

## Kinase-Disease Associations

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. Several kinase inhibitors have been approved for cancer treatment (Herceptin, Gleevec, Iressa, Erbitux, Avastin) and scores more are under development for cancer and other diseases.

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			<b>Zap-70</b>

## Kinase-Disease Associations

Name	Group	Disease Type	Molecular Basis	Notes
<b>Abi</b>	TK	Cancer	Trans	The Philadelphia chromosome translocation t(9;22)(q34;q11) creates a Bcr-Abl fusion protein, responsible for 90% of chronic myelogenous leukemia [OMIM: 608232] and approximately 25% of acute lymphoblastic leukemia [OMIM: 159555]. Inhibitors: Gleevec (imatinib, Glivec) Dasatinib. OMIM: 189980.
<b>ABL2 (ARG)</b>	TK	Cancer	Trans, Expr	Translocation events fusing ARG to ETV6 (TEL) are seen in some cases of acute myeloid leukemia. Differentially expressed (increased and decreased) in several cancer types. OMIM: 164690.
<b>ACK</b>	TK	Cancer	Amp	Amplification in primary tumors correlates with metastatic potential. OMIM: 606994.
<b>ACTR2B</b>	TKL	Development	Mut	Two human mutations and a mouse model implicate ACTR2B in left-right axis malformations. OMIM: 602730.
<b>Akt1</b>	AGC	Cancer	Act, Amp, OE	Mediates survival signals downstream of PI3 kinase and several growth factor receptors by phosphorylating apoptotic proteins. First found in a mouse transforming retrovirus. Tumorigenic in a mouse lymphoma model and activated (by phospho-Akt staining) and/or overexpressed in a number of cancers including breast, prostate, lung, pancreatic, liver, ovarian and colorectal. Inhibitor: RX-0201 (Rexahn; Phase 1 cancer). OMIM: 164730.
<b>Akt2</b>	AGC	Cancer, Diabetes	Amp, OE, LOF mut, Mut	Amplified and overexpressed in human ovarian carcinoma cell lines and amplified in some primary ovarian and pancreatic tumors. Antisense blocks invasiveness in xenografts. Expressed in several insulin-responsive tissues, and one case of Type II diabetes [OMIM: 125853] has been associated with a likely LOF point mutation. Mouse mutants have defects in insulin response. OMIM: 164731.
<b>ALK</b>	TK	Cancer	Trans	About one third of large-cell lymphomas are caused by a t(2;5)(p23;q35) translocation that fuses ALK to nucleophosmin (NPM1). Other cases caused by fusions of ALK to moesin, non-muscle myosin heavy chain 9, clathrin heavy chain and other genes. Several fusions also seen in inflammatory myofibroblastic tumors, and expression has been briefly noted in a range of tumors (Medline:15095281). Proposed as tumor antigen (Medline:11877285). OMIM: 105590.
<b>ALK1 (ACVRL1)</b>	TKL	Cardiovascular	Mut	Numerous distinct mutations linked to Osler-Rendu-Weber syndrome 2 [OMIM: 600376], a disorder associated with intestinal bleeding, arterial hypertension and arteriovenous malformations. OMIM: 601284.
<b>ALK2 (ACVR1)</b>	TKL	Development	Mut	Single heterozygous mutation seen in many independent cases of fibrodysplasia ossificans progressiva [OMIM: 135100], causing skeletal malformations and extra-skeletal bone formation. OMIM: 102576.
<b>ALK4 (ACVR1B)</b>	TKL	Cancer	Mut, Splice	Two deletion truncation mutations seen in pancreatic carcinoma [OMIM: 260350]. Unique splice forms with predicted dominant negative activity expressed in pituitary tumors. OMIM: 601300.
<b>ANKK1 (Sgk288)</b>	TKL	Behavior	SNP	One coding SNP in ankyrin repeat may change substrate binding specificity; linked to neuropsychiatric disorders including addiction. OMIM: 608774.
<b>ANP<math>\alpha</math> (NPR1)</b>	RGC	Hypertension	Expr, SNP	Animal models indicate a role in blood pressure regulation. Hypertensive SHR Rat has polymorphism at the locus. Human non-coding polymorphisms can alter expression up to two-fold (Medline:12483301), and have been associated with hypertension (Medline:12872042). A coding SNP is associated with hypertension [OMIM: 145500] and myocardial infarction (Medline:14646971). OMIM: 108960.
<b>ANP<math>\beta</math> (NPR2)</b>	RGC	Development	Mut	Numerous mutations are linked to the Maroteaux form of acromesomelic dysplasia [OMIM: 602875; Medline:15146390]. OMIM: 108961.
<b>ATM</b>	Atypical	Cancer, CNS	LOF Mut, Mut	LOF mutations associated with ataxia telangiectasia [OMIM: 208900], causing progressive loss of motor control (ataxia), dilation of superficial blood vessels (telangiectasia), cancer and immune deficiency. Approximately 30% of cases develop tumors, mostly lymphomas and leukemias, due to defects in DNA damage repair. Somatic mutations seen in leukemias and lymphomas. OMIM: 607585.

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Name	Group	Disease Type	Molecular Basis	Notes
<b>ATR</b>	Atypical	Cancer, Development, Virology	Mut, Splice	Functions in DNA damage responses. A splice-altering mutation seen in cases of Seckel syndrome [OMIM: 210600], featuring dwarfism and mental retardation. Mouse heterozygous knockouts are cancer-prone. Mutations seen in cancers of the stomach and endometrium (Medline:11691784, 12124347), tumors with high mutation rates due to microsatellite instability. May also be required for retroviral DNA integration (Medline:12679521). OMIM: 601215.
<b>AurA</b>	Other	Cancer	Amp, OE, SNP	Required for centrosome duplication and chromosome segregation. Overexpression in culture drives transformation and aneuploidy, and negatively regulates p53. Amplified or overexpressed in many tumors or cell lines. Found as a skin tumor susceptibility gene in mouse, and a human SNP in a degradation domain is weakly cancer-associated and undergoes allele-specific amplification (Medline:15466974, 15271853, 12881723). Inhibitors: VX-680 (Vertex), ZM447439 (Astra-Zeneca), Hesperadin (Boehringer Ingelheim), SNS-595 (Sunesis). OMIM: 603072.
<b>AurB</b>	Other	Cancer	OE	Required for chromosome segregation and cytokinesis. Overexpressed in colorectal and other cancer cell lines (Medline:9809983) and thought to cause aneuploidy via histone phosphorylation (Medline:12884918). OMIM: 604970.
<b>Axl</b>	TK	Cancer	OE	Overexpression in tissue culture causes oncogenic transformation. Overexpressed in several cancers including thyroid (Medline:10411118), ovarian (Medline:15452374), gastric (Medline:12168903), ER-associated breast cancer (Medline:11484958) and acute myeloid leukemia, where it is associated with poor prognosis (Medline:10482985). OMIM: 109135.
<b>BARK1</b> (GRK2, ADRBK1)	AGC	Cardiac	Expr, Model	Expression level is consistently elevated in chronic human heart failure. Mouse models of severe heart failure have been used to demonstrate that inhibition of BARK1 with a peptide inhibitor is sufficient to increase mean survival, reduce dialation and improve cardiac function. OMIM: 109635.
<b>BCR</b>	Atypical	Cancer	Trans	Translocation involving the BCR gene generates the Philadelphia Chromosome seen in many cases of chronic myelogenous leukemia [OMIM: 608232]. See ABL above. OMIM: 151410.
<b>BMPR1A</b> (ALK3)	TKL	Cancer	LOF Mut	Truncations and point mutations are one cause of juvenile polyposis syndrome [OMIM: 174900], which is associated with increased susceptibility to gastrointestinal cancers. OMIM: 601299.
<b>BMPR1B</b> (ALK6)	TKL	Development	Mut	Two mutations are associated with a hand malformation known as type A2 brachydactyly [OMIM: 112600]. A homozygous truncation associated with one case of acromesomelic chondrodysplasia with external genital abnormalities [OMIM: 609441]. OMIM: 603248
<b>BMPR2</b>	TKL	Cardiopulmonary	Mut	Mutations cause primary pulmonary hypertension [OMIM: 178600], a weakly penetrant dominant disorder associated with lesions in pulmonary arterioles, elevated pulmonary arterial pressure, and right ventricular failure. OMIM: 600799.
<b>B-Raf</b>	TKL	Cancer, Cardiac, Development	GOF Mut, LOF Mut	An activating mutation, mimicking phosphorylation of the activation loop, is seen in 60% of malignant melanoma samples (Medline:15035987). Raf mutations are generally exclusive to Ras activating mutations. Activating mutations are also seen in ~10% of colorectal cancers, in lung cancers and gliomas, and at a lower rate in several other tumors. Inactivating mutations are also seen and may result in activation of c-Raf and Erk (Medline:15035987). Mutations in B-Raf, MEK1 and MEK2 also associated with cardiofaciocutaneous syndrome, displaying morphological, cardiac and mental defects. Approved Inhibitor: Nexavar/Sorafenib (Bayer/Onyx). OMIM: 164757.
<b>BRD4</b>	Atypical	Cancer, Virology	Trans	Chromosome-associated kinase with cell cycle function. Translocation creates fusion protein with testis-specific NUT gene in juvenile midline carcinomas. Binds to papillomavirus E2 protein and is required for its transforming ability. OMIM: 608749.
<b>BRK</b>	TK	Cancer	Expr	Selectively expressed in breast tumors and cell lines, and perhaps in colon and prostate cancers. Enhances anchorage-independent growth and responsiveness to EGF. RNAi reduces proliferation in breast cancer cells. Kinase-inactive mutant indicates tumor function may be independent of catalytic function. OMIM: 602004.

