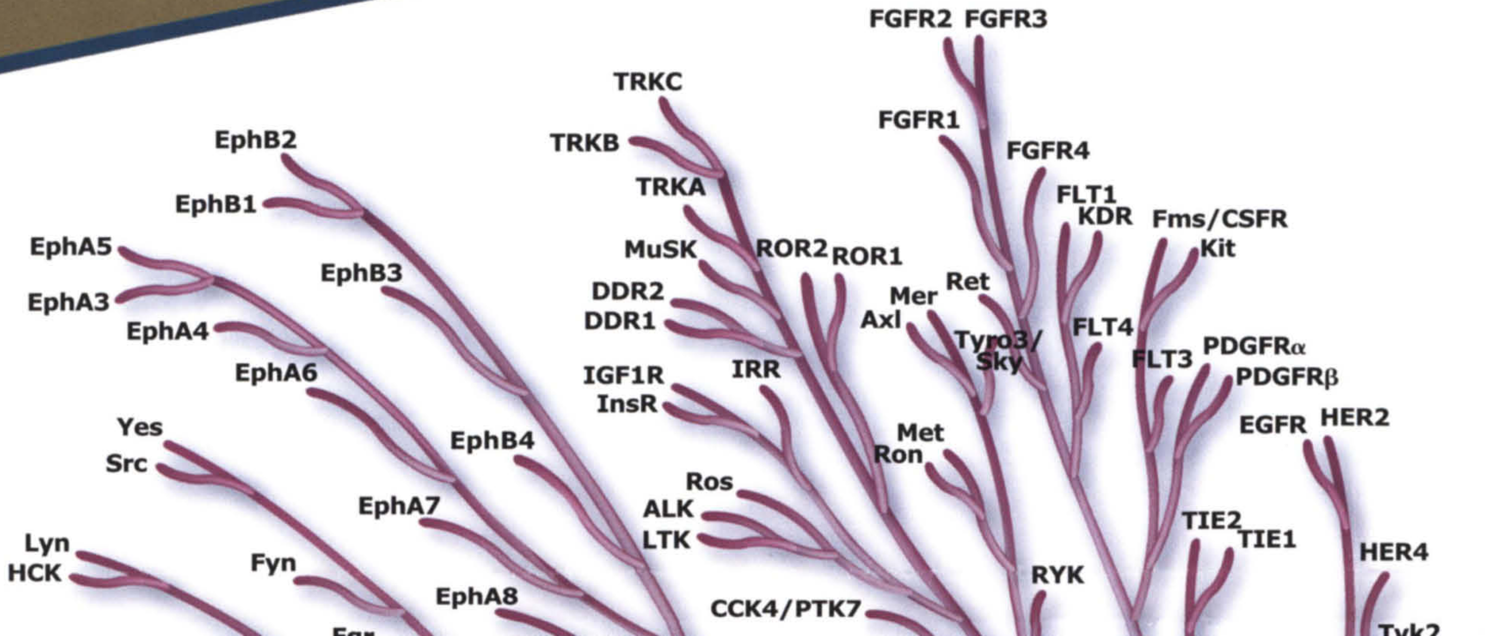
Science

This phylogenetic tree depicts the relationships between members of the complete superfamily of human protein kinases. Protein kinases constitute one of the largest human gene families and are key regulators of cell function. The 518 human protein kinases control protein activity by catalyzing the addition of a negatively charged phosphate group to other proteins. Protein kinases modulate a wide variety of biological processes, especially those that carry signals from the cell membrane to intracellular targets and coordinate complex biological functions.

Most protein kinases belong to a single superfamily of enzymes whose catalytic domains are related in sequence and structure. The main diagram illustrates the similarity between the protein sequences of these catalytic domains. Each kinase is at the tip of a branch, and the similarity between various kinases is inversely related to the distance between their positions on the tree diagram. Most kinases fall into small families of highly related sequences, and most

families are part of lar
Other kinases are sho
tree can be used to pr
uncharacterized kinas

The inset diagr
have verified or strong
members of the protei
families of one or two



art of larger groups. The seven major groups are labeled and colored distinctly.
are shown in the center of the tree, colored gray. The relationships shown on the
sed to predict protein substrates and biological function for many of the over 100
ed kinases presented here.
set diagram shows trees for seven atypical protein kinase families. These proteins
or strongly predicted kinase activity, but have little or no sequence similarity to
he protein kinase superfamily. A further eight atypical protein kinases in small
e or two genes are not shown.

