The Human Kinome

Protein kinases are key regulators of cell function that constitute one of the largest and most functionally diverse of gene families. By adding phosphate groups to substrate proteins, they direct the activity, localization and overall function of up to 30% of all cellular proteins, and serve to orchestrate the activity of almost all cellular processes. Kinases are particularly prominent in signal transduction and co-ordination of complex functions such as cell cycle. If transcription changes mediate the long-term identity of cells, phosphorylation can be thought of as largely determining their short term physiology.

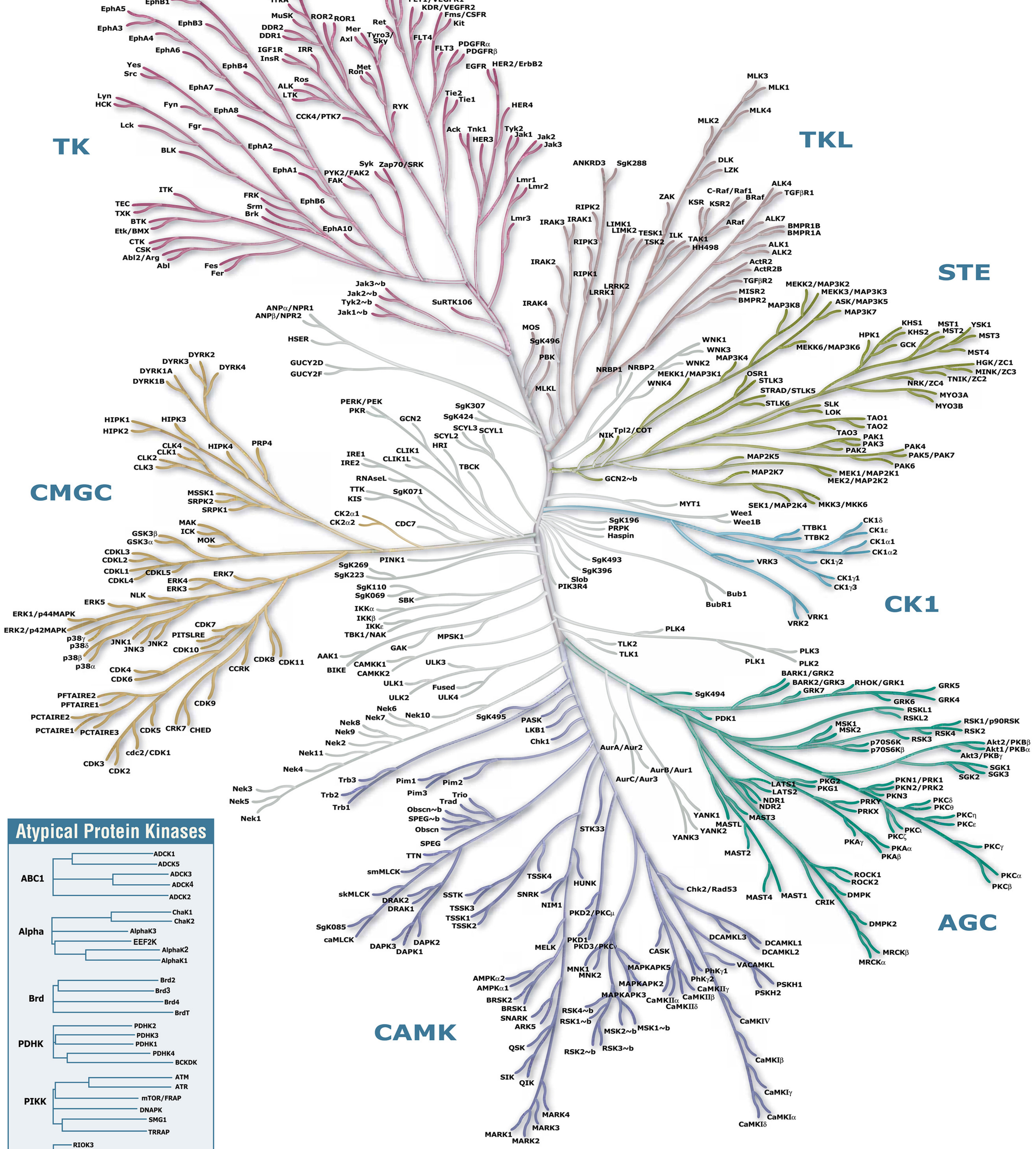
40 'atypical' kinases have no sequence similarity to typical kinases, but are known or predicted to have enzymatic activity. Some are predicted to have a similar structural fold to typical kinases. The inset shows trees for seven atypical protein kinase families; a further eight atypicals are in small families of one or two genes and are not shown. Detailed trees of the main groups, along with schematics showing the domain organization of each kinase, can be found at: **www.cellsignal.com/reference/kinase**.