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Name	Group	Disease Type	Molecular Basis	Notes
<b>Btk</b>	TK	Cancer, Immunity	LOF Mut, Splice	LOF mutations cause X-linked agammaglobulinemia [OMIM: 300300], arresting development of B cells and causing recurrent bacterial infections. Truncated splice forms found in childhood leukemias may underlie radiation resistance of tumors through inhibition of apoptosis (Medline:12854903). OMIM: 300300.
<b>BUB1</b>	Other	Cancer	LOF Mut, OE	LOF mutations seen in two colon cancer cell lines exhibiting chromosomal instability, in several leukemias, and in lymphomas (Medline:12096343), and in a pancreatic cancer cell line (Medline:12655561). BUB1 functions in mitotic spindle assembly, and may cause chromosomal instability. In mouse BRCA2 knockouts, mutations in BUB1 and BUBR1 are frequently seen in the resulting tumors (Medline:14646599). BUB1 and BUBR1 are overexpressed, but not mutated, in many gastric cancers (Medline:12692836). OMIM: 602452.
<b>BUBR1 (BUB1B)</b>	Other	Cancer	Mut, OE	Two mutations found in colon cancer cell lines. In mouse BRCA2 knockout, mutations in BUB1 and BUBR1 are frequently seen in the resulting tumors (Medline:14646599). BUB1 and BUBR1 are overexpressed, but not mutated, in many gastric cancers (Medline:12692836). BUBR1-deficient mice show early aging phenotypes. OMIM: 602860.
<b>cdc2 (CDK1)</b>	CMGC	Cancer	Act, Splice	Cell cycle checkpoint protein. Activated in many cancers including colon, liver and breast (Medline:10091728, 12100577, 11091571). The T isoform, which lacks a regulatory region, is expressed in breast cancer. Inhibition in cancer cells may drive cells into apoptosis (Medline:12150824). May also drive cell migration (Medline:12771130). Inhibitors: BMS-265246, BMS-265246-01 (Bristol-Myers Squibb). OMIM: 116940.
<b>CDK2</b>	CMGC	Cancer	Inh	Cell cycle checkpoint, and part of the Rb pathway dysregulated in most tumors (Medline:12888290). Target of several candidate cancer drugs. However, inhibition does not always prevent cancer cell growth (Medline:12676582), possibly due to CDK redundancy. Inhibitors: BMS-265246, BMS-265246-01 (Bristol-Myers Squibb), R-roscovitine (CYC200, CYC202) (Cyclacel), SU9516 (Sugen), R547 (Roche), L868276. OMIM: 116953.
<b>CDK4</b>	CMGC	Cancer	Act, GOF Mut, Amp, Meth	Point mutations found in somatic and familial melanoma. Amplified in sarcomas (Medline:9703873, 9935200), glioma (Medline:14756442) and lymphoma (Medline:12203778). Amplified, methylated or deleted in head and neck squamous cell carcinoma (Medline:14586645). Overexpression drives epithelial tumors in mice (Medline:14647432). Disruption makes mice resistant to cancer (Medline:12435633). Inhibitor: PD332991 (Onyx). OMIM : 123829.
<b>CDK5</b>	CMGC	Neurodegeneration	Act, Model	Implicated in the pathology of neurofibrillary tangles and formation of senile plaques, hallmarks of Alzheimer's disease [OMIM: 104300]. Induces tau phosphorylation and aggregation and neurofibrillary tangle deposition and neurodegeneration in in vitro and in vivo animal models. Brain samples from Alzheimer patients show elevated CDK5 activity. OMIM: 123831.
<b>CDK6</b>	CMGC	Cancer	OE, Trans	Overexpressed and/or disrupted by translocation in leukemias, lymphomas and other cancers and amplified in gliomas (Medline:9102208) and rodent cancers (Medline:12538879, 11719459). OMIM: 603368.
<b>CDK9</b>	CMGC	Cardiovascular, Viral infection	Expr, Inh	Transcriptional elongation factor and cofactor for HIV Tat protein; RNAi blocks HIV replication, and inhibitors also block varicella zoster replication. Mediates signals leading to cardiac hypertrophy (Medline:12695656). Inhibitor: Flavopiridol. OMIM: 603251.
<b>CDKL5</b>	CMGC	CNS, Development	Mut, Trans	Missense, splice and truncating mutations linked to the neurodevelopmental Rett Syndrome [OMIM: 312750]. A chromosomal translocation which silences the gene is associated with severe X-linked infantile spasm syndrome [OMIM: 308350]. OMIM: 300203.
<b>Chk1 (CHEK1)</b>	CAMK	Cancer	Mut	Cell cycle G2 checkpoint kinase, implicated in resistance to apoptosis in response to chemotherapy. Inhibitors under development to chemosensitize tumors. Somatic mutations found in stomach tumors (Medline:11691784), and in colon and endometrial tumors, where CHK1 may be a target of microsatellite instability (Medline:14657665). Inhibitors: SB218078, UNC-01. OMIM: 603078.

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Name	Group	Disease Type	Molecular Basis	Notes
<b>Chk2</b>	CAMK	Cancer	Mut	Cell cycle checkpoint protein and putative tumor suppressor involved in DNA damage response and cell cycle arrest. LOF mutants cause type 2 Li-Fraumeni syndrome [OMIM: 609265], a highly penetrant familial cancer predisposition phenotype. Familial mutations also associated with prostate and breast cancer, and mutations also seen in a variety of sporadic cancers and cell lines. OMIM: 604373.
<b>CK1<math>\delta</math>, CK1<math>\alpha</math></b> (CSNK $\alpha$ 1, CSNK2)	CK1	Behavior, Neurodegeneration	Expr, Mut, Inh	Several CK1 isoforms (including CK1 $\delta$ and CK1 $\alpha$ ) associate with and phosphorylate tau, which forms the neurofibrillary tangles of Alzheimer's disease. Tau phosphorylation and microtubule association is inhibited by the CK1 inhibitor IC261 (Medline:14761950). CK1 phosphorylation is involved in trafficking of the Alzheimer's plaque component, beta secretase (Medline:11278841). CK1 $\delta$ is also associated with tau tangles in several other neurodegenerative diseases (Medline:10924763). CK1 $\delta$ mRNA and protein are upregulated in Alzheimer's brain regions with most pathology (Medline:10814741). CK1 also phosphorylates the Parkinson's-associated a synuclein protein (Medline:10617630). Mutation in CK1 $\delta$ is associated with autosomal dominant familial advanced sleep-phase syndrome [OMIM: 604348]. OMIM: 600864, 600505.
<b>CK1<math>\epsilon</math></b> (CSNK1)	CK1	Behavior, Cancer	SNP, Mut, LOH	Mutations in hamster and Drosophila orthologs have circadian rhythm phenotypes, and the circadian gene period (per) is a substrate in both human and fly. A coding SNP variant in human increases CK1 $\epsilon$ activity and is negatively associated with circadian disorder (Medline:15187983). LOF mutations and LOH seen in mammary ductal carcinoma (Medline:14871824). OMIM: 600863.
<b>CK2<math>\alpha</math>1, CK2<math>\alpha</math>2</b> (CSNK $\alpha$ 1, CSNK2)	Other	Cancer, Circadian Rhythm, Neurodegeneration	OE, Act	Two gene products (a1/a2 or a/a) complex with each other and a regulatory subunit. The isoforms are rarely specified in publications. Mouse transgene causes mammary gland hyperplasia and lymphoma, and activation by bovine parasites leads to fatal lymphoproliferation (Medline:7846532). Expression and activity are elevated in lung tumors (Medline:15355908, 12017291) and breast tumors (Medline:11423974). Antisense CK2 drives apoptosis of tumor cell lines (Medline:11827168) and xenografts (Medline:14965269). Involved in DNA break repair by phosphorylation of scaffold protein XRCC1 (Medline:15066279), phosphorylation of BRCA1 (Medline:10403822), and phosphorylation of p53 in response to UV irradiation. Drosophila CK2a ("timekeeper") is involved in circadian regulation. Phosphorylates and binds to a major component of the inclusion bodies seen in Parkinson's patients (Medline:14645218). Inhibitors: Antisense, P15 peptide, 4,5,6,7-tetrabromobenzotriazole (TBB). OMIM: 115440, 115442.
<b>CTK (MATK)</b>	TK	Cancer	OE	Expressed in cancerous but not normal breast tissue; interacts with activated ERBB2 receptor and is likely to inhibit proliferation. OMIM: 600038.
<b>CYGD</b> (GUCY2D)	RGC	Vision	Mut	Implicated in several visual diseases including dominant cone-rod dystrophy (CORD) type 5 [OMIM: 600977] and type 6 [OMIM: 601777], in which photoreceptor cells degenerate, leading to partial or total blindness, and Leber congenital amaurosis type 1 [OMIM: 204000], characterized by total blindness or loss of central vision. OMIM: 600179.
<b>CYGF</b> (GUCY2F)	RGC	Cancer	Mut	Ten point mutations seen in a survey of 182 colon tumors and cell lines (Medline:12738854), despite previous expectation of expression restricted to sensory tissues. OMIM: 300041.
<b>DAPK1</b>	CAMK	Cancer, Epilepsy	Meth, Expr, SNP	Putative tumor suppressor, activating p53-dependent apoptosis. Expression is reduced in some cancers, and the promoter is frequently hypermethylated in invasive cancers. Increased expression and mislocalization is seen in epilepsy, where it may regulate neuronal death. Polymorphism associated with late-onset Alzheimer's disease (Medline:16847012) OMIM: 600831.
<b>DCAMKL1</b>	CAMK	Neuro		Genetic and physical interactions with Doublecortin (Medline:16387638), which causes X-linked lissencephaly [OMIM: 300067]. OMIM: 604742.

