Supplemental Table I. Genes and SNPs of the Illumina SNP Cancer Panel, grouped by pathway

Genes and SNPs included in the Illumina SNP Cancer Panel. These are described and grouped in major cancer pathways by using information from the NCBI Web pages, the genecards website of the Crown Human Genome Centre & Weizmann Institute of Science.

DNA MISMATCH REPAIR, MICROSATELLITE AND CHROMOSOMAL INSTABILITY PATHWAYS

Stability genes or caretakers act to keep genetic alterations to a minimum. Depending on the type of damage inflicted on the DNA's double helical structure, a variety of repair strategies have evolved to restore lost information. They include the mismatch repair (MMR), nucleotide-excision repair (NER), and base-excision repair (BER) genes, as well as genes responsible for mitotic recombination and chromosomal segregation. The types of molecules involved and the mechanism of repair that is mobilized depend on the type of damage that has occurred and the phase of the cell cycle that the cell is in.

Gene	Location	SNP	Group and function of protein	Related disease
APEX1	14q11.2-q12	rs1760944 rs3136814 rs3136820	APEX nuclease (multifunctional DNA repair enzyme) 1; major AP endonuclease; Apurinic/apyrimidinic (AP) sites occur frequently in DNA molecules by spontaneous hydrolysis, by DNA damaging agents or by DNA glycosylases that remove specific abnormal bases, they are pre-mutagenic lesions that can prevent normal DNA replication; class II AP endonucleases cleave the phosphodiester backbone 5' to the AP site	rhabdomyosarcoma
RAD23B	9q31.2	rs1805329 rs1805330 rs1805334 rs1805335	RAD23 homolog B (S. cerevisiae); one of two human homologs; involved in the nucleotide excision repair (NER)	melanoma
RAD51	15q15.1	rs11852786 rs1801320 rs2304579 rs2412546 rs2412547 rs2619679 rs2619681 rs4144242 rs4924496	RAD51 homolog (RecA homolog, E. coli) (S. cerevisiae); involved in homologous recombination and repair of DNA; interacts with the ssDNA-binding protein RPA and RAD52; plays role in homologous pairing and strand transfer of DNA; interacts with BRCA1 and BRCA2, which may be important for the cellular response to DNA damage	
RAD52	12p13-p12.2	rs11226 rs6413436	RAD52 homolog (S. cerevisiae); important for DNA double-strand break repair and homologous recombination; binds single-stranded DNA ends, and mediates the DNA-DNA interaction necessary for the annealing of complementary DNA strands; interacts with DNA recombination protein RAD51 à role in RAD51 related DNA recomb. and repair	
RAD54L	1p32	rs1048771	RAD54-like; DEAD-like helicase superfamily; involved in the homologous recombination and repair of DNA; homologous recombination related repair of DNA double-strand breaks; binding of this protein to double-strand DNA induces a DNA topological change, which is thought to facilitate homologous DNA paring and stimulate recombination	pancreatic cancer
BRCA1	17q21	rs1060915 rs16940 rs1799949 rs1799950 rs1799966 rs4986852 rs799923 rs8176212	breast cancer 1, early onset; nuclear phosphoprotein that plays a role in maintaining genomic stability and acts as a **tumor suppressor**; protein thus plays a role in transcription, DNA repair of double-stranded breaks, and recombination; responsible for approximately 40% of inherited breast cancers and more than 80% of inherited breast and ovarian cancers	young onset breast cancer, ovarian cancer

