
Genomic overview of protein kinases*

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Abstract

Protein kinases are one of the largest and most influential of gene families: constituting some 2% of the proteome, they regulate almost all biochemical pathways and may phosphorylate up to 30% of the proteome. Bioinformatics and comparative genomics were used to determine the *C. elegans* kinome and put it in evolutionary and functional context. Kinases are deeply conserved in evolution, and the worm has family homologs for over 80% of the human kinome. Almost half of the 438 worm kinases are members of worm-specific or worm-expanded families. Such radiations include genes involved in spermatogenesis, chemosensation, Wnt signaling and FGF receptor-like kinases. The *C. briggsae* kinome is largely similar apart from the expanded classes, showing that such expansions are evolutionarily recent.

1. Introduction

Protein kinases constitute one of the largest and most important of protein families, accounting for ~2% of genes in a variety of eukaryotic genomes. By phosphorylating substrate proteins, kinases modify the activity, location and affinities of up to 30% of all cellular proteins, and direct most cellular processes, particularly in signal transduction and co-ordination of complex pathways. Many of these pathways are highly conserved, and 53 distinct kinase functions and subfamilies appear to have been conserved between yeasts, nematodes, insects and vertebrates, with a further 91 subfamilies of kinases being seen throughout metazoan genomes. This makes kinase signaling particularly amenable to comparative studies, and kinase activity a particularly good readout of the physiological state of any cell.

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This chapter will introduce the diversity of kinases in *C. elegans*, and compare them to those of fungi and other metazoans, as well as to preliminary results from analysis of the *C. briggsae* kinome.

2. The *C. elegans* kinome

Most protein kinases share a common ePK (eukaryotic protein kinase) catalytic domain, and can be identified by sequence similarity with Blast or profile hidden Markov models (HMMs). The remaining atypical protein kinases (aPK) belong to several families, some of which have structural, but not sequence similarity to ePKs. We used ePK and aPK HMMs, and Blast/psi-Blast with divergent kinase sequences, to identify protein kinase sequences in *C. elegans* genomic and expressed sequences (Manning et al., 2002; Plowman et al., 1999). We identified 438 protein kinase genes, including 20 atypical kinases, and an additional 25 kinase fragments or pseudogenes. All sequences and supporting data are available at <http://kinase.com>, and all but 8 sequences are now identical to wormpep (v. 141) sequences.

3. Kinase evolution

To put worm kinases into an evolutionary and functional context, we compared them with the distant kinomes of human, fly, and yeast. At these distances, 1:1 orthology is rare, so we classified each kinase into a hierarchy of groups, families, and sometimes subfamilies (Manning et al., 2002a; Manning et al., 2002b). The classification is based on sequence similarity within the kinase domain, the presence of additional domains, known biological functions, and conservation across divergent genomes. Across the four kinomes, there are 10 groups, 143 families and 212 subfamilies. The classification of each worm kinase is given in Appendix A.

Since kinases perform such a variety of distinct basic cellular functions, it is not surprising to see that 53 subfamilies and functions are present in all four kinomes (Figure 1). A further 91 subfamilies were found in all three metazoan kinomes, including the tyrosine kinase (TK) group and the TKL group, which mediate much of the complexity of intercellular signal transduction. The gain and loss of kinase functions and subfamilies in each evolutionary lineage is also seen. In general, the data support the coelomate clade, where insects are more closely related to vertebrates than to nematodes, rather than the ecdysozoa clade, which groups insects and nematodes together.

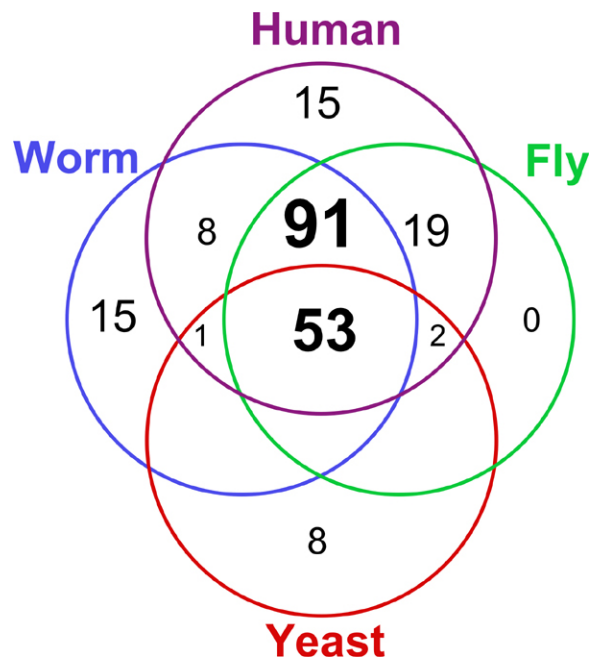


Figure 1. Distribution of 212 kinase subfamilies throughout four kinomes: the yeast *Saccharomyces cerevisiae*, the nematode worm *Caenorhabditis elegans*, the fruit fly *Drosophila melanogaster* and human.

Nematodes share 153 subfamilies with human, providing close homologs for 81% (419/518) of all human kinases. 6 families appear to have been lost from nematodes, based on their presence in fly, human and more basal

organisms (Table 1), and several new families have been invented within the coelomate lineage, whose functions predominantly map to immunity/angiogenesis, neurobiology, cell cycle and morphogenesis. There are 13 such human-specific families, and 16 shared between fly and human.

Table 1. Kinases lost in worm, or gained in fly or human kinomes.