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Name	Group	Disease Type	Molecular Basis	Notes
<b>DMPK1</b>	AGC	Neurodegeneration	Mut	An extended CTG triplet repeat in the noncoding sequence reduces protein expression and causes myotonic dystrophy [OMIM: 160900], leading to myotonia, muscle wasting, cataracts, hypogonadism, defective endocrine functions, male baldness, and cardiac arrhythmias. Normally localized to the neuromuscular junction. The repeat can expand during aging by somatic mutation, and can act in trans as a dominant negative, possibly affecting several other genes. OMIM: 605377.
<b>DNAPK</b>	Atypical	Cancer	Mut, LOF	Required for repair of radiation-induced dsDNA breaks. Loss of function in mice or horses leads to the severe combined immune deficiency (SCID) phenotype due to failure of immunoglobulin rearrangement. Target of mutation in mismatch repair-deficient colorectal cancer (Medline:1188892). Inhibitor: KU-7059 (Kudos). OMIM: 600899.
<b>DYRK1A</b>	CMGC	Cognition	Amp	Candidate gene for some aspects of Down's Syndrome (DS). Located in DS critical region, and overexpression in mice gives rise to similar neurological abnormalities (Medline:15198122). OMIM: 600855.
<b>eEF2K</b> (CaMKIII)	Atypical	Cancer	OE, Act	Overexpressed in breast cancer cell lines and tumors (Medline:10408694). Activated in rat glioblastoma (Medline:7647041), with growth inhibited by the drug Rottlerin. Activity induced in ischemic heart muscle (Medline:12920134). OMIM: 606968.
<b>EGFR</b>	TK	Cancer	Amp, OE, GOF Mut	Overexpressed in breast, head and neck cancers (Medline:15254682), correlating with poor survival. Activating somatic mutations seen in lung cancer, corresponding to minority of patients with strong response to EGFR inhibitor Iressa (gefitinib). Mutations and amplification also seen in glioblastoma, and upregulation seen in colon cancer and neoplasms. In xenografts, inhibitors synergized with cytotoxic drugs in inhibition of many tumor types (Medline:10815932). Inhibitors: Iressa/ZD1839 (Astra Zeneca), Erbitux (mAb, Imclone), Tarceva (OSI/Genentech) lapatinib (Tykerb, GSK). OMIM: 131550.
<b>Eph family</b>	TK	Cancer, Sensory	Amp, OE	A 14-member family of receptor tyrosine kinases with similar functions in intercellular communication, migration, patterning and angiogenesis. Ephrin receptors are implicated in development of tumor vasculature and intercellular contacts required for metastasis. Several members are overexpressed in cancers. Soluble forms act as competitive receptors and have shown some anti-tumor activity; extracellular domains have been used as tumor-specific antigens.
<b>EphA1</b>	TK	Cancer	Expr	Altered expression in several cancers, including upregulation in head and neck cancer (Medline:15023838), and downregulation in invasive breast cancer cell lines (Medline:15147954) and glioblastoma (Medline:14726470). OMIM: 179610.
<b>EphA2</b>	TK	Cancer	OE	Overexpressed in many cancers including aggressive ovarian (Medline:15297418), cervical (Medline:15297167) and breast carcinomas (Medline:15147954), and lung cancer (Medline:12576426). Expression correlates with degree of angiogenesis (Medline:14965363), metastasis (Medline:14767510) and xenograft tumor growth (Medline:14973554). Soluble receptor inhibits tumor growth and angiogenesis in mice (Medline:12370823, 14670182). OMIM: 176946.
<b>EphA3</b> (HEK)	TK	Cancer	Mut	Two point mutations seen in a survey of colorectal tumors (Medline:12738854). Soluble receptors reduce tumor growth and angiogenesis in mouse models (Medline:12370823, 14670182). OMIM: 179611.
<b>EphB2</b>	TK	Cancer	OE, Mut	Point mutations seen in prostate cancer (Medline:15300251). Overexpressed and required for migration of glioblastoma (Medline:15126357). Overexpressed and correlated with poor survival in breast cancer (Medline:15029258). Overexpression and loss of heterozygosity seen in colorectal cancers (Medline:11920461, 11166921). Target for immunoconjugate drug therapy (Medline:14871799). OMIM: 600997.

## Kinase-Disease Associations

Name	Group	Disease Type	Molecular Basis	Notes
<b>EphB4</b> (HTK)	TK	Cancer	OE	Required for normal development and angiogenesis of the mammary gland. Angiogenic functions may be kinase-independent, by means of retrograde signaling through its ephrin-B2 ligand (Medline:15067119). High expression correlates with malignancy in breast cancer in human and mouse models. Upregulated in head and neck (Medline:14661437), endometrial (Medline:12562648) and colon carcinomas (Medline:11801186). OMIM: 600011.
<b>Erk5</b> (BMK1)	CMGC	Cancer, Cardiovascular	Expr	Mouse knockout shows a role in development and integrity of blood vessels. May block apoptosis in endothelial cells (Medline:14670836). Required for transduction of EGF growth signal (Medline:9790194), constitutively activated in ErbB2-overexpressing breast cancer (Medline:11739740), and downstream of activated Mek5 in metastatic prostate cancer (Medline:12618764). Inhibitor: PD98059. OMIM: 602521.
<b>FAK</b> (PTK2)	TK	Cancer	OE, Amp, Act	Required for cell migration and contact-dependent survival signaling. Downstream of integrins and Src, upstream of Ras/MAPK. Required for full Ras transformation of fibroblasts. Increased expression in breast and other cancers, related to chromosome 8q amplification (Medline:10523844). Overexpression and activation associated with increased migration, invasion and progression of ovarian cancer (Medline:15466376), and with progression in hepatocellular carcinoma (Medline:15246215), thyroid cancer (Medline:8770310), and acute myeloid leukemia (Medline:15126359). siRNA increases chemosensitivity of pancreatic adenocarcinoma xenografts (Medline:14623342). Inhibitor: ISI15421 (antisense, ISIS). OMIM: 600758.
<b>FER</b>	TK	Cancer	Expr	Increased expression associated with prostate cancer proliferation, and antisense blocks soft agar growth (Medline:10687853). OMIM: 176942.
<b>FES</b>	TK	Cancer	Mut, Trans?	Four LOF point mutations seen in colorectal cancer (Medline:12738854, 16455651). Orthologous to v-fes from feline leukemia virus and v-fps from avian transforming virus. Mutant forms are angiogenic. Promotes survival during differentiation, and may act both to promote and inhibit tumors. May be disrupted in the t(15q+;17q-) found in acute promyelocytic leukemia, but the breakpoint does not occur within the gene. OMIM: 190030.
<b>FGFR1</b>	TK	Cancer, Development	Mut, Trans	Point mutations cause malformed digits and skeletal errors associated with Pfeiffer syndrome [OMIM: 101600], and hypogonadism in dominant Kallmann syndrome 2 [OMIM: 147950]. Stem cell leukemia lymphoma syndrome may be caused by a t(8;13)(p12;q12) translocation that fuses a zinc finger gene (ZNF198) to FGFR1. Various myeloproliferative disorders have been linked to translocations that fuse FGFR1 to FOP, FIM, CEP1 or the atypical kinase, Bcr. Inhibitor: SU5402. OMIM: 136350.
<b>FGFR2</b>	TK	Cancer, Development	Mut, Amp, Del	Mutations cause syndromes with defects in facial and limb development, including Crouzon syndrome [OMIM: 123500], Beare-Stevenson cutis gyrata syndrome [OMIM: 123790], Pfeiffer syndrome [OMIM: 101600], Apert syndrome [OMIM: 101200], and Jackson-Weiss syndrome [OMIM: 123150]. Somatic mutations seen in gastric cancer (Medline:11325814). Amplified in gastric (Medline:14595756), breast (Medline:11564899) and some B cell cancers (Medline:12203778), but deleted in glioblastoma (Medline:14756442). OMIM: 176943.
<b>FGFR3</b>	TK	Cancer, Development	GOF Mut, Trans	Activating point mutations cause dwarfism, including achondroplasia [OMIM: 100800], hypochondroplasia [OMIM: 146000], and thanatophoric dysplasia [OMIM: 187600, 187601]. FGFR3 mutations are also responsible for facial and other morphogenetic disorders, including Crouzon syndrome [OMIM: 123500], craniosynostosis Adelaide type [OMIM: 600593], San Diego skeletal dysplasia [OMIM: 270230] and Muenke syndrome [OMIM: 602849]. Translocations t(4;14) involving the IgH region are common in multiple myeloma and frequently involve FGFR3. Activated FGFR3 found in 30% of bladder cancers and several cervical cancers, but not in other tumors. Two mutations found in colorectal cancer. OMIM: 134934.