BRCA2	13q12.3	rs144848 rs15869 rs1799943 rs1799955 rs1801406 rs206147 rs543304	breast cancer 2, early onset; BRCA2 mutations are typically microdeletions; functions as a tumor suppressor gene; however, its exact function has not been well characterized; transcriptional activation potential and the two proteins are associated with the activation of double-strand break repair and/or homologous recombination; **tumor suppressor**	young onset breast cancer
BARD1	2q34-q35	rs2070096 rs2229571 rs5031011	BRCA1 associated RING domain 1; formation of a stable complex between BARD1/BRCA1 may be an essential aspect of BRCA1 **tumor suppression**; may, as part of the RNA polymerase-2 holoenzyme, function in the cellular response to DNA damage	breast cancer, ovarian cancer
BRIP1	17q22-q24	rs1015771 rs2048718 rs4986763 rs4986764 rs4986765 rs4988340	BRCA1 interacting protein C-terminal helicase 1; member of the RecQ DEAH helicase family and interacts with the BRCT repeats of breast cancer, type 1 (BRCA1); important in the normal double-strand break repair function of breast cancer, type 1 (BRCA1)	breast cancer
WRN	8p12-p11.2	rs1346044 rs1800392 rs2725349 rs2725362 rs4987236	Werner syndrome; member of the RecQ subfamily and the DEAH (Asp-Glu-Ala-His) subfamily of DNA and RNA helicases; involved in many aspects of DNA metabolism, including transcription, replication, recombination, and repair; may be involved in repair of double strand DNA breaks	Werner syndrome; leukemia
POLB	8p11.2	rs2953983 rs2979895 rs3136717	polymerase (DNA directed), beta; performs base excision repair (BER) required for DNA maintenance, replication, recombination, **drug resistance**	
MDM2	12q14.3-q15	rs769412	Mdm2, transformed 3T3 cell double minute 2, p53 binding protein (mouse); nuclear phosphoprotein that binds and inhibits transactivation by tumor protein p53 as part of an autoregulatory negative feedback loop; overexpression can result in excessive inactivation of tumor protein p53, diminishing its tumor suppressor function; also affects the cell cycle, apoptosis, and tumorigenesis through interactions with other proteins, including retinoblastoma 1 and ribosomal protein L5; **Oncogene; p53 signaling pathway**	rhabdomyosarcoma, leukemia, ependymoma
ATM	11q22-q23	rs170548 rs1800889 rs1801516 rs189037 rs3092993 rs4585 rs664143 rs664677	ataxia telangiectasia mutated; regulator of a wide variety of downstream proteins, including tumor suppressor proteins p53 and BRCA1, checkpoint kinase CHK2, checkpoint proteins RAD17 and RAD9, and DNA repair protein NBS1; master controllers of cell cycle checkpoint signaling pathways that are required for cell response to DNA damage and for genome stability, **tumor suppressor gene; p53 signaling pathway**	ataxia telangiectasia; pancreatic cancer
TERT	5p15.33	rs13167280 rs1801075 rs2075786 rs2735940 rs2853677 rs2853690	telomerase reverse transcriptase; protein component with reverse transcriptase activity, and an RNA component which serves as a template for the telomere repeat; Telomerase expression plays a role in cellular senescence, as it is normally repressed in postnatal somatic cells resulting in progressive shortening of telomeres	Wilm`s tumor, osteosarcoma
NBN	8q21	rs1063045	Nibrin; member of the MRE11/RAD50 double-strand break repair complex which consists of 5	Nijmegen breakage syndrome; ALL

		rs1063053 rs1805794 rs867185	proteins; involved in DNA double-strand break repair and DNA damage-induced checkpoint activation; **tumor suppressor gene**	
PARP1	1q41-q42	rs1136410 rs1805407 rs1805414 rs1805415 rs747657 rs747659	poly (ADP-ribose) polymerase family, member 1; chromatin-associated enzyme, poly(ADP-ribosyl)transferase, which modifies various nuclear proteins by poly(ADP-ribosyl)ation; regulation of important cellular processes such as differentiation, proliferation, tumor transformation, recovery from DNA damage, genomic stability (modulation of chromatin structure, replication, transcription, single-strand break/base excision repair)	Fanconi anemia, type I diabetes; pediatric B-precursor ALL
ERCC1	19q13.2-q13.3	rs11615 rs3212948	excision repair cross-complementing rodent repair deficiency, complementation group 1 (includes overlapping antisense sequence); structure-specific DNA repair endonuclease responsible for the 5'-incision during DNA repair	leukemia
ERCC2	19q13.3	rs13181 rs1799787	excision repair cross-complementing rodent repair deficiency, complementation group 2 (xeroderma pigmentosum D); nucleotide excision repair pathway is a mechanism to repair damage to DNA; involved in transcription-coupled nucleotide excision repair and is an integral member of the basal transcription factor BTF2/TFIIH complex	xeroderma pigmentosum, Cockayne syndrome
ERCC3	2q21	rs4150416 rs4150474	excision repair cross-complementing rodent repair deficiency, complementation group 3 (xeroderma pigmentosum group B complementing); ATP-dependent DNA helicase; functions in nucleotide excision repair; complements xeroderma pigmentosum group B mutations; subunit of basal transcription factor 2 (TFIIH) à functions in class II transcription	lung cancer, esophageal cancer, ovarian cancer
ERCC4	16p13.3-p13.11	rs1799800 rs1800067	excision repair cross-complementing rodent repair deficiency, complementation group 4; structure-specific DNA repair endonuclease responsible for the 5-prime incision during DNA repair; involved in homologous recombination that assists in removing interstrand cross-link	osteosarcoma
ERCC5	10q11.23	rs1047768 rs17655 rs2227869	excision repair cross-complementing rodent repair deficiency, complementation group 5 (xeroderma pigmentosum, complementation group G (Cockayne syndrome)); involved in excision repair of UV-induced DNA damage	Cockayne syndrome
ERCC6	10q11.23	rs2228527 rs2228529	excision repair cross-complementing rodent repair deficiency, complementation group 6; DNA-binding protein important in transcription-coupled excision repair; interact with several transcription and excision repair proteins, and may promote complex formation at repair sites	melanoma
MLH1,2, 3 and 6	3p21.3; 2p16; 2p22-p21;	rs1799977 rs2286940	mutL homolog 1, mut S homolog 2 (colon cancer), and mutS homolog 3, mutS homolog 6 (E. coli); mismatch repair proteins	HNPCC, leukemia, ovarian cancer, medulloblastoma
PMS1	2q31-q33/2q31.1	rs1233255 rs1233258 rs1233284 rs1233288 rs1233291 rs1233297 rs1233299 rs1233302 rs12618262 rs256550 rs256552 rs256563	PMS1 postmeiotic segregation increased 1 (S. cerevisiae); mismatch repair gene	HNPCC; pancreatic cancer, lymphomas