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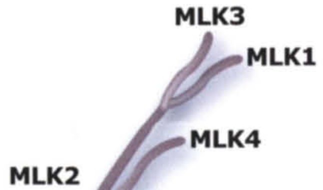
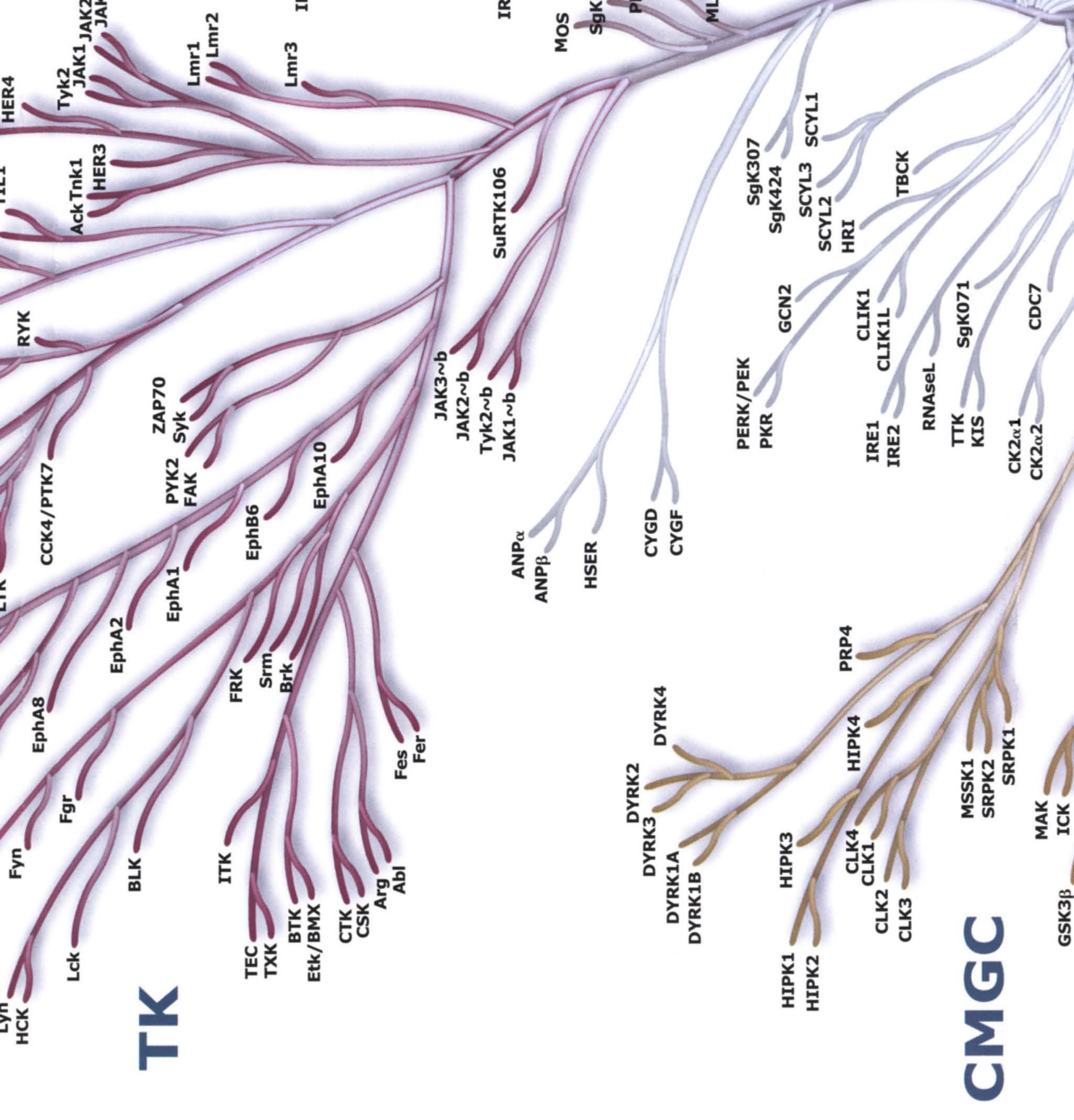
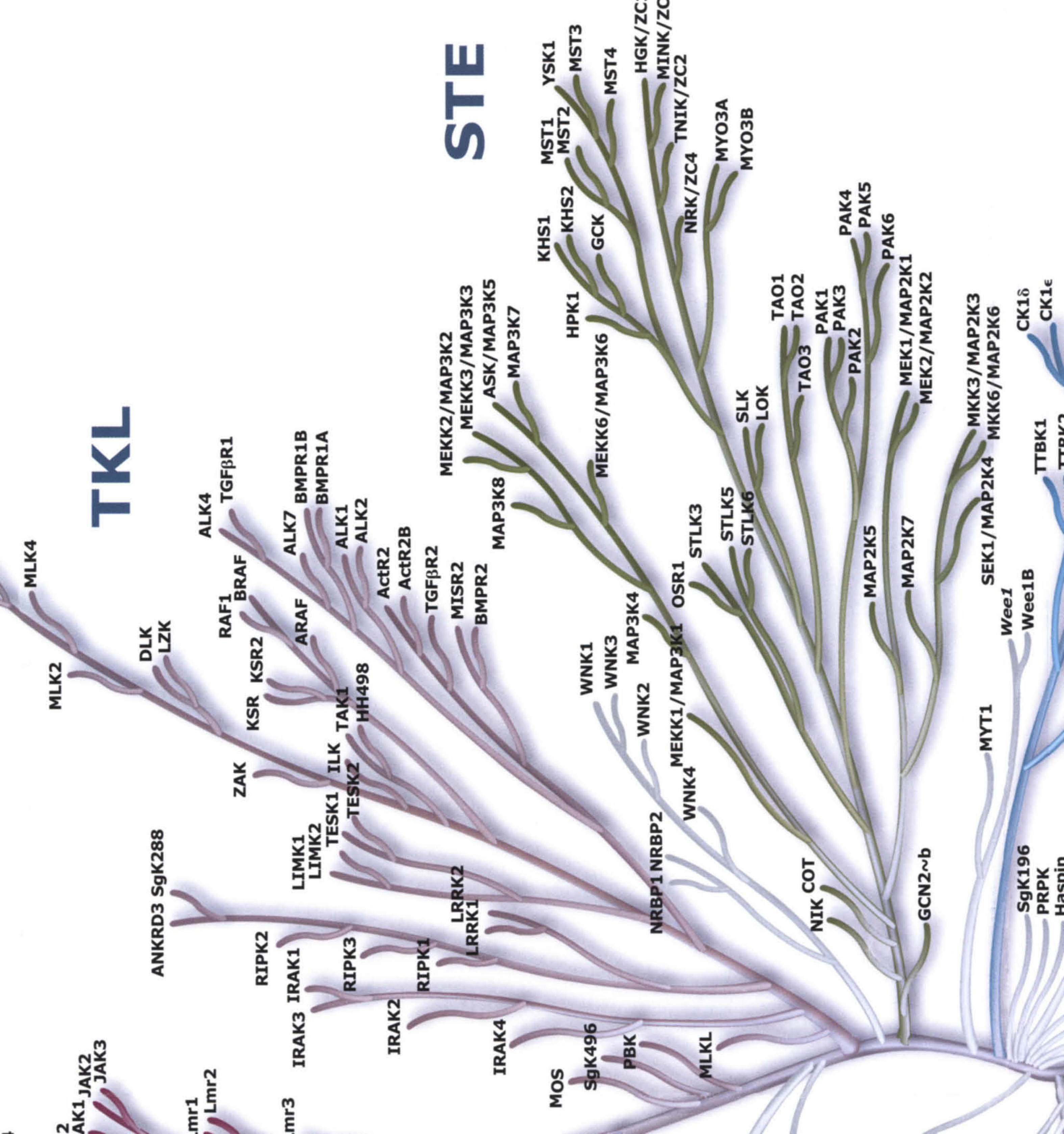