## Kinase-Disease Associations

Name	Group	Disease Type	Molecular Basis	Notes
<b>FGFR4</b>	TK	Cancer	SNP, Expr	A common SNP variant associated with increased motility and progression of breast cancer (Medline:11830541, but see also Medline:14710228), head and neck cancer (Medline:15197773) and soft tissue sarcomas (Medline:14601095). Increased expression seen in pituitary adenomas, pancreatic cancer and breast cancer cell lines. OMIM: 134935.
<b>FGR</b>	TK	Cancer	Amp	Ortholog of v-fgr feline oncogene. Mildly amplified in hormone-resistant prostate cancer (Medline:14614009). Copy number either increased or decreased in other cancers. OMIM: 164940.
<b>FLT1</b> (VEGFR1)	TK	Cancer	Meth, OE	Angiogenesis modulator which may both co-operate with and antagonize KDR/VEGFR2 (Medline:14984769). Overexpressed in several tumor types (Medline:12681367, 9582527, 10738243, 10893635), while an antagonistic soluble form is inhibited in progressive tumors (Medline:15112269, 14605010, 15173272). Downregulated by hypermethylation in prostate cancer (Medline:12824880). The soluble receptor and mutant forms have anti-tumor activity in model systems (Medline:15221961, 15126877). Inhibitors: SU11248, PKC412, CEP-5214. OMIM: 165070.
<b>FLT3</b>	TK	Cancer	GOF Mut	Activating mutations found in one third of cases of acute myeloid leukemia (AML), as well as in acute lymphoblastic leukemia, acute promyelocytic leukemia and myelodysplastic syndrome. Inhibitors: Sutent and PKC412. OMIM: 136351.
<b>FLT4</b> (VEGFR3)	TK	Lymphangiogenesis	Act, LOF Mut	Lymphatic-specific VEGF receptor. LOF mutations cause hereditary lymphedema [OMIM: 153100], and at least one case of capillary infantile hemangioma [OMIM: 602089]. Expression of FLT4 ligands is seen in a variety of tumors, including colorectal, prostate, gastric, breast and thyroid cancers, where it is associated with lymph node metastasis (Medline:15086167, 14614015, 14534690, 10430087, 14716745, 15107801). In model systems, overexpression of ligand increases lymph node metastasis, and blocking antibodies and soluble receptors have been used to reduce lymphangiogenesis (Medline:15072591, 11175849). Inhibitors: BAY 43-9006, CEP-7055. OMIM: 136352.
<b>FMS</b> (CSF1R)	TK	Cancer	Mut	Two point mutations seen in 10-20% of patients with acute myeloid leukemia, chronic myelomonocytic leukemia, or myelodysplasia. One mutation is both somatic and germline, and disrupts Cbl binding and receptor turnover (Medline:11847211). v-fms lacks the Cbl binding site and causes feline leukemia. Mutations may also develop after chemotherapy for acute myeloid leukemia (Medline:9403002). A distinct point mutation was found in some cases of hepatocellular carcinoma and related to increased expression, and another mutation was found in 5% of idiopathic myelofibrosis patients (Medline:12580961). Expression is elevated in breast tumors and cell lines, and expression in xenografts and transgenic mice has been correlated with xenograft growth and breast cancer development (Medline:15289345, 15205327, 11205275). Inhibitors: Ki-20227 (Kirin) and other Kit/PDGFR inhibitors. OMIM: 164770.
<b>Fyn</b>	TK	Cancer, Epilepsy	Expr, Model	Induced expression aids in cellular transformation and xenograft metastasis (Medline:3287380, 8325712). In squamous cell carcinoma, Fyn transduces signals from EGFR and Src and is required for cell migration and invasiveness (Medline:11684709). Activity linked to migration in a murine melanoma model (Medline:13129922). Appears to block late stage development of neuroblastoma (Medline:12450793). Mouse knockout deficient in kindling response, a model for human epilepsy. OMIM: 137025.
<b>GRK4</b> (GPRK2L, GPRK4)	AGC	Hypertension	SNP	Multiple SNPs implicated in hypertension, believed to increase kinase activity on dopamine D1 receptor, one SNP validated in rodent model. OMIM: 137026.

## Kinase-Disease Associations

Name	Group	Disease Type	Molecular Basis	Notes
<b>GSK3<math>\alpha</math>, GSK3<math>\beta</math></b>	CMGC	Cardiovascular, CNS, Diabetes, Neurodegeneration	SNP, Act	GSK3 $\alpha$ and GSK3 $\beta$ have similar functions. GSK3 $\alpha$ phosphorylates tau, the principal component of neurofibrillary tangles in Alzheimer disease [OMIM: 104300] and is required for maximal production of amyloid plaque peptides by $\gamma$ secretase. A GSK3 $\beta$ promoter SNP effects progression of bipolar disorder [OMIM: 125480]. The GSK3 inhibitor, lithium, is used to treat bipolar disorder and is seen to block plaque formation. GSK3 generally opposes the action of insulin, and GSK3 hyperactivity is thought to contribute to insulin resistant (type II) diabetes (Medline:15102436, 15078145). GSK3 $\beta$ also negatively regulates cardiac hypertrophy (Medline:12039794). A tumor suppressor role is indicated by the oncogenic potential of stabilized $\beta$ -catenin mutants that lack GSK3 phosphorylation sites. Inhibitor: AR-A014418 (Astra Zeneca). OMIM: 606784, 605004.
<b>HER2 (ErbB2)</b>	TK	Cancer	Amp, OE, Mut	EGF family receptor. Overexpression induces constitutive activity, and the gene is amplified or overexpressed in up to 30% of breast cancers, correlating with poor survival. The antibody Herceptin is approved for treatment of metastatic breast cancer with HER2 amplification/overexpression. Somatic mutations seen in 4% of lung cancers and also in breast, gastric, ovarian cancer and glioblastoma. One SNP shows predisposition to breast and gastric cancer (Medline:10699071, 14520697). Inhibitors: Herceptin (mAb, Genentech), lapatinib (Tykerb, GSK), PKI-166 (Novartis), EKB-569, CI-1033. OMIM: 164870.
<b>HER3 (ErbB3)</b>	TK	Cancer	OE	EGF family receptor. Protein lacks kinase activity, but forms heterodimers with other EGF receptors to transduce growth signals. May be required for HER2 activity (Medline:12853564). Elevated expression in breast and other tumors is indicative of poor outcome (Medline:12866037, 12896906, 14614020, 15150091, 7656248). A secreted form is expressed in metastatic prostate cancer (Medline:15141384). OMIM: 190151.
<b>HER4 (ErbB4)</b>	TK	Cancer	Expr	Heterodimerizes and signals with other EGF receptors and may act as a tumor suppressor. Overexpressed in head and neck cancer (Medline:15476268), but downregulated in renal cancer, papillary carcinoma, high-grade gliomas, and invasive breast cancer (Medline:15360049, 15279891, 15148612, 15084248). Increased receptor activation is associated with schizophrenia (Medline:16767099). OMIM: 600543.
<b>HGK (ZC1)</b>	STE	Cancer	OE	Upregulated in primary tumors and tumor cell lines and is required for anchorage-independent growth and ras-dependent focus formation in multiple cell lines (Medline:12612079). OMIM: 604666.
<b>HIPK1</b>	CMGC	Cancer	OE	Expression elevated in many breast cancer cell lines. Null mice are resistant to carcinogens. Binds the p53 tumor suppressor (Medline:12702766). OMIM: 608003.
<b>HIPK2</b>	CMGC	Cancer	LOH, Expr	Possible tumor suppressor that activates p53 in response to UV light, causing growth arrest and apoptosis. Required for cisplatin-induced apoptosis (Medline:14729469). Downregulated in breast and thyroid carcinomas, but upregulated in some colon carcinomas and familial adenomatous polyposis cases (Medline:11798164, 16467083). OMIM: 606868.
<b>IGF1R</b>	TK	Cancer, Growth, Longevity	Mut, SNP, OE	Mutated in rare cases of pre- and post-natal growth retardation associated with IGF1 resistance. One SNP associated with increased human longevity. Increased expression of IGF1R and other pathway members associated with progression and malignancy in a range of cancers (Medline:15050909, 15050914, 14710347, 12884909). Inhibitors: AG1024, AEW541 (Novartis; Phase 1 multiple myeloma). OMIM: 147370.
<b>IKK<math>\alpha</math>, IKK<math>\beta</math></b>	Other	Cancer, Diabetes, Inflammation		Two closely related kinases that comprise the IKK complex along with the non-kinase nemo (IKK $\gamma$ ). Part of NF $\kappa$ B pathway, with inhibitors under development to treat arthritis, inflammation, and apoptotic aspects of cancer (Medline:14579522, 15013524). Aspirin (sodium salicylate) selectively binds IKK $\beta$ and reduces inflammation. Misexpression and inhibitors show involvement in insulin sensitization in obese rodents. Mutations in nemo [OMIM: 300248] are found in several immune deficiencies, including incontinentia pigmenti [OMIM: 308300], hypohidrotic ectodermal dysplasia [OMIM: 300291], and non-developmental immunodeficiency (Medline:15356572). Inhibitors: CHS 828, NBD peptide, BMS-345541. OMIM: 600664, 603258.