		rs256564 rs256567 rs5742926 rs5742938 rs5743030 rs5743112 rs5743116		
PMS2	7p22.2	rs2345060 rs3735295 rs6463524	PMS2 postmeiotic segregation increased 2 (S. cerevisiae); PMS2 gene family member; involved in DNA mismatch repair; forms a heterodimer with MLH1 and this complex interacts with MSH2 bound to mismatched bases	HNPCC, Turcot syndrome; supratentorial PNET
MGMT	10q26	rs12917 rs16906252 rs2296675 rs2308327	O-6-methylguanine-DNA methyltransferase; involved in the cellular defense against the biological effects of O6-methylguanine (O6-MeG) in DNA; repairs alkylated guanine in DNA by stoichiometrically transferring the alkyl group at the O-6 position to a cysteine residue in the enzyme	glioma, soft tissue sarcoma
EXO1	1q42-q43	rs4149963 rs735943	exonuclease 1; encodes a protein with 5' to 3' exonuclease activity as well as an RNase H activity; DNA mismatch repair protein	lung / colorectal cancer
XRCC1	19q13.2	rs25486 rs25487	X-ray repair complementing defective repair in Chinese hamster cells 1; involved in the efficient repair of DNA single-strand breaks formed by exposure to ionizing radiation and alkylating agents; interacts with DNA ligase III, polymerase beta and poly (ADP-ribose) polymerase to participate in the base excision repair pathway; may play a role in DNA processing during meiogenesis and recombination in germ cells	cancer in patients of varying radiosensitivity
XRCC3	14q32.3	rs1799794 rs1799796	X-ray repair complementing defective repair in Chinese hamster cells 3; member of the RecA/Rad51-related protein family that participates in homologous recombination to maintain chromosome stability and repair DNA damage; functionally complements Chinese hamster irs1SF, a repair-deficient mutant that exhibits hypersensitivity to a number of different DNA-damaging agents and is chromosomally unstable	cancer in patients of varying radiosensitivity
XRCC4	5q13-q14	rs1805377 rs2075685 rs2662238 rs2891980 rs3777015	X-ray repair complementing defective repair in Chinese hamster cells 4; functions together with DNA ligase IV and the DNA-dependent protein kinase in the repair of DNA double-strand break by non-homologous end joining and the completion of V(D)J recombination events; the non-homologous end-joining pathway is required both for normal development and for **suppression of tumors**	breast cancer
XRCC5	2q35	rs1051685 rs207916 rs2440 rs828702 rs828910	X-ray repair complementing defective repair in Chinese hamster cells 5 (double-strand-break rejoining; Ku autoantigen, 80kDa; also known as ATP-dependant DNA helicase II or DNA repair protein XRCC5; functions together with the DNA ligase IV-XRCC4 complex in the repair of DNA double-strand break by non-homologous end joining and the completion of V(D)J recombination events	cancer in patients of varying radiosensitivity; malignant melanomas
XPA	9q22.3	rs1800975	Xeroderma pigmentosum, complementation group A; DNA excision repair protein; initiates DNA repair by binding to damaged sites; binds to replication protein A (RPA) which enhances the affinity of XPA for damaged DNA and is essential for Nucleotide Excision Repair ; binds to ERCC1 and TFIIH	xeroderma pigmentosum
XPC	3p25	rs2228000 rs2228001 rs3731151	Xeroderma pigmentosum, complementation group C; involved in early recognition of DNA damage present in chromatine; only required for global genome repair; **important role in the cisplatin treatment-mediated cellular response** and may suggest a possible mechanism of **cancer cell drug resistance**	xeroderma pigmentosum