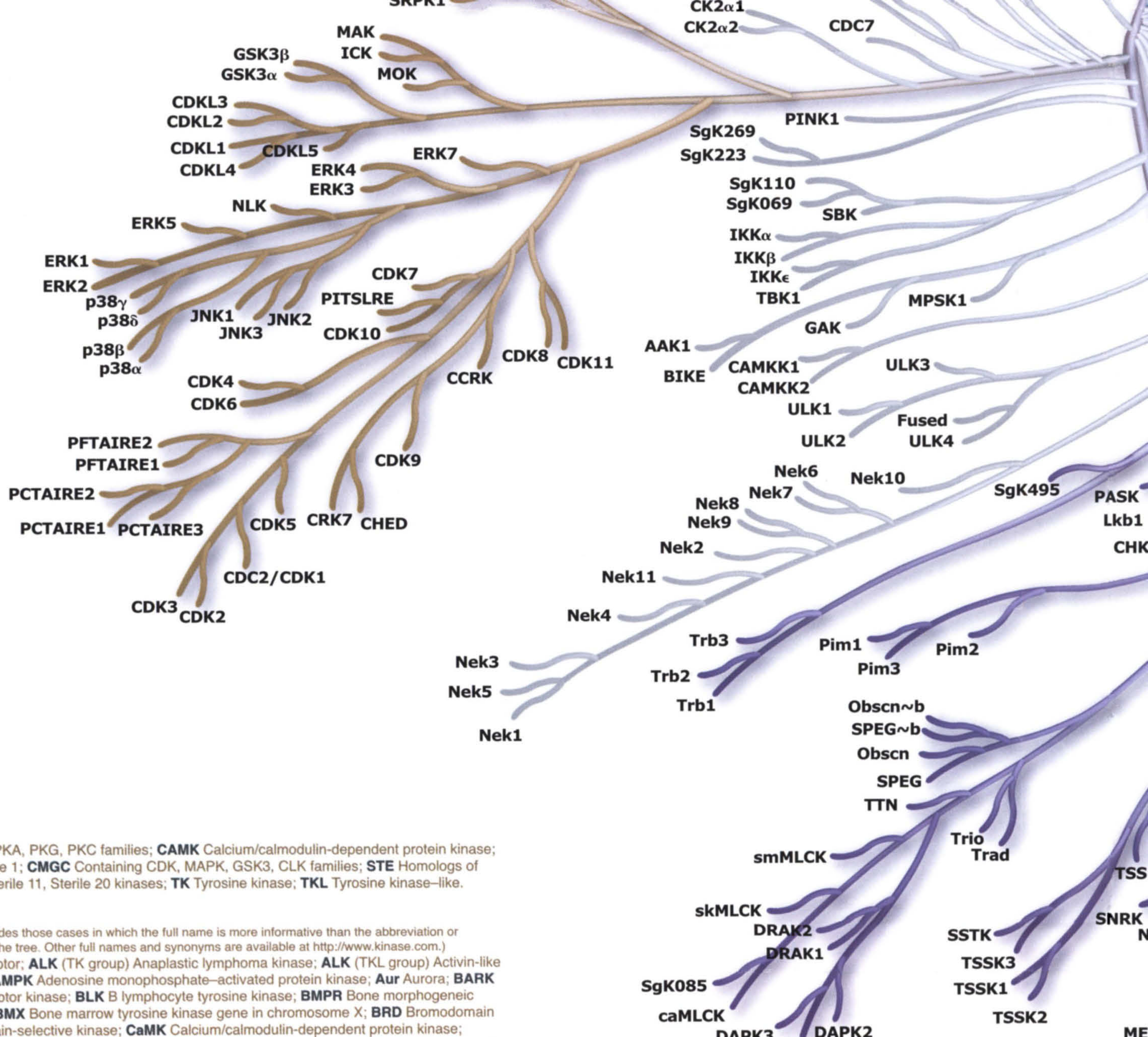
THE Human Kinome