## Kinase-Disease Associations

Name	Group	Disease Type	Molecular Basis	Notes
<b>ILK</b>	TKL	Cancer	OE	Increased expression correlates with progression of several tumor types (breast, prostate, and colon carcinomas) and associates with aggressive tumor growth and poor survival rates in pancreatic cancer patients (Medline:16407822). Overexpression drives anchorage-independent growth and faster cell cycle. OMIM: 602366.
<b>INSR</b>	TK	Development, Diabetes	Mut, SNP	Key regulator of energy metabolism, closely linked to diabetes and obesity. Familial mutations are associated with insulin resistant diabetes, acanthosis nigricans [OMIM: 100600], pineal hyperplasia [OMIM: 262190] and polycystic ovary syndrome [OMIM: 184700]. Mutations also cause leprechaunism [OMIM: 246200], a severe insulin resistance syndrome causing growth retardation and death in early infancy. SNP variants may associate with polycystic ovary syndrome, typical migraine, and diabetic hyperlipidemia (Medline:12477518, 11735220, 11846745). OMIM: 147670.
<b>IRAK2</b>	TKL	Cancer, Inflammation	Mut	One liver tumor linked to a hepatitis B virus insert into this locus (Medline:12813464). A dominant negative construct inhibits bacterial-induced macrophage apoptosis (Medline:11971008). OMIM: 603304.
<b>IRAK4</b>	TKL	Infection	Mut	Two truncation mutations associated with recurrent pyrogenic bacterial infections [OMIM: 607676]. OMIM: 606883.
<b>Jak1</b>	TK	Cancer	Mut, LOF, Act	A selective Jak1 inhibitor induces apoptosis in NRP-154 prostate cancer cell line. A single mutation seen in some colon cancers (Medline:12738854, see supplementary materials), while a loss of function mutation is associated with prostate cancer (Medline:16102578). Activated in B cell lines from patients with post-transplant lymphoproliferative disorder (Medline:12177620), and in a mouse Lck-driven T cell lymphoma (Medline:9548458). Inhibitor: Piceatannol. OMIM: 147795.
<b>Jak2</b>	TK	Cancer	Trans, Act, Mut	Fusion of Jak2 to TEL1 (ETV6) by t(9;12)(p24;p13) causes myeloproliferative disease in humans and mouse models. The Jak inhibitor AG490 inhibits constitutive Jak2 phosphorylation and causes apoptosis in cells from breast cancer and relapsing acute lymphoblastic leukemia (Medline:8628398, 11420660). A single activating mutation is associated with several hematological malignancies, a pair of mutations may associate with acute myelogenous leukemia (Medline:15837627, 16247455). Inhibitor: AG490. OMIM: 147796.
<b>Jak3</b>	TK	Immunity	LOF Mut	Several LOF mutations associated with T-/B+/NK- Severe Combined Immune Deficiency [OMIM: 600802]. Inhibitor: (Rigel) R017s for organ transplants. OMIM: 600173.
<b>JNK1</b>	CMGC	Cancer, Diabetes, Inflammation		Activity increased in obesity. Inhibition or mouse knockout increases insulin sensitivity (Medline:12447443). Part of NF- $\kappa$ B pathway involved in inflammation and cancer, and signals downstream of Ras, though possibly as an apoptotic negative regulator of growth (Medline:12734425). OMIM: 601158.
<b>JNK3</b>	CMGC	Cancer, CNS	Expr	Brain-selective JNK isoform. Pro-apoptotic gene and potential tumor suppressor. Expression lost in brain tumors (Medline:11322657). May function in neuronal cell death from injury and neurodegeneration, for which inhibitors are being developed (Medline:15501728, 14657393, 14704277). OMIM: 602897.
<b>KDR (FLK1, VEGFR2)</b>	TK	Cancer	Mut	Required for tumor angiogenesis in solid cancers, and the target of several anti-angiogenic therapies. Point mutation found in one case of capillary infantile hemangioma [OMIM: 602089], and several mutations seen in survey of colon cancers (Medline:12738854). Inhibitors: Sutent (Sugen), Avastin (mAb, Genetech), Nexavar (Bayer/Onyx), PTK787 (Novartis). OMIM: 191306.
<b>Kit</b>	TK	Cancer, Depigmentation	GOF Mut, LOF Mut, Act?	Activating mutations cause >90% of gastrointestinal stromal tumors [OMIM: 606764]; successfully treated with inhibitors Gleevec (imatinib, Glivec) and Sutent (Sutinib, SU11248). Activating mutations also induce mast cell disease and the associated skin disorder urticaria pigmentosa [OMIM: 154800; Medline:15507672]. Autocrine/paracrine stimulation may drive some lung and other tumors (Medline:15036937). Loss of expression associated with melanoma progression (Medline:9687504). Familial loss of function mutations cause piebaldism [OMIM: 172800], with defects in hair and skin pigmentation due to lack of melanocytes. OMIM: 164920.

## Kinase-Disease Associations

Name	Group	Disease Type	Molecular Basis	Notes
<b>LATS1</b>	AGC	Cancer	Meth, Expr, Mut	Likely tumor suppressor and ortholog of Drosophila warts tumor suppressor. Binds and inactivates cdc2, causing G2 arrest. Knockout mice are susceptible to soft-tissue sarcomas and sensitive to chemical carcinogenesis. Human soft tissue sarcomas have downregulated, mutated, and/or hypermethylated LATS1 (Medline:12379777). Transgenic expression blocks anchorage independent growth in culture and tumor growth in xenografts (Medline:11850843). OMIM: 603473.
<b>LATS2</b>	AGC	Cancer	Expr	Tumor suppressor, blocks CDK2 activity, leading to G1 arrest. Ectopic expression induces apoptosis in lung cancer cell lines (Medline:15265683). Negatively regulates androgen receptor, and is downregulated in prostate cancer (Medline:15131260). OMIM: 604861.
<b>Lck</b>	TK	Cancer, Immunity	Trans, Mut, Expr, Splice	Overexpression in mice leads to thymic tumors (Medline:1708890). Aberrant expression is seen in T cell leukemias (Medline:10706447) and colon cancer (Medline:9416836). The leukemic translocation t(1;7)(p34;q34) has breakpoints at the T cell receptor gene and close to the Lck promoters, can cause increased Lck expression, and in one case, point mutations (Medline:8139546). A mutated Lck has also been seen in a cell line. One patient with aberrant Lck splicing suffered from SCID-like T cell deficiency. Inhibitor: BMS-279700. OMIM: 153390.
<b>LIMK1</b>	TKL	Cancer, Development	OE, Amp, LOH	Mediates Rho signaling to cytoskeleton. Overexpressed in prostate tumors and prostate and breast cancer cell lines; manipulation of activity correlates with invasiveness in breast and prostate cancer models. Located within the 7q11.2 amplicon associated with metastatic prostate cancer (Medline:12821664, 12777619). Loss of one copy of LIMK1 is the likely cause of visuospatial cognition defects seen in small chromosomal deletions associated with a partial form of Williams-Beuren syndrome [OMIM: 194050]. OMIM: 601329.
<b>LKB1 (STK11)</b>	CAMK	Cancer	LOF Mut, LOH	Several distinct loss of function point mutants cause Peutz-Jeghers syndrome [OMIM: 175200], causing gastrointestinal polyps and cancer susceptibility. Sporadic mutations and loss of heterozygosity also seen in melanoma, pancreatic cancer and testicular cancer. OMIM: 602216.
<b>LRRK2</b>	TKL	Neurodegeneration	Mut	A G2019S activating mutation within the activation loop is the most common cause of autosomal dominant Parkinson's disease [OMIM: 607060]. Seven other mutations also linked to Parkinson's. OMIM: 609007.
<b>LTK</b>	TK	Immunity	SNP	Polymorphism associated with the autoimmune disease Systemic Lupus Erythematosus [OMIM: 152700] in both mice and humans; likely impact via PI3K signaling. OMIM: 151520.
<b>Lyn</b>	TK	Cancer	Act	Mouse knockout develops monocyte/macrophage tumors, while an activated transgene does not induce tumors. Hyperactivated in acute myeloid leukemia; treatment by antisense or drug inhibitors reduces proliferation (Medline:10360372). Lyn-specific inhibitors block proliferation in three prostate cancer cell lines (Medline:14871838). OMIM: 165120.
<b>MASTL</b>	AGC	Hematopoiesis	Mut	One mutation found in autosomal dominant thrombocytopenia [OMIM: 188000], which is associated with incomplete megakaryocyte differentiation. OMIM: 608221.
<b>MEK1, MEK2 (MAP2K1, MAP2K2)</b>	STE	Cancer, Cardiac, Development, Virology	Mut, OE	Two closely related kinases, targeted by the small molecule CI-1040 (PD184352), which inhibits colon cell line growth and motility in culture and xenografts. Overexpressed/overactivated in multiple tumor types. The Mek1/2 inhibitor U0126 blocks export of influenza viral particles and has been suggested as an antiviral treatment. Single mutations at homologous points within each gene are associated with cardiofaciocutaneous syndrome [OMIM: 115150], morphological, cardiac and mental defects. Inhibitors: U0126, CI-1040/PD184352, PD-0325901 (Pfizer, Phase I cancer), ARRY-142886 (Phase 1, cancer). OMIM: 176872, 601263.
<b>MER</b>	TK	Vision	LOF Mut	LOF mutations cause photoreceptor degeneration in retinitis pigmentosa [OMIM: 268000], thought to be due to lack of clearance of apoptotic cells. OMIM: 604705.