LIG1	19q13.2-q13.3	rs13436 rs156641 rs20579 rs20580 rs3729512	ligase I, DNA, ATP-dependent; functions in DNA replication and the base excision repair process; mutations in LIG1 that lead to DNA ligase I deficiency result in immunodeficiency and increased sensitivity to DNA-damaging agents	immunodeficiency, sensitivity to DNA-damage
LIG3	17q11.2-q12	rs1052536	ligase III, DNA, ATP-dependent; member of the DNA ligase family; involved in excision repair and is located in both the mitochondria and nucleus, with translation initiation from the upstream start codon allowing for transport to the mitochondria and translation initiation from a downstream start codon allowing for transport to the nucleus	
LIG4	13q33-q34	rs1805386	ligase IV, DNA, ATP-dependent; DNA ligase that joins single-strand breaks in a double-stranded polydeoxynucleotide in an ATP-dependent reaction; essential for V(D)J recombination and DNA double-strand break (DSB) repair through nonhomologous end joining (NHEJ); forms a complex with the X-ray repair cross complementing protein 4 (XRCC4), and further interacts with the DNA-dependent protein kinase (DNA-PK)	
FANCA	16q24.3	rs1061646 rs12931267 rs1800345 rs2016571 rs2159116 rs2239359 rs2239360 rs3785275 rs7195906 rs7203907 rs886951	Fanconi anemia, complementation group A; DNA repair protein that may operate in a postreplication repair or a cell cycle checkpoint function; may be involved in interstrand DNA cross-link repair and in the maintenance of normal chromosome stability; the Fanconi anemia complementation group (FANC) currently includes FANCA, FANCB, FANCC, FANCD1 (also called BRCA2), FANCD2, FANCE, FANCF, FANCG, and FANCL	Fanconi anemia
BLM	15q26.1	rs16944831 rs2072351 rs2072352 rs2073919 rs2238335 rs2270132 rs389480	Bloom syndrome; participates in DNA replication and repair; exhibits a magnesium-dependent ATP-dependent DNA-helicase activity that unwinds single- and double-stranded DNA in a 3'-5' direction	Bloom syndrome
PCNA	20pter-p12	rs17349 rs17352 rs25406	proliferating cell nuclear antigen; found in the nucleus and is a cofactor of DNA polymerase delta; acts as a homotrimer and helps increase the processivity of leading strand synthesis during DNA replication; in response to DNA damage, this protein is ubiquitinated and is involved in the RAD6-dependent DNA repair pathway	
POLD1	19q13.3	rs1726787	polymerase (DNA directed), delta 1, catalytic subunit 125kDa; possesses two enzymatic activities: DNA synthesis (polymerase) and an exonucleolytic activity that degrades single stranded DNA in the 3'- to 5'-direction; required with its accessory proteins (proliferating cell nuclear antigen (PCNA) and replication factor C (RFC) or activator 1) for leading strand synthesis; also involved in completing Okazaki fragments initiated by the DNA polymerase alpha/primase complex	
JTV1	7p22	rs2009115	function of the JTV1 gene product is unknown; probable core protein of the multisynthetase complex that serves as a template for the assembly of the supramolecular structure; mediates ubiquitination of FUBP1 and its degradation by the proteasome	

MBD2	18q21	rs1145315 rs603097 rs609791 rs7614	methyl-CpG binding domain protein 2; DNA methylation (major modification of eukaryotic genomes and plays an essential role in mammalian development); human proteins MECP2, MBD1, MBD2, MBD3, and MBD4 comprise a family of nuclear proteins related by the presence in each of a methyl-CpG binding domain (MBD); may function as a mediator of the biological consequences of the methylation signal and may function as a demethylase to activate transcription, as DNA methylation causes gene silencing.	
MBD4	3q21-q22	rs140696	methyl-CpG binding domain protein 4; family of nuclear proteins; capable of binding specifically to	therapy related myelodysplasia and
MSH2 MSH3 MSH6	2p21 5q11-12 2p16	rs17036577 rs17036614 rs1863332 rs1981928 rs2042649 rs2303428 rs3771281 rs3821227 rs4608577 rs4952887 rs6544991 rs7585925 rs7602094 rs7607076 rs1650697 rs1677649 rs1805355 rs26279 rs32983 rs3797896 rs836802 rs1800935 rs3136228	MutS Homolog 2 gene	HNPCC, Lynch syndrome
STK6/ AURKA	20q13.2-q13.3	rs1047972 rs10485805 rs2273535 rs2298016 rs6024840 rs732417 rs8173 STK6-08	aurora kinase A; cell cycle-regulated kinase; involved in microtubule formation and/or stabilization at the spindle pole during chromosome segregation; **Oncogene**	rhabdomyosarcoma

