, et al. Recurrent somatic mutations underlie corticotropin-independent Cushing's syndrome. Science 344:917-920 (2014).

ICD-11 を公開

ICD-11 による疾患分類

[Brite menu | Download htext | Download json]

ICD-11 による疾患分類 Go

One-click mode

- 01 Certain infectious or parasitic diseases
  - Gastroenteritis or colitis of infectious origin
    - Bacterial intestinal infections
      - 1A00 Cholera
        - H00110 コレラ
      - 1A01 Intestinal infection due to other Vibrio
        - H00307 腸炎ビブリオ感染症
        - H00308 ビブリオ・パルニフィカス感染症
      - 1A02 Intestinal infections due to Shigella
        - H00299 細菌性赤痢
      - 1A03 Intestinal infections due to Escherichia coli
        - H00278 腸管病原性大腸菌感染症
        - H00280 腸管毒素原性大腸菌感染症
        - H01311 腸管組織侵襲性大腸菌感染症
        - H00277 腸管出血性大腸菌感染症
        - H01312 腸管凝集性大腸菌感染症
      - 1A04 Enterocolitis due to Clostridium difficile
        - H00338 偽膜性大腸炎
      - 1A05 Intestinal infections due to Yersinia enterocolitica
        - H00298 エルシニア感染症
      - 1A06 Gastroenteritis due to Campylobacter
        - H00321 カンピロバクター感染症
      - 1A07 Typhoid fever
        - H00111 腸チフス
      - 1A08 Paratyphoid Fever
        - H00112 パラチフス
      - 1A09 Infections due to other Salmonella
        - H00113 サルモネラ感染症
      - 1A0Y Other specified bacterial intestinal infections
        - H01454 結腸スピロヘータ症
      - 1A0Z Bacterial intestinal infections, unspecified
    - Bacterial foodborne intoxications
      - 1A10 Foodborne staphylococcal intoxication
        - H01175 ブドウ球菌感染症
      - 1A11 Botulism
        - H00339 ボツリヌス中毒症
      - 1A12 Foodborne Clostridium perfringens intoxication
        - H00335 ウェルシュ菌食中毒
      - 1A13 Foodborne Bacillus cereus intoxication
        - H00329 セレウス菌食中毒
      - 1A1Y Other specified bacterial foodborne intoxications
        - H00300 エンテロバクター感染症
      - 1A1Z Bacterial foodborne intoxications, unspecified