## Kinase-Disease Associations

Name	Group	Disease Type	Molecular Basis	Notes
<b>Met</b>	TK	Cancer	GOF Mut, OE, Trans	Activating point mutations cause hereditary papillary renal carcinoma [OMIM: 605074]. Mutations also seen in sporadic renal cell carcinoma and childhood hepatocellular carcinoma. Upregulation in carcinomas and sarcomas correlates with metastasis and poor outcome (Medline:14617781). Some gastric carcinomas harbor a translocation that creates an activated TPR-Met fusion protein (Medline:2052572). A small molecule inhibitor (PHA-665752) shows an effect in gastric carcinoma xenografts (Medline:14612533). Inhibitors: SU11274, PHA-665752, mAbs. OMIM: 164860.
<b>MISR2</b> (AMHR2)	TKL	Reproduction	Mut	Mutations cause Mullerian duct syndrome type II [OMIM: 261550], a developmental failure of Mullerian duct (female genital primordia) to regress in males. OMIM: 600956.
<b>MKK3</b> (MAP2K3)	STE	Cancer	Mut, Del	A deletion and two point mutants found in lung cancer cell lines (Medline:11414763). OMIM: 602315.
<b>MKK4</b>	STE	Cancer	LOF, Mut, Del	Inactivating mutations or deletions seen in approximately 5% of tumors from diverse backgrounds (Medline:11754110). OMIM: 601335.
<b>MLK4</b>	TKL	Cancer	Mut	Nine distinct point mutations found in a sample of 182 colon cancer tumors and cell lines (Medline:12738854).
<b>Mst4</b>	STE	Cancer	OE	Expression correlates with tumorigenicity in prostate tumors and cell lines. Expression of wild type and inactivating mutant transgenes indicates a role in anchorage-independent growth and tumorigenic proliferation downstream of the EGFR family (Medline:12810671). OMIM: 300547.
<b>mTOR</b> (FRAP)	Atypical	Cancer		Controls cell growth through protein synthesis regulation. Downstream of PI3K/Akt pathway and required for cell survival. Inhibitors: rapamycin, temsirolimus (CCI-779; Wyeth). OMIM: 601231.
<b>MusK</b>	TK	Neuro	Auto-antibodies, Mut	Agrin receptor expressed on neuromuscular junction. Auto-antibodies, seen in some neuromuscular disease myasthenia gravis (Medline:16155434) cases, cause the disease in an animal model (Medline:16557298), and may be pathogenic in humans (Medline:16857268). Two LOF mutations seen in one human case (Medline:16550915). OMIM: 601296.
<b>MYO3A</b>	STE	Sensory	Mut	Three mutations associated with progressive deafness. OMIM: 606808.
<b>NEK1</b>	Other	Development, Renal	Model	Mouse mutants lead to facial malformation, male sterility, and polycystic kidney disease [OMIM: 601313]. OMIM: 604588.
<b>NEK2</b>	Other	Cancer	OE	Overexpressed in Ewing's tumors (Medline:11836553) and diffuse large B cell lymphoma (Medline:12594241). OMIM: 604043.
<b>NEK8</b>	Other	Cancer, Renal	OE	Mutations cause polycystic kidney disease in mouse and (by gene knockdown) in Zebrafish (Medline:12421721). Overexpressed in breast tumors (Medline:15019993). OMIM: 609799.
<b>p38</b> ( $\alpha, \beta, \delta, \gamma$ )	CMGC	Cancer, Inflammation		Four closely related isoforms ( $\alpha, \beta, \delta, \gamma$ ) involved in apoptosis and stress responses. Mediate actions of pro-inflammatory cytokines; inhibitors under development to treat inflammation, autoimmunity, diabetes, and cancer (Medline:12725866, 12783612, 12790339). Inhibitors: doramipimod/BIRB-796 (Boehringer Ingelheim; Phase 2-3 for psoriasis, Crohn's disease, and arthritis), SCIO-469, SCIO-323 (Scios; Phase 1 arthritis), AMG-548 (Amgen), ARQ-101 (ArQule), CDP-11 (Celltech), VX-702 (Vertex; Phase 2 acute coronary syndrome). OMIM: 600289, 602898, 602899, 602399.
<b>p70S6K</b> (RPS6KB1)	AGC	Cancer, Diabetes	OE, Amp	Mouse knockout shows symptoms of insulin resistance, and increased insulin sensitivity, resulting in protection against diet-induced obesity (Medline:15306821). Protein expression and activation upregulated in colon adenocarcinoma cell lines (Medline:14578160). Increased expression in breast cancer correlated with poor survival (Medline:15083183). Selectively amplified and overexpressed within the 17q23 breast cancer amplicon (Medline:12755490, 11331760). Mediator of signaling from the oncogenic kinase mTOR. OMIM: 608938.
<b>PAK3</b>	STE	Cognition	LOF Mut	Missense and truncation mutations linked to nonsyndromic X-linked mental retardation [OMIM: 300558] (Medline:12884430, 10946356, 9731525). OMIM: 300142.

## Kinase-Disease Associations

Name	Group	Disease Type	Molecular Basis	Notes
<b>PAK4</b>	STE	Cancer	OE	Overexpressed in several cancers from diverse backgrounds. Required for ras-dependent anchorage-independent growth of tumor cell lines (Medline:11668177). OMIM: 605451.
<b>PDGFR<math>\alpha</math></b>	TK	Cancer, Development	Trans, Del, Mut, Act	Chromosomal rearrangements activate PDGFR $\alpha$ by fusion to BCR, causing atypical chronic myelogenous leukemia [OMIM: 608232], and to FIP1L1, causing idiopathic hypereosinophilic syndrome [OMIM: 607685]. Activating point mutations cause a minority of gastrointestinal stromal tumors [OMIM: 606764]. Promoter polymorphisms linked to neural tube defects including spina bifida (Medline:11175793), verified by mouse mutant model (Medline:9826722). Inhibitors: Gleevec, Sutent. OMIM: 173490.
<b>PDGFR<math>\beta</math></b>	TK	Cancer	Trans, Act, OE	A variety of myeloproliferative disorders and cancers result from translocations that activate PDGFR $\beta$ by fusion with proteins such as TEL/ETV6, H2, CEV14/TRP11, rabaptin 5, and huntington interacting protein 1. Gleevec treatment of TEL fusions has been successful. Overexpressed in metastatic medulloblastoma. Inhibitors: Gleevec, Sutent. OMIM: 173410.
<b>PEK (PERK)</b>	Other	Diabetes	LOF Mut	Functions in the ER unfolded protein response and linked to insulin processing. LOF mutations cause Wolcott-Rallison syndrome [OMIM: 226980], characterized by insulin-dependent diabetes in early infancy and, later, multiple system abnormalities. Neuronal death in Alzheimer's and Parkinson's diseases is thought to be due to ER stress and has been weakly linked to PEK. OMIM: 604032.
<b>PHK<math>\gamma</math>2</b>	CAMK	Metabolism	LOF Mut	LOF mutations cause liver glycogenosis and one form of liver cirrhosis. OMIM: 172471.
<b>Pim1</b>	CAMK	Cancer	Trans, OE, Mut	Expression increased in prostate cancer, where it may lead to genomic instability (Medline:14678956) and reduce androgen receptor-dependent transcription (Medline:13679438). Expression level has prognostic value. Overexpression also seen in hematopoietic malignancies, and is a target of aberrant somatic hypermutation in diffuse large-cell lymphomas. T cell lymphomas are induced in Pim1 transgenic mice and by frequent viral insertions at the Pim1 locus. OMIM: 164960.
<b>Pim2</b>	CAMK	Cancer	Expr, Model	Increased expression is seen in chronic lymphocytic leukemia and non-Hodgkin's lymphomas (Medline:15291354). Similar to Pim1, mouse T cell lymphomas are induced by a PIM2 transgene, and by viral insertions. OMIM: 300295.
<b>Pim3</b>	CAMK	Cancer	Expr	Aberrant expression seen in hepatocellular carcinoma (Medline:15540201). May substitute for Pim1 and Pim2 in mouse virally driven cancer models (Medline:12185366).
<b>PINK1</b>	Other	Cancer, Neurodegeneration	Mut, Expr	Two mutations cause hereditary early onset Parkinson's disease [OMIM: 605909; Medline:15087508]. Association with PTEN tumor suppressor and decreased expression in ovarian tumors may indicate a role in cancer. OMIM: 608309.
<b>PKC<math>\alpha</math></b>	AGC	Cancer, Cardiovascular	Mut, Del, OE, Act	A point mutation seen in several pituitary and thyroid tumors (Medline:9167945). Deleted in a melanoma cell line. Complex expression pattern in breast cancer (Medline:15459489, 15454252). Therapeutic target in lung, gastric and prostate cancer (Medline:15447994, 15313921, 15174974). May mediate multidrug resistance (Medline:12390766). Mouse models indicate a role in heart contractility (Medline:14966518). Inhibitors: LY-900003 (antisense, aka Affinitak/ISIS 3521/aprincarsen), Safingol, Go6976 . OMIM: 176960.