CELL CYCLE REGULATION

The cell cycle is a process of replicating and dividing a cell. At least two types of cell cycle control mechanisms are recognized: a **cascade of protein phosphorylations** that relay a cell from one stage to the next and a **set of checkpoints** that monitor completion of critical events and delay progression to the next stage if necessary. The first type of control involves a highly regulated **kinase family**. Kinase activation generally requires association with a second subunit that is transiently expressed at the appropriate period of the cell cycle; the periodic "cyclin" subunit associates with its partner "cyclin-dependent kinase" (CDK) to create an active complex with unique substrate specificity. Regulatory phosphorylation and dephosphorylation fine-tune the activity of CDK-cyclin complexes, ensuring well-delineated transitions between cell cycle stages. A second type of cell cycle regulation, **checkpoint control**, is more supervisory. It is not an essential part of the cycle progression machinery. Cell cycle checkpoints sense flaws in critical events such as DNA replication and chromosome segregation. When checkpoints are activated, for example by underreplicated or damaged DNA, signals are relayed to the cell cycle-progression machinery. These signals cause a delay in cycle progression, until the danger of mutation has been averted.

Gene	Location	SNP	Group and function of protein	Related disease
TP53	17p13.1	rs12951053 rs1614984 rs2078486 rs2909430 rs8079544	tumor protein p53 (Li-Fraumeni syndrome); plays an essential role in the regulation of cell cycle, specifically in the transition from G0 to G1; p53 causes the expression of target genes whose gene products suppress the cell cycle at stage G1 by inhibiting the activity of Cdk2-cyclin D and Cdk2-cyclin E; **tumor suppressor gene, MAPK signaling pathway, Wnt signaling pathway; p53 signaling pathway**	somatic mutations in human malignancies; Li-Fraumeni syndrome
CDK4	12q14	rs2072052	cyclin-dependent kinase 4; member of the Ser/Thr protein kinase family; catalytic subunit of the protein kinase complex that is important for cell cycle G1 phase progression, activity restricted to the G1-S phase, which is controlled by the regulatory subunits D-type cyclins and CDK inhibitor p16(INK4a); **Oncogene; Rb pathway**	astrocytoma, ALL, retinoblastoma
CDK5	7q36	rs1549760 rs2069442 rs2069456	cyclin-dependent kinase 5; member of a small Ser/Thr cyclin-dependent kinase family; needs to bind with a regulator to perform kinase activity, e.g. p35; crucial role of the Cdk5-p35 complex in development of the central nervous system; numerous extraneuronal functions of Cdk5-p35, e.g. in several types of endocrine cells; activation of the **STAT3 pathway**	medullary thyroid carcinoma, leukemia
CDK7	5q12.1	rs2972388	cyclin-dependent kinase 7 (MO15 homolog, Xenopus laevis, cdk-activating kinase); cyclin-dependent protein kinase (CDK) family; essential component of the transcription factor TFIIH, that is involved in transcription initiation and **DNA repair;** may serve as a direct link between the regulation of transcription and the cell cycle	ALL
CDKN1B	12p13.1-p12	rs7330	cyclin-dependent kinase inhibitor 1B (p27, Kip1); prevents the activation of cyclin E-CDK2 or cyclin D-CDK4 complexes, and thus controls the cell cycle progression at G1; the degradation of this protein, which is triggered by its CDK dependent phosphorylation and subsequent ubiquitination by SCF complexes, is required for the cellular transition from quiescence to the proliferative state	Ewing's family tumors, malignant lymphomas
CDKN1C	11p15.5	rs431222	Cyclin-dependent kinase inhibitor 1C is a tight-binding inhibitor of several G1 cyclin/Cdk complexes and a negative regulator of cell proliferation; **tumor suppressor**	Beckwith-W., sporadic cancers
CDKN2A	9p21	rs2518719 rs2518720 rs2811708 rs3088440 rs3218020 rs3731198 rs3731211 rs3731217 rs3731239	cyclin-dependent kinase inhibitor 2A (melanoma, p16, inhibits CDK4), function as inhibitors of CDK4 kinase, cell cycle G1 control; **tumor suppressor gene; Rb pathway**	ALL