Group	Family	Subfamily	Fly count	Human count	Function	Notes
Secondarily lost from worm						
Atypical	G11		1	1	Unknown	Also in yeast and plants
CAMK	CAMKL	PASK	1	1	Glucose sensor	Also in yeast
Other	TTK		1	1	Cell cycle	Also in yeast and plants
Atypical	PIKK	DNAPK	1	1	DNA repair	Also in Dictyostelium
Atypical	TIF		1	3	Transcriptional control	Also in Dictyostelium. NHR co-factor
TK	CCK4		1	1	Neuronal; cell growth	Also in Hydra. Neuronal pathfinding; cancer
Fly + Human						
CAMK	Trbl		1	3	Cell cycle	
CMGC	CDK	CDK10	1	1	Cell cycle?	
Other	IKK		2	4	Immunity	NFkb signaling
Other	MOS		1	1	Cell cycle	Meiosis
Other	SLOB		2	1	Neuronal	Synaptic transmission
Other	TOPK		1	1	Cell cycle	
STE	Ste20	NinaC	1	2	Neuronal	Phototransduction
TK	Jak		1	4	Immunity	Cytokine signaling
TK	Musk		1	1	Neuronal	Synaptic transmission
TK	PDGFR/ VEGFR		2	8	Angiogenesis; morphogenesis; immunity	
TK	Ret		1	1	Immunity, development	Growth factor receptor
TK	Sev		1	1	Morphogenesis	
TK	Syk		1	2	Immunity; morphogenesis	
TK	Tec		1	5	Immunity; morphogenesis	
TKL	LISK	LIMK	1	2	Cytoskeletal	
TKL	LISK	TESK	1	2	Testis development	
Human						
Atypical	Alpha	ChaK	0	2	Neuronal	Human adds kinase to metazoan-wide channel
Atypical	BCR		0	1	Cell growth	Ras/MAPK growth factor responses
Atypical	FAST		0	1	Apoptosis	
Atypical	H11		0	1	Apoptosis?	
CAMK	CAMKL	HUNK	0	1	Development	Mammary gland development
CAMK	Trio		0	6	Muscle	Human adds kinase to conserved protein

Group	Family	Subfamily	Fly count	Human count	Function	Notes
Other	NKF3		0	2	Unknown	
Other	NKF4		0	2	Cytoskeletal	
Other	NKF5		0	2	Testis development?	
TK	Axl		0	3	Cell growth; adhesion	
TK	Lmr		0	3	Cell growth?	
TK	Tie		0	2	Angiogenesis	
TKL	RIPK		0	5	Immunity	

On the other hand, the worm shares eight subfamilies with human which are absent from *Drosophila* (Table 2). These include two receptor tyrosine kinase families, an atypical elongation factor 2 kinase (eEF2K), several members of the CAMK group (MELK, PSK, PIM) and the HH498 subfamily of Mixed Lineage Kinases (MLK). In some but not all cases, the fly genome has related genes that may fulfill a similar function. SGK, eEF2K and HH498 are found in *Dictyostelium*, and ABC1-C in yeast, reinforcing their secondary loss from insects. The secondary loss of conserved kinases within each lineage highlights how essential functions are dependent on the context of other genes and pathways in the organism.

Table 2. Kinase subfamilies shared by worm and human, but not fly.

Group	Family	Subfamily	Worm genes	Human genes	Notes
AGC	SGK		1	3	Close relative to the AKT (PKB) family
Atypical	ABC1	ABC1-C	1	1	Other ABC1 subfamilies may compensate.
Atypical	MHCK	eEF2K	1	1	Eukaryotic elongation factor 2 kinase.
CAMK	CAMKL	MELK	1	1	MELK is an outgroup of MARK, which is present in fly. Splicing function?
CAMK	PSK		1	2	Human PSKH1 has a Golgi function.
CAMK	PIM		2	3	Related to PASK, which is present in fly and absent from worm.
TKL	MLK	HH498	1	1	Human form is cardiac-specific, worm is neuronal- restricted. Divergent functions?
TK	Trk		1	3	Neurotrophin receptor. Fly has closely related Ror and Musk families.
TK	Met		2	2	Worm has a clear Met homolog and a divergent family member.

4. Recent expansions and inventions in the worm kinome

The *C. elegans* kinome is also marked by a dramatic expansion of a small number of kinase classes. *C. elegans* has almost twice as many kinases as *Drosophila* (438 vs. 241 genes), but virtually all the difference (195 of 197 genes) is accounted for by expansions of a small number of families and of worm-specific families.

Fifteen kinase subfamilies are nematode-specific, accounting for almost a quarter of the kinome (105 genes). They include 8 distinct subfamilies within a large expansion of CK1 group kinases, containing 78 kinases, and two FGFR-like receptor tyrosine kinase families. An additional 5 families are in the Other group, and have very little similarity to any non-worm kinases. In general, they are not well characterized.

Table 3. Worm-specific and worm-expanded kinase classes. Counts of genes in kinomes. *C. briggsae* data from unpublished analysis of genome-predicted peptides.