TK
CMGC
JAK2
JAK1
Tyk2
Lmr1
Lmr2
Lmr3
MOS
HER4
HER3
Ack
Tnk1
SuRTK106
SgK307
SgK424
SCYL1
SCYL3
SCYL2
HRI
TBCK
GCN2
CLIK1
CLIK1L
SgK071
CDC7
RYK
JAK3~b
JAK2~b
Tyk2~b
JAK1~b
PERK/PEK
PKR
IRE1
IRE2
RNAseL
TTK
KIS
CK2α1
CK2α2
ZAP70
Syk
PYK2
FAK
CCK4/PTK7
EphA10
EphB6
EphA1
EphA2
ANPα
ANPβ
HSER
CYGD
CYGF
PRP4
DYRK4
DYRK2
DYRK3
DYRK1A
DYRK1B
HIPK4
HIPK3
HIPK1
HIPK2
CLK4
CLK1
CLK2
CLK3
MSSK1
SRPK2
SRPK1
MAK
ICK
GSK3β
FRK
Srm
Brk
EphA8
Fgr
Fyn
BLK
Lck
Lyn
HCK
ITK
TEC
TXK
BTK
Etk/BMX
CTK
CSK
Arg
Abl
Fes
Fer


TKL
STE
MLK4
MLK2
DLK
LZK
ZAK
ALK4
TGFβR1
RAF1
BRAF
KSR2
KSR
ARAF
ALK7
BMPR1B
BMPR1A
ALK1
ALK2
ActR2
ActR2B
TGFβR2
MISR2
BMPR2
TAK1
HH498
ILK
TESK2
TESK1
LIMK1
LIMK2
ANKRD3
SgK288
RIPK2
IRAK1
RIPK3
RIPK1
LRRK2
LRRK1
IRAK3
IRAK2
IRAK4
MOS
SgK496
PBK
MLKL
JAK2
JAK3
AK1
Lmr1
Lmr2
Lmr3
MEKK2/MAP3K2
MEKK3/MAP3K3
ASK/MAP3K5
MAP3K7
MAP3K8
MEKK6/MAP3K6
MAP3K4
MEKK1/MAP3K1
OSR1
STLK3
STLK5
STLK6
WNK1
WNK3
WNK2
WNK4
NRBP1
NRBP2
NIK
COT
GCN2~b
KHS1
KHS2
GCK
HPK1
MST1
MST2
YSK1
MST3
MST4
HGK/ZC1
MINK/ZC3
TNIK/ZC2
NRK/ZC4
MYO3A
MYO3B
SLK
LOK
TAO1
TAO2
TAO3
PAK1
PAK3
PAK2
PAK4
PAK5
PAK6
MEK1/MAP2K1
MEK2/MAP2K2
MAP2K5
MAP2K7
MKK3/MAP2K3
MKK6/MAP2K6
SEK1/MAP2K4
CK1δ
CK1ε
TTBK1
Wee1
Wee1B
MYT1
SgK196
PRPK
Haspin