		rs3731246		
CCNH	5q13.3-q14	rs2266690 rs3093816	cyclin H; forms a complex with CDK7 kinase and ring finger protein MAT1; important link between basal transcription control and the cell cycle machinery	Burkitt lymphoma, diffuse large B-cell lymphoma
CCNA2	4q25-q31	rs1396080 rs3217773 rs769242	cyclin A2, cyclin family; binds and activates CDC2 or CDK2 kinases, and thus promotes both cell cycle G1/S and G2/M transitions	embryonal malignancies
CCND1	11q13	rs603965 rs678653 rs7177	Cyclin D1; forms a complex with and functions as a regulatory subunit of CDK4 or CDK6, whose activity is required for cell cycle G1/S transition; interact with tumor suppressor protein Rb; **oncogene; Rb pathway**	ALL
CCND3	6p21	rs2479717 rs9529	cyclin D3; forms a complex with and functions as a regulatory subunit of CDK4 or CDK6, whose activtiy is required for cell cycle G1/S transition; interact with and be involved in the phosphorylation of tumor suppressor protein Rb	anaplastic large cell lymphomas
FBXW7	4q31.3	rs2292743 rs2676329 rs2676330 rs2714804 rs2714805	F-box and WD repeat domain containing 7; member of the F-box protein family, which constitute one of the four subunits of ubiquitin protein ligase complex called SCFs (SKP1-cullin-F-box), which function in phosphorylation-dependent ubiquitination; this protein binds directly to cyclin E and probably targets cyclin E for ubiquitin-mediated degradation	breast cancer
CHEK1	11q24-q24	rs491528 rs506504 rs558351	CHK1 checkpoint homolog (S. pombe); required for checkpoint mediated **cell cycle** arrest in response to **DNA damage** or the presence of unreplicated DNA; may also negatively regulate cell cycle progression during unperturbed cell cycles; binds to and phosphorylates CDC25A, CDC25B and CDC25C; **tumor suppressor**	
TNKS	8p23.1	rs11249938 rs12542457 rs13276464 rs6601361 rs6985140 rs6992432 rs7001395 rs7006985 rs7462102 rs7462910 rs7464476 rs9644708 TNKS-01 TNKS-03 TNKS-05 TNKS-26 TNKS-35 TNKS-36 TNKS-46 TNKS-64	tankyrase, TRF1-interacting ankyrin-related ADP-ribose polymerase; may regulate vesicle trafficking and modulate the subcellular distribution of SLC2A4/GLUT4-vesicles; has PARP activity and can modify TERF1, and thereby contribute to the regulation of telomere length	
POT1	7q31.33	POT1-03 rs10244817 rs10250202 rs10263573	protection of telomeres 1 homolog (S. pombe); member of the telombin family; nuclear protein involved in telomere maintenance; regulating telomere length and protecting chromosome ends from illegitimate recombination, catastrophic chromosome instability, and abnormal chromosome segregation	stomach cancer

		rs6959712 rs727506 rs7784168		
PIN1	19p13	rs1985604 rs2010457 rs2233678 rs2233679 rs889162	protein (peptidylprolyl cis/trans isomerase) NIMA-interacting 1; regulates mitosis presumably by interacting with NIMA and attenuating its mitosis-promoting activity; displays a preference for an acidic residue N-terminal to the isomerized proline bond; catalyzes pSer/Thr-Pro cis/trans isomerizations	
PLK1	16p12.1	rs40076	polo-like kinase 1 (Drosophila); may be required for cell division and may have a role during G1 or S phase	hepatoblastomas
CDC25A	3p21	rs936426	cell division cycle 25 homolog A (S. pombe); member of the CDC25 family of phosphatases; required for progression from G1 to the S phase of the cell cycle; activates the cyclin-dependent kinase CDC2 by removing two phosphate groups; degraded in response to DNA damage, which prevents cells with chromosomal abnormalities from progressing through cell division; **oncogene**	retinoblastoma
CDC25B	20p13	rs910656	cell division cycle 25 homolog B (S. pombe); member of the CDC25 family of phosphatases; activates the cyclin dependent kinase CDC2 by removing two phosphate groups; required for entry into mitosis; oncogene	neuroblastoma
CDC25C	5q31	rs1042124	cell division cycle 25 homolog C (S. pombe); plays a key role in the regulation of cell division; belongs to the Cdc25 phosphatase family; directs dephosphorylation of cyclin B-bound CDC2 and triggers entry into mitosis; suppresses p53-induced growth arrest; overexpression associated with poor prognosis in cancer	leukemia
HUS1	7p13-p12	rs1056663 rs2242478	HUS1 checkpoint homolog (S. pombe); component of genotoxin-activated checkpoint complex that is involved in the cell cycle arrest in response to DNA damage; forms a heterotrimeric complex with checkpoint proteins RAD9 and RAD1	breast cancer
MYBL2	20q13.1	rs285164 rs285171 rs385345 rs419842 rs420755 rs619289 rs826950	v-myb myeloblastosis viral oncogene homolog (avian)-like; member of the MYB family of transcription factor genes; nuclear protein involved in cell cycle progression; activates the cell division cycle 2, cyclin D1, and insulin-like growth factor-binding protein 5 genes	neuroblastoma
TERF1	8q13	rs10106086 rs2306492 rs2306494 rs3863242 TERF1-02	telomeric repeat binding factor (NIMA-interacting) 1; telomere specific protein which is a component of the telomere nucleoprotein complex; functions as an inhibitor of telomerase, acting in cis to limit the elongation of individual chromosome ends	leukemia, Ewing`s
TERF2	16q22.1	rs153045 rs251796 TERF2-03	telomeric repeat binding factor 2; component of the telomere nucleoprotein complex; negative regulator of telomere length; plays a key role in the protective activity of telomeres	leukemia
TEP1	14q11.2	rs1713449 rs1760897 rs1760898 rs1760904 rs872072	telomerase-associated protein 1; component of the ribonucleoprotein complex responsible for telomerase activity which catalyzes the addition of new telomeres on the chromosome ends. The telomerase-associated proteins are conserved from ciliates to humans.	leukemia