Name/Classification	<i>C. elegans</i>	<i>C. briggsae</i>	Fly	Human
CK1/Dual	3	3	0	0
CK1/TTBKL	31	22	0	0
CK1/Worm6	28	19	0	0
CK1/Worm7	2	1	0	0
CK1/Worm8	3	1	0	0
CK1/Worm9	2	0	0	0
CK1/Worm10	2	2	0	0
CK1/Worm11	1	2	0	0
CK1/Unique	6	3	0	0
TK/Fer	38	24	1	2
RGC group	27	20	6	5
TK/KIN-16	16	6	0	0
Other/Haspin	13	1	1	1
CMGC/GSK3	7	6	3	2
CAMK/CAMKL/CHK1	7	1	1	1
Ste/Ste7	10	8	4	7
CMGC/MAPK/Jnk	5	3	1	3
TK/KIN-9	5	5	0	0
Other/Worm1	2	1	0	0
Other/Worm2	3	2	0	0
Other/Worm3	2	1	0	0
Other/Worm4	1	1	0	0
Other/Worm5	3	0	0	0
Total	217	132	17	21

These kinases may hold a key to several nematode-specific biological functions. In several cases, the expansions appear recent, as the members are closely related by sequence and chromosomal location, and several appear to have been generated since the *C. elegans/C. briggsae* split. Many may have reduced or no function: several have lost catalytic or other conserved residues and 20 of the 25 worm kinase pseudogenes are from these families, indicating a high rate of gene turnover. A similar expansion is seen in *C. briggsae*, and though it appears that this is more modest, some of this may be due to the preliminary nature of the annotation and kinase analysis of this genome.

Reproductive functions often drive rapid evolution, and there is some evidence implicating kinase expansions in nematode spermatogenesis. One CK1 gene (*spe-6*) and one Fer gene (*spe-8*) function in spermatogenesis, and half or more of these classes are selectively expressed in sperm by microarray analysis (Muhlrad and Ward, 2002; Reinke et al., 2000; P. Muhlrad and S. Ward, pers. commun.).

Receptor guanylate cyclases (RGC) have a catalytically inactive kinase domain, and have separately expanded in all three metazoans, but most dramatically in worm (Morton, 2004). Most are uncharacterized, but several are expressed in highly restricted sets of neurons and are implicated in chemosensation, and one (*daf-11*) is involved in dauer formation (Vowels and Thomas, 1992).

The KIN-9 (previously known as *kin-6*) and KIN-16 families encode receptor tyrosine kinases, whose kinase domains and overall structure most resemble the FGF receptor family. Some of the KIN-16 family have arrays of extracellular immunoglobulin repeats, and some have vestigial extracellular regions (Popovici et al., 1999), while KIN-6 members have diverse novel extracellular regions. KIN-16 includes the *old-1* and *old-2* genes thought to be involved in age and stress resistance (Rikke et al., 2000). Many of the KIN-16 genes are chromosomally clustered, and are poorly conserved in *C. briggsae*, indicating a recent origin (Figure 2A). The KIN-9 genes are not clustered and all have *briggsae* orthologs.

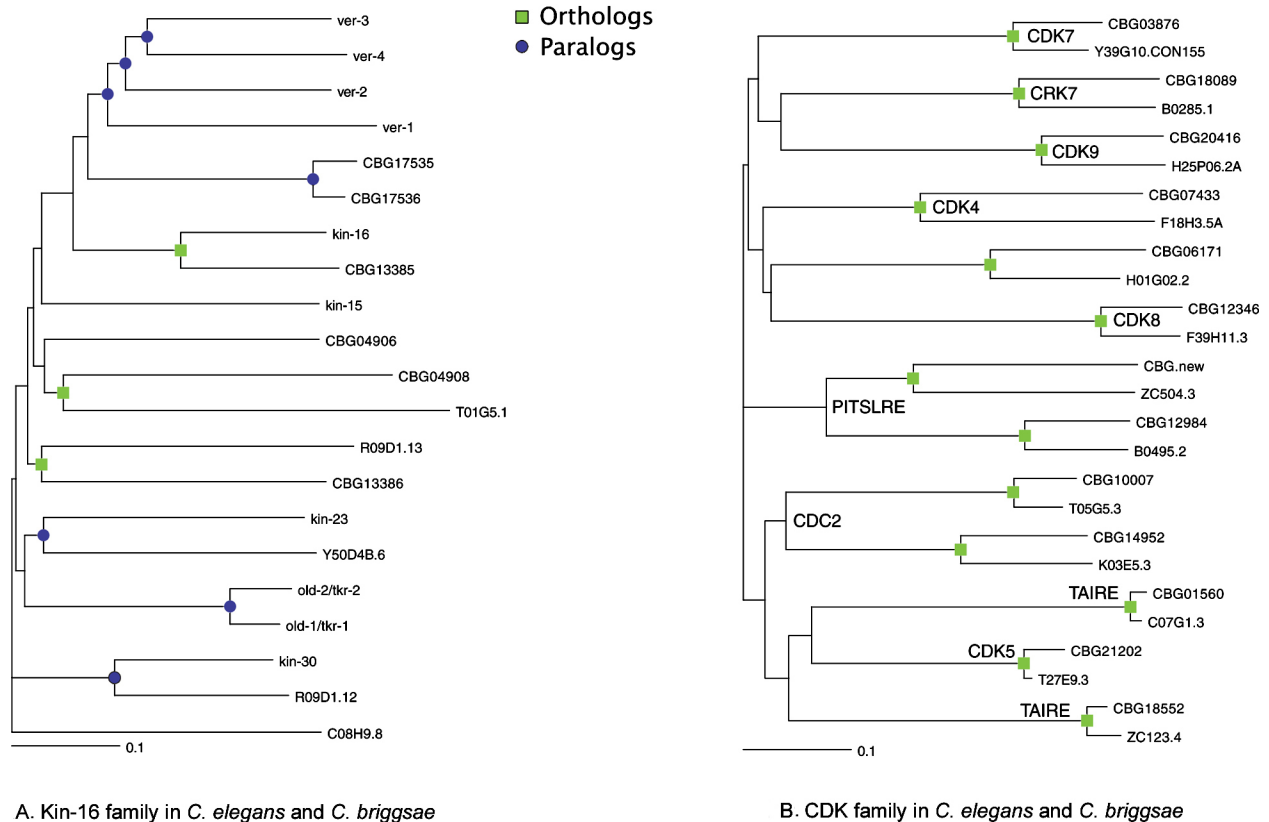


Figure 2. Orthology between *C. elegans* and *C. briggsae* kinases. Squares indicate likely orthologous pairs of kinases, and circles denote paralogous expansions. *C. briggsae* sequences are predictions (CBGnnnnn) from the genome project. (A) In the worm-specific KIN-16 family, new genes continue to arise in the *elegans* and *briggsae* lineages, as indicated by circles. (B) In the CDK family, all 13 members exist as orthologous pairs and subfamilies (labeled) are also conserved in *Drosophila* and human.