## Kinase-Disease Associations

Name	Group	Disease Type	Molecular Basis	Notes
<b>PKC<math>\beta</math></b>	AGC	Autism, Cancer, Diabetes	SNP	Two promoter SNPs associated with diabetic nephropathy (Medline:12874455), correlating with induction of renal expression by high glucose, reduction in renal function by a specific PKC $\delta$ inhibitor, and successful inhibitor treatment of rodent models of diabetic nephropathy (Medline:12955673). Inhibition also proposed to treat diabetic retinopathy (Medline:12507628) and diabetic vascular complications (Medline:11903393). Ectopic expression in mouse heart leads to cardiac hypertrophy. Elevated expression is seen in and promotes early stages of colon cancer in mouse models (Medline:11245437). May mediate multidrug resistance (Medline:12697075). Activation protects astrocytes from ischemic injury (Medline:15165841). SNPs associated with autism (Medline:16027742). Inhibitors: LY333531 (ruboxistaurin; Phase 3 for diabetic neuropathy and retinopathy), LY317615 (Eli Lilly; isoform selective). OMIM: 176970.
<b>PKC<math>\delta</math></b>	AGC	Cancer, Cardiovascular, CNS	Expr	Pro-apoptotic. Reduced expression correlated with progression of colon and other cancers (Medline:15054085, 12657722, 12591726). Inhibition may drive chemo-resistant cancers to apoptosis. Activated and promotes apoptosis in cardiac and neuronal cells after ischemic-reperfusion injury (Medline:14654063, 15295022). Activator: bistrane A. Inhibitors: rottlerin, KAI-9803 (KAI; Phase 2 trials for reperfusion injury), dV1-1. OMIM: 176977.
<b>PKC<math>\epsilon</math></b>	AGC	Cancer, Cardiovascular, CNS	Amp, Mut	Amplified and rearranged in thyroid cancers (Medline:9683604, 10438519, 11994357). Promotes growth of an androgen-independent prostate cancer cell line (Medline:11956106) and transforms fibroblasts in culture (Medline:11968018). Activation protects cardiac myocytes and neurons from ischemic injury (Medline:15165841), antagonizing PKC $\delta$ . Amyloid $\beta$ peptide inhibits PKC $\epsilon$ activity and may contribute to the pathogenesis of Alzheimer disease (Medline:15207847). Inhibitor studies indicate role in pain perception (Medline:10433272). Multi-isoform inhibitors include: Bryostatin-1 (BRYO; Aphios) and Perifosine/D-21266 (Baxter.) OMIM: 176975.
<b>PKC<math>\gamma</math></b>	AGC	Pain, Neurodegeneration	Mut	Point mutations linked to dominant spinocerebellar ataxia type 14 [OMIM: 605361]. Knockout and inhibitor studies show role in pain perception (Medline:14762097, 9323205). OMIM: 176980.
<b>PKC<math>\eta</math></b>	AGC	Cancer	Expr, Model, Inh	Expression progressively increased in renal cell carcinoma (Medline:14666709). Antisense knockdown enhances apoptotic effect of TRAIL on cancer cells (Medline:15252138) and of chemotherapeutics (Medline:15159020). May act as a tumor suppressor in mouse skin knockout model (Medline:12750259, 12473186). OMIM: 605437.
<b>PKC<math>\tau</math></b>	AGC	Cancer, Immunity	Model	Required for activation and proliferation of mature T cells. Proposed as a target for T cell leukemias (Medline:12188914). Knockout is resistant to fat-induced insulin resistance. OMIM: 600448.
<b>PKG</b>	AGC	Pain	Model	Rat studies indicate role of PKG in chronic pain response (Medline:16730916). Inhibitor: KT5823.
<b>PKR (PRKR)</b>	Other	Cancer, Neurodegeneration, Virology	Mut, Expr, Act	Mediates translational arrest and apoptosis in response to viral infection and inflammation. Activation by dsRNA against tumor transcripts under investigation as an anti-tumor agent (Medline:15174900). Posttranslationally inactivated in leukemia (Medline:14961569) and rearranged in a mouse leukemia line (Medline:9806790). Expression and activity are elevated in breast cancer lines (Medline:10871861) and hepatocellular carcinoma (Medline:14638359); prognostic of neoplastic progression in melanoma and colon carcinoma (Medline:12483527). Binds to transcripts containing trinucleotide repeats, including Huntingtin and DMPK, which underlies myotonic dystrophy (Medline:11468270,10668800, 12437593). OMIM: 176871.
<b>PLK1</b>	Other	Cancer	Expr	Elevated expression in many cancers including prostate and colon. Transforms cells to grow in soft agar. Involved in cell cycle. siRNA induces apoptosis in cancer cells and xenografts. Inhibitor: <Cyclacel>. OMIM: 602098.
<b>PRKX, PRKY</b>	AGC	Reproduction	Trans	A chromosomal translocation with breakpoints at the PRKX and PRKY loci [t(X;Y)(p22;p11)] accounts for approximately 30% of sex reversal cases (XX males and XY females). OMIM: 300083, 400008.

## Kinase-Disease Associations

Name	Group	Disease Type	Molecular Basis	Notes
<b>Raf1</b> (c-Raf)	TKL	Cancer	Amp	Mediator of ras signaling and of an anti-apoptotic signal downstream from VEGF and FGFR receptors (Medline:12843393). Amplified in several tumors including bladder, nasopharyngeal carcinoma, hormone resistant prostate cancer, and anaplastic large cell leukemia (Medline:11389083, 12696066, 15666389, 11836556). Antisense regresses xenograft tumors (Medline:12022686). Inhibitors: sorafenib/BAY-43-9006 (Bayer), ISIS5132 (Isis, antisense). OMIM: 164760.
<b>Ret</b>	TK	Cancer, Development	LOF and GOF Mut, Trans	Familial GOF mutations cause endocrine cancers, including medullary thyroid carcinoma [OMIM: 155240] and multiple neoplasia types IIA and IIB [OMIM: 171400, 162300], which predispose individuals to thyroid carcinoma and pheochromocytoma. Translocation-mediated fusion of Ret to various genes (H4, ELE1, PKA-R1, TIF1A, TIF1G) results in papillary thyroid carcinoma [OMIM: 188550]. Familial LOF mutations cause Hirschsprung disease [OMIM: 142623], in which enteric (intestinal) neurons fail to develop. OMIM: 164761.
<b>RHOK</b> (GRK1)	AGC	Vision	LOF Mut	Phosphorylates and inactivates photon-activated rhodopsin. LOF mutations lead to type 2 Oguchi disease [OMIM: 258100], a form of night blindness. A link between RHOK and retinitis pigmentosa is now thought to be unlikely (Medline:9268593). OMIM: 180381.
<b>RNaseL</b>	Other	Cancer, Virology	Mut	Point mutations associated with HPC1 hereditary prostate cancer [OMIM: 601518]. Mouse model indicates a role in interferon-mediated antiviral response. OMIM: 180435.
<b>ROCK1, ROCK2</b>	AGC	Cardiovascular, Hypertension, Neurodegeneration		Two related Rho-activated kinases, ROCK1 and ROCK2, regulate smooth muscle contractility. A ROCK-specific inhibitor causes smooth muscle relaxation and is effective in rat models of hypertension (Medline:9353125) and in reduction of intraocular pressure (Medline:11584347). ROCK1 controls formation of A- $\beta$ amyloid protein in Alzheimer plaques; inhibitors reduce A- $\beta$ levels in a mouse model. ROCK2 null mice indicate a role in blood coagulation (Medline:12832488). ROCK-cytoskeletal links are associated with metastasis and invasion in bladder cancer (Medline:12855641) and in cellular and animal models (Medline:12524136, 12823259, 9930872). The inhibitor fasudil is approved for treatment of cerebral vasospasm and under investigation for treatment of angina and hypertension. Inhibitors: fasudil, Ki29035 (Kirin), Y-27632, Wf-536, HA-1077, H-1152P. OMIM: 601702, 604002.
<b>RON</b>	TK	Cancer	OE, Splice	Functions in cell migration and epithelial-mesenchymal transition. Highly expressed in tumors, including head and neck cancer (Medline:15023838), colon (Medline:12527888), breast (Medline:9671413) ovarian carcinoma (Medline:12915129), and renal oncocytoma (Medline:15252311). Unusual splice variants seen in cancer, including a constitutively active form lacking the extracellular domain (Medline:12527888, 15289319). Overexpression in mouse lung leads to pulmonary adenomas (Medline:12214279). OMIM: 600168.
<b>ROR2</b>	TK	Development	GOF Mut, LOF Mut	Carboxy-terminal deletions produce both gain and loss of function mutations seen in a pair of skeletal malformation disorders. GOF mutations produce dominant brachydactyly type B [OMIM: 113000] while LOF results in autosomal recessive Robinow syndrome [OMIM: 268310]. OMIM: 602337.
<b>ROS</b>	TK	Cancer	Trans, Expr	Fused to the FIG1 gene through chromosomal deletion to produce a constitutively activate RTK in at least case of glioblastoma. Reportedly misexpressed in CNS meningiomas. OMIM: 165020.
<b>RSK2</b> (RPS6KA3)	AGC	CNS, Development	LOF Mut	LOF mutations cause dominant Coffin-Lowry syndrome [OMIM: 303600], characterized by severe mental retardation with facial, digital and progressive skeletal deformations. OMIM: 300075.
<b>SGK1</b>	AGC	Cancer, Cognition, Diabetes	Expr	Expression elevated in diabetic nephropathy, stimulating sodium transport. Mediates anti-apoptotic effect of glucocorticoids in breast cancer cell lines. Expression elevated in brains of fast-learner rats in a water maze test, and transient transfection of normal and mutant gene indicates a positive role in learning. OMIM: 602958.
<b>skMLCK</b> (MYLK2)	CAMK	Cardiovascular	Mut	A single case of familial hypertrophic cardiomyopathy [OMIM: 192600] linked to a mutation in skMLCK. OMIM: 606566.