		rs872074		
PARP4	13q11	rs13428 rs1539096 rs1807111 rs6413414 rs750771	poly (ADP-ribose) polymerase family, member 4; capable of catalyzing a poly(ADP-ribosyl)ation reaction; catalytic domain which is homologous to that of poly (ADP-ribosyl) transferase, but lacks an N-terminal DNA binding domain which activates the C-terminal catalytic domain of poly (ADP-ribosyl) transferase	
TSG101	11p15	rs12574333 rs2279900 rs2279902 rs2291752 rs2292176 rs2292179	tumor susceptibility gene 101; belongs to a group of apparently inactive homologs of ubiquitin-conjugating enzymes; contains a coiled-coil domain that interacts with stathmin, a cytosolic phosphoprotein implicated in tumorigenesis; plays a role in cell growth and differentiation and act as a negative growth regulator; important for maintenance of genomic stability and cell cycle regulation	breast cancer
SEPT2	2q37	rs7568	septin 2; involved in the coordination of several key steps of mitosis; involved in the process of cytokinesis in human brain tumours	Leukemia, brain tumours

REGULATION OF TRANSCRIPTION

Regulation of gene expression (or gene regulation) refers to the cellular control of the amount and timing of changes to the appearance of the functional product of a gene. Although a functional gene product may be an RNA or a protein, the majority of the known mechanisms regulate the expression of protein coding genes. Any step of the gene's expression may be modulated, from DNA-RNA transcription to the post-translational modification of a protein. Gene regulation gives the cell control over its structure and function, and is the basis for cellular differentiation, morphogenesis and adaptability of the organism.

Gene	Loc.	SNP	Group and function of protein	Disease
RXRB	6p21.3	rs2072915 rs2076310	member of the retinoid X receptor (RXR) family of nuclear receptors; involved in mediating the effects of retinoic acid (RA); forms homodimers with the retinoic acid, thyroid hormone, and vitamin D receptors, increasing both DNA binding and transcriptional function on their respective response elements; lies within the major histocompatibility complex (MHC) class II region on chromosome 6; **PPAR signaling pathway**	thyroid cancer, small cell lung cancer, non-small cell lung cancer
MATR3	5q31.2	rs11738738	matrin 3; localized in the nuclear matrix; role in transcription or may interact with other nuclear matrix proteins to form the internal fibrogranular network	
APBB3	5q31	rs10463297 rs801459 rs801460	amyloid beta (A4) precursor protein-binding, family B, member 3; member of the APBB protein family; found in the cytoplasm and binds to the intracellular domain of the Alzheimer's disease beta-amyloid precursor protein (APP) as well as to other APP-like proteins	
RB1CC1	8q11	RB1CC1-50 rs1129660 rs17337252 rs2305427	RB1-inducible coiled-coil 1; DNA-binding transcription factor; potent regulator of the RB1 pathway; crucial role in muscular differentiation; maturation of human embryonic musculoskeletal cells; may regulate the proliferative activity and maturation of tumor cells derived from these tissues	
ZFPM1	16q24.2	rs904797	zinc finger protein, multitype 1; transcription regulator; role in erythroid and megakaryocytic cell differentiation; cofactor that acts via the formation of a heterodimer with transcription factors of the GATA family; heterodimer can both activate or repress transcriptional activity, depending on the cell and promoter context; heterodimer is essential to activate expression of genes such as NFE2, ITGA2B, alpha- and beta-globin, while it represses expression of KLF1; involved in regulation of some genes in gonads and in cardiac development; **nuclear transcription factor**	