Of the 7 GSK3 members, 6 have clear *briggsae* homologs, but only one (*gsk-3*) has been characterized, and it acts in a defined Wnt signaling pathway (Schlesinger et al., 1999). The additional members may act in an expanded Wnt-like pathway, as worms have other duplicated pathway members including three members each of the beta-catenin and dishevelled families. Both CK1 and Fer kinases are implicated in mammalian Wnt signaling, and some of their worm expansions may also function in this pathway. The role of GSK3 in insulin signaling may also correlate with the expansion of insulin genes in nematodes.

The expansion of the Jnk stress-response MAPK family is partially paralleled by the expansion of the MAPKK (Ste7) family, which now includes 4 putative Jnk kinases (JNKs).

5. The *C. briggsae* kinome

A preliminary analysis of *C. briggsae* predicted proteins (release 25; Stein et al., 2003) indicates the presence of 341 kinase genes, using the *C. elegans* kinome as blast query set. An additional 30 or more kinases or kinase fragments were detected by direct search of the genome, but are still poorly predicted. The majority (320) of *C. briggsae* kinases appear orthologous to a single *C. elegans* kinase, by bidirectional blast searches. The main differences between the two kinomes are in the recently-expanded families, where the expansion appears to have continued since the *elegans/briggsae* split. Of 21 *briggsae*-unique kinases, 19 are from expanded families, and 98 of

117 *elegans*-unique kinases are from expanded families. More thorough sequence analysis will likely reveal more *briggsae* kinases and more ortholog pairs, but this data does strongly support both continued gene birth and death, and sequence diversification, within these expanded families. The difference between conserved and expanded families is shown in [Figure 2A](#) of the nematode-specific KIN-16 family, in which few pairs of obvious orthologs are seen between the two species. By contrast, the CDK family has 13 members in both species, all of which pair off in an orthologous fashion ([Figure 2B](#)).

6. Phosphatases

Phosphatases remove phosphates from kinase substrates, both reversing kinase-based activation, and relieving kinase-mediated repressions. Phosphatases belong to several different families, including a number of distinct phosphatase domains: the PTP (protein tyrosine phosphatase), DSP (dual-specificity phosphatase which dephosphorylates both tyrosine and serine/threonine) and several families of STP, or serine-threonine phosphatases. While ‘phosphatome’ analysis lags behind that of the kinomes, an initial survey of *C. elegans* phosphatases identified 83 PTPs, 26 DSPs and 65 STPs ([Plowman et al., 1999](#)). The completion of two nematode genomes and multiple other eukaryotic genomes now opens the door for comparative analysis to identify additional *C. elegans* phosphatases and to compare their distribution with those of other organisms, and with the expansions of their cognate kinomes.

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A. Appendix A: Classification of worm kinases

Table 4. Classification of worm kinases

Group	Family	Subfamily	# Kinases (domains)	Distribution	Names	Other Wormbook entries	Name/ function overview
AGC			2	Nematodes, Dictyostelium	F31E3.2, F28C10.3		
AGC	AKT		2	All kinomes	<i>akt-1, akt-2</i>		PI3K signaling
AGC	DMPK	GEK	1	All metazoans	K08B12.5		Myotonic dystrophy protein kinase
AGC	DMPK	ROCK	1	Metazoans, Dictyostelium	<i>let-502</i>		Myotonic dystrophy protein kinase/Rho kinase
AGC	GRK	BARK	1	All metazoans	<i>grk-2</i>		Beta adrenergic receptor kinase
AGC	GRK	GRK	1	All metazoans	<i>grk-1</i>		G protein coupled kinase
AGC	MAST		1	Metazoans, Dictyostelium	<i>kin-4</i>		Microtubule associated serine/threonine kinase
AGC	NDR		2	All kinomes	<i>sax-1</i> , T20F10.1		
AGC	PDK1		2	All kinomes	<i>pdk-1</i> , W04B5.5		PI3K signaling
AGC	PKA		2	All kinomes	<i>kin-1</i> , F47F2.1		cAMP-dependent protein kinase
AGC	PKC	Alpha	1	All metazoans	<i>pkc-2</i>		Protein kinase C isoforms
AGC	PKC	Delta	1	All metazoans	<i>tpa-1</i>		Protein kinase C isoforms
AGC	PKC	Eta	1	All metazoans	<i>kin-13</i>		Protein kinase C isoforms
AGC	PKC	Iota	1	All metazoans	<i>pkc-3</i>		Protein kinase C isoforms
AGC	PKG		2	All metazoans	<i>egl-4</i> , C09G4.2		cGMP-dependent protein kinase
AGC	PKN		1	All metazoans	F46F6.2		Protein kinase N
AGC	RSK	MSK	1	All metazoans	C54G4.1		Ribosomal S6 kinase
AGC	RSK	p70	2	Metazoans, fungi	Y43D4A.6, R04A9.5		Ribosomal S6 kinase
AGC	RSK	RSK	1	All metazoans	T01H8.1a		Ribosomal S6 kinase
AGC	RSKL		1	All metazoans	F55C5.7		Ribosomal S6 kinase-like
AGC	SGK		1	Nematodes,	W10G6.2		Serum/glucocor-