jp08403

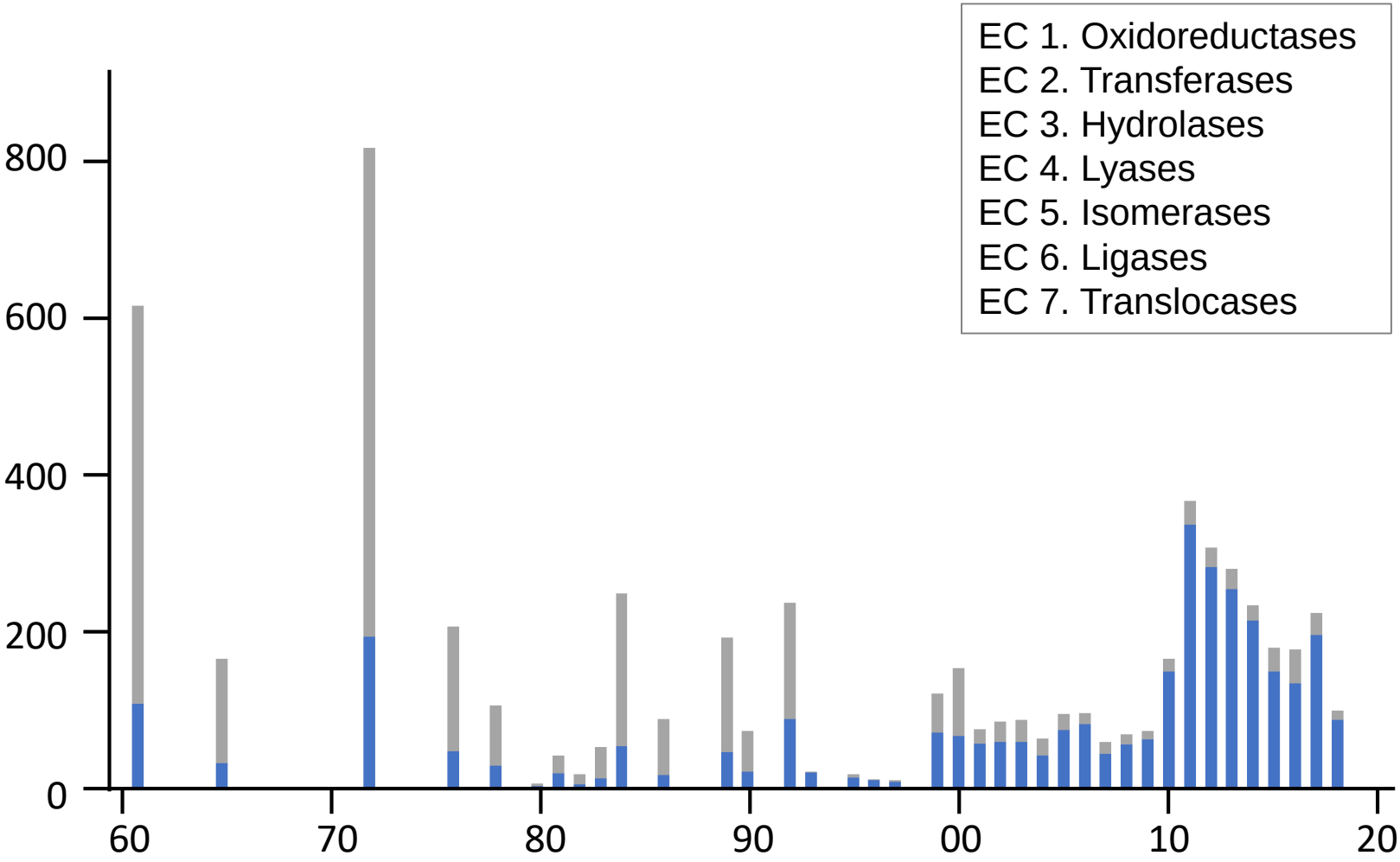
DISEASE: コレラ

Help

エントリ	H00110
名称	コレラ
概要	コレラはコレラ菌（Vibrio cholerae）を病原体とする腸管感染症である。コレラ毒素を産生するコレラ菌のほとんどはO1血清型であるが、O139血清型も知られている。1817年以来これまでに7回コレラの世界的な流行があり、6回目まではインドから、1961の7回目はインドネシアから広がった。最後の流行はEl Torと名づけられたO1血清型の新しいバリアントによるもので、これは現在も続いている。O139血清型は1992年にインドで見いだされたが、世界的な流行には至っていない。
カテゴリ	感染症
階層分類	感染症疾患 [BR:jp08401] 細菌感染症 その他のガンマプロテオバクテリアによる感染症 H00110 コレラ ICD-11 による疾患分類 [BR:jp08403] 01 Certain infectious or parasitic diseases Gastroenteritis or colitis of infectious origin Bacterial intestinal infections 1A00 Cholera H00110 コレラ 感染症法による感染症分類 [jp08406.html] H00110 BRITE hierarchy
パスウェイ	hsa05110 コレラ菌感染
病原体	Vibrio cholerae O1 [GN:vch vcf vcs vce vcq vcj vci vco vcr vcm]
モジュール	M00852 Vibrio cholerae pathogenicity signature, toxin coregulated pilus M00850 Vibrio cholerae pathogenicity signature, cholera toxins
治療薬	レボフロキサシン水和物 [DR:D00588] ドキシサイクリン塩酸塩水和物 [DR:D02129]
リンク	ICD-11: 1A00 ICD-10: A00 MeSH: D002771 MedlinePlus: 000303
文献	PMID:7704895
著者	Kaper JB, Morris JG Jr, Levine MM
タイトル	Cholera.
雑誌	Clin Microbiol Rev 8:48-86 (1995)

H00110

EC番号について



引用文献より実験を行った酵素のアミノ酸配列が判明したものの割合を青で示した