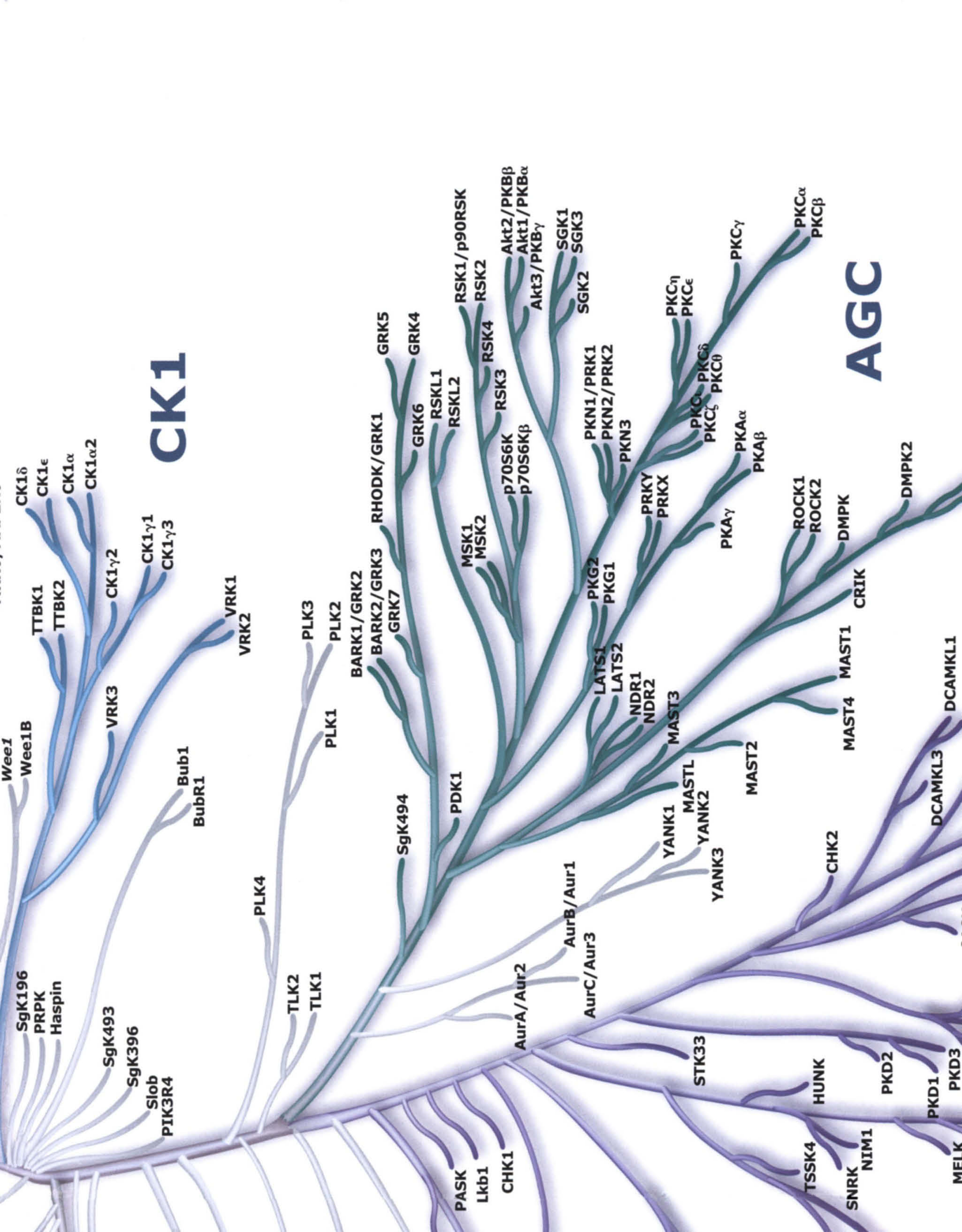
Group names

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;