Group	Family	Subfamily	# Kinases (domains)	Distribution	Names	Other Wormbook entries	Name/ function overview
				vertebrates, dictyostelium			ticoid-regulated kinase
AGC	YANK		1	All metazoans	M03C11.1		Uncharacterized
Atypical	A6		2	All kinomes	<i>unc-60</i> , F38E9.5		
Atypical	ABC1	ABC1-A	1	All kinomes	C35D10.4		
Atypical	ABC1	ABC1-B	1	All kinomes	D2023.6		
Atypical	ABC1	ABC1-C	1	All but insects	Y32H12A.7		
Atypical	Alpha	eEF2K	1	Nematodes, vertebrates, dictyostelium	<i>efk-1</i>		Elongation factor 2 kinase
Atypical	BRD		3	Metazoans, Dictyostelium	Y119C1B.8, F57C7.1b, F13C5.2		Bromodo-main-containing kinase
Atypical	PDHK		2	Metazoans, fungi	ZK370.5, aSWK467		Pyruvate dehydrogenase kinase
Atypical	PIKK	ATM	1	Metazoans, fungi	<i>atm-1</i>		DNA damage response
Atypical	PIKK	ATR	1	All kinomes	<i>atl-1</i>		DNA damage response
Atypical	PIKK	FRAP	1	All kinomes	B0261.2		Metabolic regulation (aka TOR)
Atypical	PIKK	SMG1	1	Metazoans, Dictyostelium	<i>smg-1</i>		mRNA surveillance
Atypical	PIKK	TRRAP	1	All kinomes	C47D12.1		
Atypical	RIO	RIO1	1	All kinomes	M01B12.5		
Atypical	RIO	RIO2	1	All kinomes	Y105E8B.3		
Atypical	RIO	RIO3	1	All metazoans	ZK632.3		
Atypical	TAF1		1	All kinomes	<i>taf-1</i>		Basal transcription: TFIID associated factor.
CAMK	CAMK1		1	All kinomes	<i>cmk-1</i>		Calmodulin-dependent protein kinase 1
CAMK	CAMK2		1	All metazoans	<i>unc-43</i>		Calmodulin-dependent protein kinase 1
CAMK	CAMKL	AMPK	2	All kinomes	<i>aak-1</i> , <i>aak-2</i>		Metabolic regulation

Genomic overview of protein kinases

Group	Family	Subfamily	# Kinases (domains)	Distribution	Names	Other Wormbook entries	Name/ function overview
CAMK	CAMKL	BRSK	1	Metazoans, Dictyostelium	<i>sad-1</i>		Neuronal vesicle release
CAMK	CAMKL	CHK1	5 (7)	Metazoans, fungi	<i>chk-1</i> , Y43D4A.6, R02C2.1, R02C2.2, DC2.7		Cell cycle checkpoint kinase 1
CAMK	CAMKL	LKB	1	Metazoans, Dictyostelium	<i>par-4</i>		Activator of AMPK
CAMK	CAMKL	MARK	2	All kinomes	<i>par-1</i> , F23C8.8	Asymmetric cell division and axis formation in the embryo	Microtubule affinity regulating kinase
CAMK	CAMKL	MELK	1	Nematodes and vertebrates	W03G1.6		Maternal embryonic leucine zipper kinase
CAMK	CAMKL	NIM1	1	All metazoans	F49C5.4		
CAMK	CAMKL	NuaK	1	All metazoans	B0496.3		Uncharacterized
CAMK	CAMKL	QIK	1	Metazoans, Dictyostelium	<i>kin-29</i>		Qin induced kinase
CAMK	CAMKL	SNRK	1	All metazoans	ZK524.4		
CAMK	CASK		1	All metazoans	<i>lin-2</i>		
CAMK	DAPK		1	All metazoans	K12C11.4		Death-associated protein kinase
CAMK	DCAMKL		2	All metazoans	<i>zyg-8</i> , F32D8.1		Doublecortin and CAMK-like
CAMK	MAPK-APK	MAPK-APK	2	All metazoans	K08F8.1, C44C8.6		MAPK activated protein kinase
CAMK	MAPK-APK	MNK	1	All metazoans	R166.5		MAPK activated protein kinase
CAMK	MLCK		4 (5)	All metazoans	<i>unc-22</i> , C24G7.5, ZC373.4, F12F3.2		Myosin light chain kinase
CAMK	PHK		1	All metazoans	Y50D7A.3		Phosphorylase kinase
CAMK	PIM		2	Nematodes and vertebrates	<i>prk-1</i> , <i>prk-2</i>		
CAMK	PKD		2	All metazoans	T25E12.4, W09C5.5		Protein kinase D