Most human kinases can be mapped to orthologs in model organisms. 510 of the 518 human kinases have single orthologs in mouse, and of 209 human kinase subfamilies, some 50 (~25%) have orthologs in yeast, worm and fly, showing the ancient divergence in kinase function. A further 50% of human kinase subfamilies are found in worm and fly, allowing a mapping of information and conserved sequence features from model systems to human.

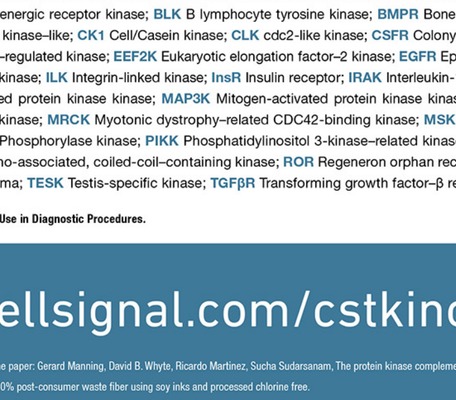
As key regulators of most cellular pathways, protein kinases are frequently associated with diseases, either as causative agents, or as therapeutic intervention points. We have summarized the disease associations for over 150 kinases at: **www.cellsignal.com/kinase**. Several kinase inhibitors have been approved for cancer treatment including Herceptin, Gleevec, Iressa, Erbitux, Avastin, Sutent and scores more are under development for cancer and other diseases.

MAPPING PROCEDURES

The main dendrogram shows the sequence similarity between protein kinase domains, derived from public sequences and gene-prediction methods detailed in Manning et al. (Science 298:1912-34). Domains were defined by hidden Markov model profile analysis and multiple sequence alignment. The initial branching pattern was built from a neighbor-joining tree derived from a ClustalW protein sequence alignment of the domains. This was extensively modified by reference to other alignment and tree-building methods (hmmalign and parsimony trees) and by extensive pairwise sequence alignment of kinase domains. The curved layout was created manually. Many branch lengths are semiquantitative, but the branching pattern is more informative than any single automatic method. The atypical kinase trees were generated automatically by ClustalW alignment of full-length protein sequences followed by neighbor-joining tree building. Unpublished kinases are named where possible according to family nomenclature. Some divergent kinases retain a numerical SgK (Sugen kinase) accession number. The second domains of dual-domain kinases are named with a "~b" suffix. Detailed subtrees and sequence alignments of individual groups and families, and comparative genomic trees are available at **http://www.kinase.com.** Information on regulation and substrates of many of these kinases is available at **www.cellsignal.com**. Information about phosphorylation sites on these kinases and their substrates is available at **www.phosphosite.org**.



Atypical Protein Kinases



GROUP NAMES: AGC Containing PKA, PKG, PKC families; CAMK Calcium/calmodulin-dependent protein kinase; CK1 Casein kinase 1; CMGC Containing CDK, MAPK, GSK3, CLK families; STE Homologs of yeast Sterile 7, Sterile 11, Sterile 20 kinases; TK Tyrosine kinase; TKL Tyrosine kinase–like.