CK1
AGC
Wee1
Wee1B
TTBK1
TTBK2
CK1δ
CK1ε
CK1α
CK1α2
CK1γ2
CK1γ1
CK1γ3
VRK1
VRK2
VRK3
Bub1
BubR1
SgK196
PRPK
Haspin
SgK493
SgK396
Slob
PIK3R4
PLK3
PLK2
PLK1
PLK4
TLK2
TLK1
AurA/Aur2
AurC/Aur3
AurB/Aur1
YANK1
YANK2
YANK3
SgK494
PDK1
BARK1/GRK2
BARK2/GRK3
GRK7
RHODK/GRK1
GRK6
GRK5
GRK4
RSKL1
RSKL2
RSK1/p90RSK
RSK2
RSK4
RSK3
p70S6K
p70S6Kβ
MSK1
MSK2
Akt2/PKBβ
Akt1/PKBα
Akt3/PKBγ
SGK1
SGK3
SGK2
PKG2
PKG1
PKN1/PRK1
PKN2/PRK2
PKN3
PKCη
PKCε
PKCδ
PKCθ
PKCι
PKCζ
PKCγ
PKCα
PKCβ
PRKY
PRKX
PKAα
PKAβ
PKAγ
LATS1
LATS2
NDR1
NDR2
MAST3
MASTL
MAST1
MAST4
MAST2
ROCK1
ROCK2
DMPK
DMPK2
CRIK
DCAMKL1
DCAMKL3
CHK2
STK33
PKD2
PKD3
PKD1
HUNK
TSSK4
SNRK
NIM1
MELK
PASK
Lkb1
CHK1

Kinase names

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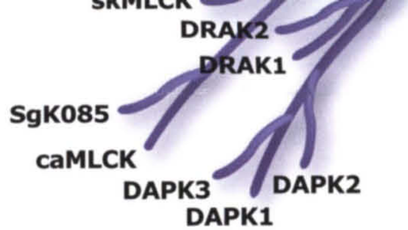
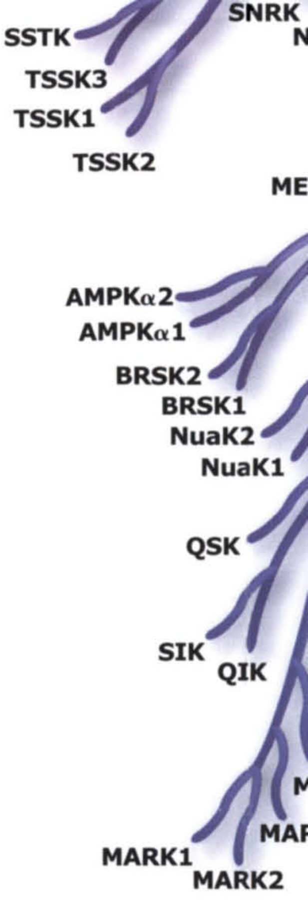
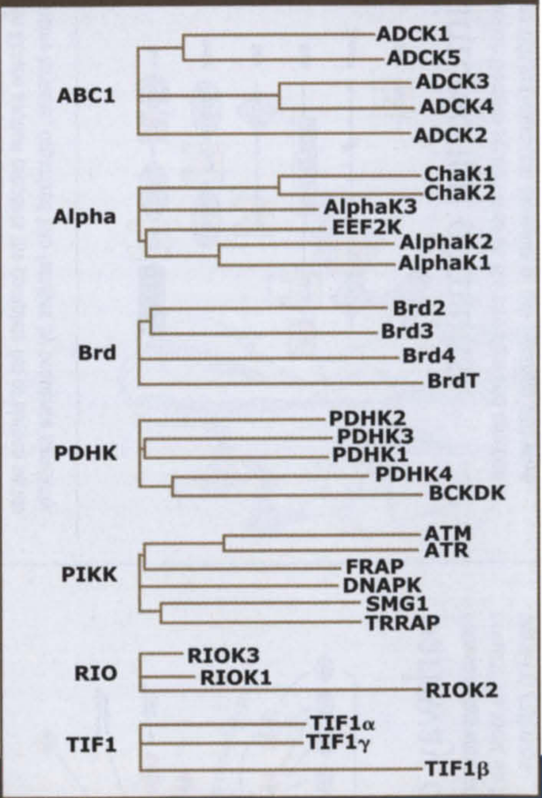