Genomic overview of protein kinases

Group	Family	Subfamily	# Kinases (domains)	Distribution	Names	Other Wormbook entries	Name/ function overview
CAMK	PSK		1	Nematodes and vertebrates	R06A10.4		Protein serine kinase
CAMK	RAD53		2	Metazoans, fungi	<i>chk-2</i> , T08D2.7		DNA damage checkpoint
CAMK	RSKb	MSKb	0(1)	All metazoans	C54G4.1		Second domain of RSK kinases
CAMK	RSKb	RSKb	0(1)	All metazoans	T01H8.1a		Second domain of RSK kinases
CAMK	TSSK		3	All metazoans	B0511.4, W02B12.12, Y38H8A.4		Testis-specific serine kinase
CK1	Unique		6	Some metazoans	T15B12.2, ZK507.3, C25H3.1, F16B12.5, ZK507.1, K09E4.1		
CK1	CK1	CK1-A	1	All metazoans	C03C10.1		Cell kinase 1/Casein kinase 1
CK1	CK1	CK1-D	1	All kinomes	F46F2.2		Cell kinase 1/Casein kinase 1
CK1	CK1	CK1-G	1	Metazoans, fungi	Y106G6E.6		Cell kinase 1/Casein kinase 1
CK1	Dual		3 (6)	Nematodes	F59A6.4, T05A7.6, H05L14.1		Dual-domain CK1 kinase subfamily
CK1	TTBK		1	Metazoans, Dictyostelium	R90.1		Tau tubulin kinase
CK1	TTBKL		31	Nematodes	M7.7, B0207.7, F35C11.3, Y71F9AL.2, C04G2.2, C45G9.1, F32B6.10, W01B6.2, C05C12.1, C49C8.1, Y73B6A.2, D2024.1, Y47G6A.13, F54H5.2, C56C10.6, C53A5.4, K06H7.8, D2045.5, W09C3.1, R10D12.10, T11F8.4, ZC581.2,		Tau tubulin kinase-like

Group	Family	Subfamily	# Kinases (domains)	Distribution	Names	Other Wormbook entries	Name/ function overview
					T05C12.1, W06F12.3, C03C10.2, T19D12.5, ZK666.8, ZK354.6, F26A1.4, C14A4.13, W03G9.5		
CK1	VRK		1	All metazoans	F28B12.3		Vaccinia-related kinase
CK1	Worm10		2	Nematodes	F26A1.3, F25F2.1		Uncharacterized
CK1	Worm11		1	Nematodes	K11C4.1		Uncharacterized
CK1	Worm6		28	Nematodes	Y38H8A.3, C39H7.1, ZK596.2, C50F4.10, C08F8.6, F36H12.8, R13H9.5, Y69F12A.1, B0218.5, F36H12.9, R13H9.6, T09B4.7, C09D4.3, C55B7.10, F41G3.5, F38E1.3, C27D8.1, Y39G8C.2, F53C3.1, F33D11.7, C34B2.3, C49C3.2, <i>spe-6</i> , C09B9.4, ZK354.2, Y65B4A.9, F59E12.3, C38C3.4		Uncharacterized
CK1	Worm7		2	Nematodes	T01H10.4, ZC373.3		Uncharacterized
CK1	Worm8		3	Nematodes	F22F1.2, F39F10.3, F39F10.2		Uncharacterized
CK1	Worm9		2	Nematodes	K04C1.5, E02H4.6		Uncharacterized
CMGC			1	Nematodes, fungi	F52B5.2		
CMGC	CDK		1	Metazoans, fungi	H01G02.2		Cyclin dependent kinase

Genomic overview of protein kinases

Group	Family	Subfamily	# Kinases (domains)	Distribution	Names	Other Wormbook entries	Name/ function overview
CMGC	CDK	CDC2	2	All kinomes	<i>cdk-1</i> , K03E5.3		Cell cycle: cyclin dependent kinase
CMGC	CDK	CDK4	1	All metazoans	<i>cdk-4</i>		Cell cycle: cyclin dependent kinase
CMGC	CDK	CDK5	1	All metazoans	<i>cdk-5</i>		Cyclin dependent kinase
CMGC	CDK	CDK7	1	All kinomes	<i>cdk-7</i>		Cell cycle: cyclin dependent kinase
CMGC	CDK	CDK8	1	All kinomes	F39H11.3		Cell cycle: cyclin dependent kinase
CMGC	CDK	CDK9	1	All metazoans	H25P06.2		Cell cycle: cyclin dependent kinase
CMGC	CDK	CRK7	1	All kinomes	B0285.1		Cell cycle: cyclin dependent kinase
CMGC	CDK	PITSLRE	2	Metazoans, Dictyostelium	ZC504.3, B0495.2		Cell cycle: cyclin dependent kinase
CMGC	CDK	TAIRE	2	All metazoans	<i>pct-1</i> , ZC123.4		Cell cycle: cyclin dependent kinase
CMGC	CDKL		1	All metazoans	Y42A5A.4		Cyclin dependent kinase-like
CMGC	CLK		3	All kinomes	C16A11.3, Y111B2A.1, E02H4.3		CDC-like kinase, involved in splicing
CMGC	Dyrk	Dyrk1	1	Metazoans, Dictyostelium	<i>mbk-1</i>		
CMGC	Dyrk	Dyrk2	3	Metazoans, Dictyostelium	<i>mbk-2</i> , C36B7.1, C36B7.2		
CMGC	Dyrk	HIPK	1	All metazoans	<i>hpk-1</i>		Hypoxia-inducible protein kinase
CMGC	Dyrk	PRP4	1	Metazoans, Dictyostelium	F22D6.5		mRNA processing
CMGC	GSK		7	All kinomes	<i>gsk-3</i> , R03D7.5, Y106G6D.4, C44H4.6, Y106G6E.1, C36B1.10, F21F3.2		Glycogen synthase kinase 3
CMGC	MAPK		3	Some metazoans	W06B3.2, F09C12.2, C04G6.1		
CMGC	MAPK	Erk	1	All kinomes	<i>mpk-1</i>	RTKRas/ MAP kinase signaling	Growth factor response MAPK
CMGC	MAPK	Erk7	1	Metazoans,	C05D10.2		Variant MAPK