KINASE NAMES: (A selective list includes those cases in which the full name is more informative than the abbreviation or acronym shown on the tree. Other full names and synonyms are available at http://www.kinase.com.) ActR Activin receptor; ALK (TK group) Anaplastic lymphoma kinase; ALK (TKL group) Activin-like receptor kinase; AMPK Adenosine monophosphate–activated protein kinase; Aur Aurora; BARK β-adrenergic receptor kinase; BLK B lymphocyte tyrosine kinase; BMPR Bone morphogeneic protein receptor; BMX Bone marrow tyrosine kinase gene in chromosome X; BRD Bromodomain kinase; BRSK Brain-selective kinase; CaMK Calcium/calmodulin-dependent protein kinase; CAMKK CaMK kinase; CCK-4 Colon carcinoma kinase–4; CDK Cyclin-dependent kinase; CDKL Cyclin-dependent kinase–like; CK1 Cell/Casein kinase; CLK cdc2-like kinase; CSFR Colony-stimulating factor receptor; DAPK Death-associated protein kinase; DCAMKL Doublecortin- and CaMK-like; DDR Discoidin domain receptor; DMPK Dystrophia myotonica protein kinase; DNAPK DNA-activated protein kinase; DRAK DAPK-related apoptosis-inducing kinase; DYRK Dual-specificity tyrosine phosphorylation–regulated kinase; EEF2K Eukaryotic elongation factor–2 kinase; EGFR Epidermal growth factor receptor; Eph Ephrin receptor; ERK Extracellular signal–regulated kinase; FAK Focal adhesion kinase; FGFR Fibroblast growth factor receptor; FRK Fos-regulatory kinase; GRK G protein–coupled receptor kinase; GSK Glycogen synthase kinase; HIPK Homeodomain-interacting protein kinase; IKK I-κB kinase; ILK Integrin-linked kinase; InsR Insulin receptor; IRAK Interleukin-1 receptor–associated kinase; IRE Inositol-requiring enzyme; IRR Insulin receptor–related; JAK Janus kinase; JNK c-Jun NH_2-terminal kinase; KSR Kinase suppressor of Ras; LATS Large tumor suppressor; LIMK Lim domain–containing kinase; LMR Lemur kinase; LRRK Leucine rich–repeat kinase; MAP2K Mitogen-activated protein kinase kinase; MAP3K Mitogen-activated protein kinase kinase kinase; MAPK Mitogen-activated protein kinase; MAPKAPK MAPK–activated protein kinase; MARK Microtubule-associated protein/microtubule affinity–regulating kinase; MAST Microtubule-associated serine-threonine kinase; MLCK Myosin light chain kinase; MLK Mixed lineage kinase; MNK MAPK-interacting kinase; MRCK Myotonic dystrophy–related CDC42-binding kinase; MSK Mitogen- and stress-activated protein kinase; MuSK Muscle-specific kinase; NDR Nuclear, Dbf2-related kinase; NIK Nuclear factor κB–inducing kinase; PAK p21-activated kinase; PDGFR Platelet-derived growth factor receptor; PDHK Pyruvate dehydrogenase kinase; PDK Phosphoinositide-dependent kinase; PhK Phosphorylase kinase; PIKK Phosphatidylinositol 3-kinase–related kinase; PKA Protein kinase A; PKB Protein kinase B; PKC Protein kinase C; PKD Protein kinase D; PKG Protein kinase G; PKN Protein kinase N; PKR Protein kinase, double-stranded RNA–dependent; PRK Protein kinase C–related kinase; PSKH Protein serine kinase H; RIPK Receptor-interacting protein kinase; ROCK Rho-associated, coiled-coil–containing kinase; ROR Regeneron orphan receptor; RSK Ribosomal protein S6 kinase; RSKL RSK-like; SgK Sugen kinase; SGK Serum- and glucocorticoid-regulated kinase; SRPK Serine-arginine splicing factor protein kinase; SYK Spleen tyrosine kinase; TAK Transforming growth factor–β–activated kinase; TEC Tyrosine kinase expressed in hepatocellular carcinoma; TESK Testis-specific kinase; TGFβR Transforming growth factor–β receptor; TIE Tyrosine kinase with immunoglobulin and EGF repeats; TIF1 Transcriptional intermediary factor 1; TLK Tousled-like kinase; TSSK Testis-specific serine kinase; TTBK Tau tubulin kinase; VRK Vaccinia-related kinase; WNK With no lysine.

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