## Kinase-Disease Associations

Name	Group	Disease Type	Molecular Basis	Notes
<b>Src</b>	TK	Cancer	Mut, OE, Act	Homolog of Rous sarcoma virus v-src. Truncation produces an activated protein in approximately 12% of individuals with colon cancer from a single population, though this mutation is absent from other groups (Medline:9988270, 10704743, 10485460, 11161376). The same mutation may occur in some cases of endometrial sarcoma (Medline:10804287). Expression and kinase activity are frequently increased in a wide array of cancers, including tumors from breast, colon, pancreas, lung, ovary and CNS (Medline:12884910). Inhibitors: SU6656 (Sugen), PD173955, PD166285 (Pfizer), CGP76030 (Novartis), BMS-354825 (BMS; Phase 2 cancer). OMIM: 190090.
<b>Syk</b>	TK	Allergy, Cancer	Meth, Splice	Acts as a tumor suppressor in breast tissue; expression progressively reduced by hypermethylation in developing tumors (Medline:15455373). Silencing through methylation is also seen in gastric cancer. Aberrant splice forms encoding kinase-deficient isoforms found in childhood acute lymphoblastic leukemia (Medline:11494125). Required for mast cell activation and release of allergic mediators; potential target in allergy, asthma and inflammation (Medline:15212616). Inhibitors: R-406, R-788 (Rigel), BAY 61-3606, Piceatannol, and programs at Aventis, Yamanouchi, Boehringer Ingelheim, Novartis. OMIM: 600085.
<b>TGFβ1 (ALK5)</b>	TKL	Cancer, Development	SNP, Mut, Expr	A common variant allele carried by approximately 10% of the population, TGFβ1*6A, is associated with higher incidence of breast, colon, ovarian and hematological cancers (Medline:14966109). A distinct intronic SNP is associated with both bladder and kidney carcinoma (Medline:15382067). Protein and RNA expression elevated in lung cancer (Medline:14596814), and the overall TGFβ signaling pathway has been observed as disrupted in a range of cancers. Mutated in Loews-Dietz Syndrome [OMIM: 609192], characterized by cardiovascular, craniofacial, neurocognitive, and skeletal abnormalities. Inhibitor: SB-505124. OMIM: 190181.
<b>TGFβ2</b>	TKL	Cancer, Development, Fibrosis	LOF Mut	Anti-growth receptor. Both TGFβ2 and IGFR2 have microsatellite repeat sequences, and one of the two is mutated in most colon and gastric tumors with microsatellite instability. Also linked to esophageal cancer [OMIM: 133239]. Mutations are common in a form of hereditary nonpolyposis colorectal cancer [OMIM: 120435], where microsatellite instability results from defective DNA repair. Germline mutations are associated with Marfan's syndrome type II [OMIM: 154705] and related connective tissue diseases. Mutated in Loews-Dietz Syndrome [OMIM: 609192], characterized by cardiovascular, craniofacial, neurocognitive, and skeletal abnormalities. TGFβ signaling is also implicated in fibrosis and wound healing (Medline:15117886). Inhibitor: <Fibrogen>. OMIM: 190182.
<b>Tie2 (TEK)</b>	TK	Angiogenesis, Cancer	Act, GOF Mut, OE	Point mutations cause dominantly inherited venous malformations [OMIM: 600195]. Expression is increased in non-small cell lung cancer (Medline:10499626), myeloid leukemia (Medline:11755466), and hepatocellular carcinoma (Medline:11915032), and is prognostic of metastasis in breast cancer (Medline:12527939, 15026804). Expression and activation correlate with malignancy in astrocytomas (Medline:14742253). Soluble receptor used to inhibit tumor growth in mice (Medline:14985859). OMIM: 600221.
<b>TITIN</b>	CAMK	Cardiovascular	Mut	Mutations found in hypertrophic and dilated cardiomyopathies [OMIM: 604145] and tibial muscular dystrophy [OMIM: 600334]. OMIM: 188840.
<b>Tpl2 (COT)</b>	STE	Cancer, Inflammation	OE, Amp, Act, Mut	Overexpressed and amplified in breast tumors, rarely activated in lung tumors. Viral insertions induce rat lymphomas and mouse mammary carcinomas. Isolated as a transforming factor in two cell lines. Mediates LPS activation of macrophages (Medline:15485931). Inhibitor: <Abbott>. OMIM: 191195.

## Kinase-Disease Associations

Name	Group	Disease Type	Molecular Basis	Notes
<b>TrkA</b> (NTRK1)	TK	Cancer, Sensory	Mut, Trans	Point mutations and translocations creating TrkA fusion proteins found in papillary thyroid carcinoma. Fusion partners include TPM3 (tropomyosin), TRP, TFG and Tag. Also implicated in breast and ovarian cancer (Medline:15379632, 14997042, 12796393) and some melanomas (Medline:15362372). Neuroblastomas, gliomas and astrocytomas have dynamic TrkA expression, and increased expression has been correlated with good prognosis (Medline:9049830). Mutations have been seen in cases of congenital insensitivity to pain with anhidrosis [OMIM: 256800], characterized by insensitivity to pain and noxious stimuli, anhidrosis (absence of sweating), self-mutilation and mental retardation. A mouse TrkA knockout has a similar phenotype. Inhibitor: K-252a. OMIM: 191315.
<b>TrkB</b> (NTRK2)	TK	Cancer	Mut	Two separate point mutations found in a set of 182 colon tumors and cell lines (Medline:12738854). In rat, TrkB inhibits anoikis and enhances metastasis (Medline:15329723). Hepatitis B viral insertion into this locus can result in hepatocellular carcinoma (Medline:12813464). TrkB elevated expression is associated with poor prognosis in neuroblastoma (Medline:10994551) and may mediate chemoresistance (Medline:12438236). OMIM: 600456.
<b>TrkC</b> (NTRK3)	TK	Cancer	Trans, Mut, Expr	Fusion gene EV6-TrkC found in pediatric mesenchymal cancers (Medline:9462753) and rat secretory breast carcinoma. Five point mutations found in a sample of 182 colon tumors and cell lines (Medline:12738854). Expression correlates with favorable prognosis in childhood medulloblastoma (Medline:7809137) OMIM: 191316.
<b>Tyk2</b>	TK	Immunity, Inflammation	Model	Signals in immunity downstream of IFN. Natural mouse strain with Tyk2 mutation is susceptible to parasite infection and resistant to autoimmune arthritis (Medline:14500783). Inhibitor: Piceatannol. OMIM: 176941.
<b>TYRO3</b> (SKY)	TK	Cancer	OE	Transforming oncogene in culture studies (Medline:7896835). Overexpression leads to ligand-independent activation (Medline:8545119). Overexpressed in mouse mammary tumors (Medline:7896835) and human multiple myeloma (Medline:11468178). Downregulated in astrocytomas (Medline:11156382), and a triple knockout of Tyro3/Mer/Axl in mouse has hyperproliferation defects (Medline:11452127), indicating positive and negative growth control functions. OMIM: 600341.
<b>WNK1</b>	Other	Hypertension	Intronic Mut	Two separate intronic deletions found in familial hypertension (type II pseudohypoaldosteronism) [OMIM: 145260]. OMIM: 605232.
<b>WNK4</b>	Other	Hypertension	Mut	Expressed exclusively in distal convoluted tubule of kidney, localized to tight junctions. Distinct point mutations found in 4 cases of type II pseudohypoaldosteronism [OMIM: 145260]. OMIM: 601844.
<b>Yes</b>	TK	Cancer	Amp, Act	Ortholog of Yamaguchi sarcoma virus v-yes oncogene, which can transform fibroblasts <i>in vitro</i> (Medline:3303862). Amplified in one case of gastric cancer and in canine mammary tumors (Medline:3935622, 10081762). Kinase activity is increased in colon carcinoma cell lines and tumors (Medline:7690925, 7806032) and in melanoma cell lines and brain metastases (Medline:7690926, 9681823). Mouse knockouts have no strong phenotype due to compensation by Src and Fyn (Medline:7958873). OMIM: 164880.
<b>Zap-70</b>	TK	Immunity	Mut	Mutations cause selective T cell defect, a recessive form of severe combined immunodeficiency exhibiting selective absence of CD8+ T cells (Medline: 8202713). Reduced expression predicts positive outcome in B cell chronic lymphocytic leukemia. The SKG mouse is mutated at Zap-70, producing increased numbers of self-reactive T cells, resulting in chronic arthritis. OMIM: 176947.