Group	Family	Subfamily	# Kinases (domains)	Distribution	Names	Other Wormbook entries	Name/ function overview
				Dictyos- telium			
CMGC	MAPK	Jnk	5	All metazoans	<i>jnk-1</i> , T07A9.3, Y51B9A.9, ZC416.4, C49C3.10	Signaling in the immune response	Stress-response MAPK
CMGC	MAPK	nmo	1	All metazoans	<i>lit-1</i>		Variant MAPK
CMGC	MAPK	p38	3	Metazoans, fungi	<i>pmk-1</i> , <i>pmk-2</i> , <i>pmk-3</i>		Stress-response MAPK
CMGC	RCK		1	All kinomes	M04C9.5		
CMGC	SRPK		1	All kinomes	<i>spk-1</i>		mRNA splicing
Other	Unique		10	All kinomes	<i>flr-4</i> , <i>zyg-1</i> , Y106G6A.1, D2045.7, K09A9.1, Y53F4B.1, K11H12.9, K02E10.7, F37E3.3, C29H12.5		
Other	Aur		2	All kinomes	<i>air-1</i> , <i>air-2</i>		Cell cycle/chromosomal stability
Other	Bub		1	All kinomes	<i>bub-1</i>		Cell cycle
Other	Bud32		1	All kinomes	F52C12.2		Essential homolog of yeast Bud32.
Other	CAMKK	Meta	1	Metazoans, Dictyos- telium	<i>ckk-1</i>		CAMK kinase
Other	CDC7		1	All kinomes	C34G6.5		Variant cyclin-dependent kinase
Other	CK2		1	All kinomes	B0205.7		Cell kinase 2/Casein kinase 2
Other	Haspin		13	All kinomes	Y18H1A.10, K08B4.5, C50H2.7, T05E8.2, ZK177.2, H12I13.1, Y48B6A.10, C01H6.9, F22H10.5, C04G2.10, Y40A1A.1, Y73B6A.1, aSWK457		Nuclear kinase; meiosis?
Other	IRE		1	All kinomes	<i>ire-1</i>		Unfolded protein response

Group	Family	Subfamily	# Kinases (domains)	Distribution	Names	Other Wormbook entries	Name/ function overview
Other	Nak		2	All kinomes	<i>sel-5</i> , F46G11.3		
Other	Nek		4	All kinomes	F19H6.1, ZC581.1, Y39G10AR.3, pqn-25,		Cell cycle (NIMA-related kinase)
Other	NKF1		1	All metazoans	C01C4.3		Uncharacterized
Other	NKF2		1	All metazoans	EEED8.9		Uncharacterized
Other	NRBP		1	All metazoans	K10D3.5		Nuclear receptor binding protein
Other	PEK	GCN2	1	All kinomes	Y81G3A.3		
Other	PEK	PEK	2	Metazoans, Dictyostelium	<i>pek-1</i> , Y38E10A.8		
Other	PLK		3	All kinomes	<i>plk-1</i> , <i>plk-2</i> , F55G1.8		Cell cycle: polo-like kinase
Other	SCY1		2	All kinomes	W07G4.3, ZC581.9		
Other	TBCK		1	Metazoans, Dictyostelium	C33F10.2		TBC domain kinase
Other	TLK		1	All metazoans	C07A9.3		Tousled-like kinase
Other	ULK		2	All kinomes	<i>unc-51</i> , T07F12.4		Homolog of <i>Drosophila</i> Fused
Other	VPS15		1	All kinomes	ZK930.1		
Other	WEE		2	All kinomes	<i>wee-1.1</i> , <i>wee-1.3</i>		Cell cycle
Other	Wnk		1	All metazoans	C46C2.1		With no lysine[K]
Other	Worm1		2	Nematodes	<i>mes-1</i> , B0198.3		Uncharacterized
Other	Worm2		3	Nematodes	K09C6.8, T10B5.2, K09C6.7		Uncharacterized
Other	Worm3		2	Nematodes	R107.4, Y39G8B.5		Uncharacterized
Other	Worm4		1	Nematodes	C28A5.6		Uncharacterized
Other	Worm5		3	Nematodes	C44C10.7, F16B12.7, K08H2.5		Uncharacterized
RGC	RGC		27	All metazoans	<i>gcy-13</i> , <i>gcy-14</i> , <i>odr-1</i> , <i>gcy-19</i> , <i>gcy-15</i> , <i>gcy-9</i> , <i>daf-11</i> , T01A4.1b, <i>gcy-4</i> , <i>gcy-17</i> , <i>gcy-3</i> , <i>gcy-7</i> , C04H5.4a,		Receptor guanylate cyclase