ATYPICAL PROTEIN KINASES



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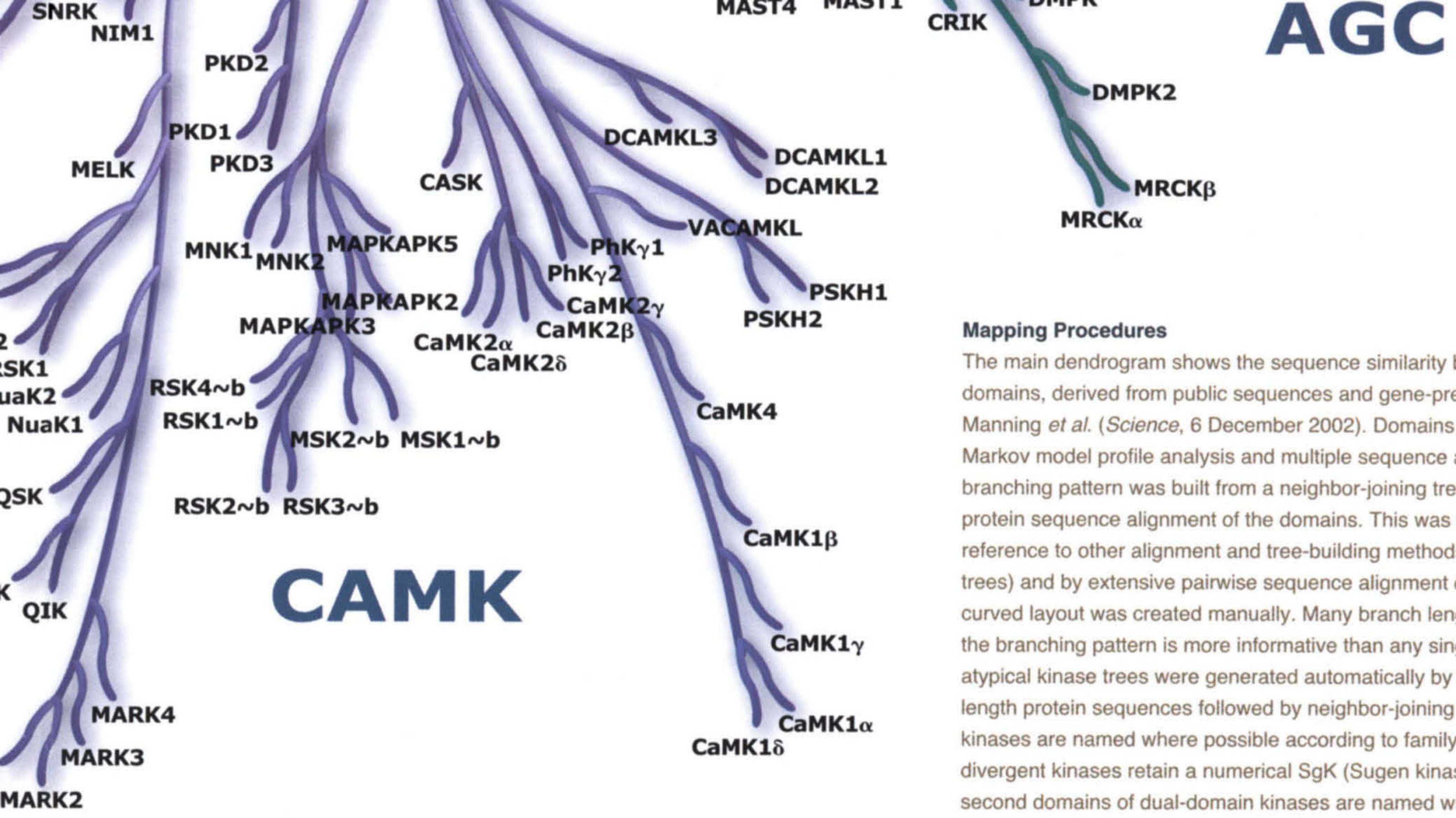

Mapping Procedures

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*, 6 December 2002). 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 http://www.cellsignal.com.

Authors Gerard Manning, David B. Whyte, Ricardo Martinez, Sucha Sudarsanam, Sugen Inc., South San Francisco, CA, USA; Tony Hunter, Salk Institute, La Jolla, CA, USA. This poster accompanies the paper "The Protein Kinase Complement of the Human Genome" (Manning *et al.*, *Science*, 6 December 2002).
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