Group	Family	Subfamily	# Kinases (domains)	Distribution	Names	Other Wormbook entries	Name/ function overview
					<i>gcy-11, gcy-18, gcy-25, gcy-21, gcy-27, gcy-23, gcy-1, gcy-20, gcy-5, gcy-6, gcy-8, gcy-22, gcy-2, gcy-12</i>		
STE	Unique		1	Metazoans, Dictyostelium	F18F11.4		
STE	Ste11		2	All kinomes	<i>nsy-1</i> , B0414.7		MAP kinase kinase kinase
STE	Ste20	FRAY	1	Metazoans, Dictyostelium	Y59A8B.23		MAP4 kinase and related
STE	Ste20	KHS	1	All metazoans	ZC404.9		Subfamily of MAP4K kinases
STE	Ste20	MSN	1	All metazoans	ZC504.4		Subfamily of MAP4K kinases
STE	Ste20	MST	1	All kinomes	F14H12.4		Subfamily of MAP4K kinases
STE	Ste20	PAKA	2	All kinomes	C09B8.7, Y38F1A.1		Couples small GTPases to cytoskeleton
STE	Ste20	PAKB	1	All metazoans	C45B11.1		Couples small GTPases to cytoskeleton
STE	Ste20	SLK	1	All metazoans	C04A11.3		Subfamily of MAP4K kinases
STE	Ste20	STLK	2	All metazoans	C03B1.5, Y52D3.1		Subfamily of MAP4K kinases
STE	Ste20	TAO	1	All metazoans	T17E9.1		Subfamily of MAP4K kinases
STE	Ste20	YSK	1	Metazoans, fungi	T19A5.2		Subfamily of MAP4K kinases
STE	Ste7		10	All kinomes	<i>jkk-1, mek-1, mek-2, sek-1, mkk-4</i> , ZC449.6, VZC374L.1, E02D9.1a, F35C8.2, F35C8.1	RTKRas/ MAP kinase signaling	MAP kinase kinase
TK	Unique		7	All metazoans	C16D9.2, Y38H6C.20, F40A3.5, F59F5.3, R151.4, C34F11.5, T22B11.3		
TK	Abl		1	All	<i>abl-1</i>		Abelson

Group	Family	Subfamily	# Kinases (domains)	Distribution	Names	Other Wormbook entries	Name/ function overview
				metazoans			leukemia virus homolog
TK	Ack		2	All metazoans	<i>ark-1, kin-25</i>		
TK	Csk		1	All metazoans	Y48G1C.2		
TK	Fer		38	All metazoans	<i>frk-1, spe-8, kin-5, kin-14, kin-21, kin-24, kin-26, kin-28,</i> aSWK454, Y43C5B.2, Y116A8C.24, K09B11.5, Y52D5A.2, Y69E1A.3, T25B9.5, M176.9, ZC581.7, F59A3.8, R05H5.4, W01B6.5, T08G5.2, F57B9.8, T21G5.1, C25A8.5, T06C10.3, F22B3.8, F01D4.3, W03F8.2, ZK622.1, R11E3.1, T25B9.4, ZK593.9, F26E4.5, W03A5.1, C35E7.10, C55C3.4, C18H7.4, F23C8.7		
TK	Src		3	All metazoans	<i>src-1, src-2,</i> Y47G6A.5a		Non-receptor tyrosine kinase
TKL	IRAK		1	All metazoans	K09B11.1		IL-1 receptor associated kinase
TKL	LRRK		1	Metazoans, Dictyostelium	T27C10.5		Leucine rich repeat kinase
TKL	MLK	HH498	1	Nematodes, vertebrates, Dictyostelium	C24A1.3		Uncharacterized
TKL	MLK	ILK	1	All	C29F9.7		Integrin linked

Group	Family	Subfamily	# Kinases (domains)	Distribution	Names	Other Wormbook entries	Name/ function overview
				metazoans			kinase
TKL	MLK	LZK	1	All metazoans	F33E2.2		
TKL	MLK	MLK	2	Metazoans, Dictyostelium	Y58A7A.f, R13F6.7		Mixed lineage kinase
TKL	MLK	TAK1	2	All metazoans	F52F12.3, Y105C5.y		
TKL	RAF		3	All metazoans	<i>raf-1, pex-1, ksr-1</i>	RTKRas/ MAP kinase signaling	Ras-MAPK signaling
TKL	STKR	Type1	2	All metazoans	<i>sma-6, daf-1</i>	TGF- β signaling	TGF β and related receptors
TKL	STKR	Type2	1	All metazoans	<i>daf-4</i>	TGF- β signaling	TGF β and related receptors
TK-RTK	Alk		1	All metazoans	<i>scd-2</i>		
TK-RTK	DDR		2	All metazoans	F11D5.3, C25F6.4		Discoidin domain receptor.
TK-RTK	EGFR		1	All metazoans	<i>let-23</i>	RTKRas/ MAP kinase signaling	Growth factor (EGF) receptor
TK-RTK	Eph		1	All metazoans	<i>vab-1</i>		Ephrin receptor
TK-RTK	Fak		1	All metazoans	<i>kin-32</i>		Focal adhesion kinase
TK-RTK	FGFR		1	All metazoans	<i>egl-15</i>	RTKRas/ MAP kinase signaling	Growth factor (FGF) receptor
TK-RTK	InsR		1	All metazoans	<i>daf-2</i>		Insulin receptor
TK-RTK	KIN-16		15 (16)	Nematodes	<i>old-1, old-2, ver-1, R09D1.13, kin-23, T17A3.8, T01G5.1, C08H9.8, F59F3.1, M176.7, F59F3.5, M176.6, kin-30, R09D1.12, Y50D4B.6</i>		Uncharacterized
TK-RTK	KIN-9		5	Nematodes	F09G2.1, F09A5.2, C24G6.2, F08F1.1, B0252.1		Uncharacterized
TK-RTK	Met		2	Nematodes and vertebrates	F11E6.8, T14E8.1		Growth factor (HGF/SF) receptor
TK-RTK	Ror		1	All	<i>cam-1</i>		Receptor tyrosine

Genomic overview of protein kinases

Group	Family	Subfamily	# Kinases (domains)	Distribution	Names	Other Wormbook entries	Name/ function overview
				metazoans			kinase
TK-RTK	Ryk		1	All metazoans	C16B8.1		
TK-RTK	Trk		1	Nematodes and vertebrates	D1073.1		Neurotrophin receptor
TOTAL			438(447)				



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