ZNF230	19q13.31	rs12753	zinc finger protein 230; may be involved in transcriptional regulation; **nuclear transcription factor**	
ZNF350	19q13.33	rs2278414 rs2278415 rs4988334	zinc finger protein 350; transcriptional repressor; binds to a specific sequence, 5'-GGGxxxCAGxxxTTT-3', within GADD45 intron 3; **transcriptional repressor**	
MYNN	3q26.2	rs1317082	Myoneurin; zinc finger protein; transcription factor activity; involved in regulation of nucleobase, nucleoside, nucleotide and nucleic acid metabolism	
NCOA3	20q12	rs2076546 rs396221 rs427967	nuclear receptor coactivator 3; interacts with nuclear hormone receptors to enhance their transcriptional activator functions; plays a central role in creating a multisubunit coactivator complex, which probably acts via remodeling of chromatin; involved in the coactivation of different nuclear receptors, such as for steroids (GR and ER), retinoids (RARs and RXRs), thyroid hormone (TRs), vitamin D3 (VDR) and prostanoids (PPARs); involved in the coactivation of the NF-kappa-B pathway; **oncogene; NF-kappa-B pathway**	
FOXA1	14q12-q13	C14orf25-11	forkhead box A1; member of the forkhead class of DNA-binding proteins; transcriptional activators for liver-specific transcripts such as albumin and transthyretin, and they also interact with chromatin	
FOXC1	6p25	FOXC1-09 rs2235716 rs2235718 rs2745599 rs6928414 rs9405496 rs984253	forkhead box C1; forkhead family of transcription factors; specific function of this gene has not yet been determined; shown to play a role in the regulation of embryonic and ocular development	glaucoma; synovial sarcoma
LITAF	16p13.13	rs4280262 rs7102	lipopolysaccharide-induced TNF factor; probable role in regulating transcription of specific genes; may regulate through NFKB1 the expression of the CCL2/MCP-1 chemokine; may play a role in tumor necrosis factor alpha (TNF-alpha) gene expression	
GATA3	10p15	rs10752126 rs10905277 rs1269486 rs2229359 rs3781093 rs406103 rs422628 rs520236 rs528778 rs569421 rs570730	GATA binding protein 3; transcriptional activator which binds to the enhancer of the T-cell receptor alpha and delta genes; binds to the consensus sequence 5'-AGATAG-3'	leukemia
METTL1	12q13	rs703842	methyltransferase like 1; similar in sequence to the S. cerevisiae YDL201w gene; contains a conserved S-adenosylmethionine-binding motif and is inactivated by phosphylation; catalyzes the formation of N(7)-methylguanine at position 46 (m7G46) in tRNA	

OXIDATIVE AND HYPOXIC STRESS PATHWAYS

It is believed that hypoxia plays a role in the malignant transformation of cells and subsequent tumor growth. In a number of different human cancers, tissue hypoxia predicts the likelihood of metastases, tumor recurrence, resistance to chemotherapy and radiation therapy, invasion, and decreased patient survival. Hypoxic stress has been linked to several phenotypic changes that are fundamental to malignant progression. This can be mediated through genomic instability, loss of apoptotic potential, alterations of gene expression, and induction of angiogenesis.

Gene	Loc.	SNP	Group and function of protein	Disease
SEPP1	5q31	rs6413428 rs7579	selenoprotein P, plasma, 1; extracellular glycoprotein; only selenoprotein known to contain multiple selenocysteine residues; binds to heparin and cell membranes and associates with endothelial cells; implicated as an oxidant defense in the extracellular space and in the transport of selenium	
SEP15	1p31	rs540049 rs5845	15 kDa selenoprotein; redox function	
CAT	11p13	rs1049982 rs475043 rs769214 rs769217 rs769218 rs9282626	Catalase; occurs in almost all aerobically respiring organisms and serves to protect cells from the toxic effects of hydrogen peroxide	Wilm`s, brain tumor
HIF1AN	10q24	rs2295780	hypoxia-inducible factor 1, alpha subunit inhibitor; functions as an oxygen sensor and, under normoxic conditions, the hydroxylation prevents interaction of HIF-1 with transcriptional coactivators including Cbp/p300- interacting transactivator; involved in transcriptional repression through interaction with HIF1A, VHL and histone deacetylases	neuroblastoma, leukemia
AKR1A1	1p33-p32	rs2088102	aldo-keto reductase family 1, member A1 (aldehyde reductase); catalyzes the conversion of aldehydes and ketones to their corresponding alcohols by utilizing NADH and/or NADPH as cofactors	Non-Hodgkin lymphoma
AKR1C3	10p15-p14	rs10795241 rs10904422 rs11252937 rs12529 rs17134288 rs1937845 rs1937920 rs2245191 rs2275928 rs28942669 rs3763676 rs6601899 rs7070041 rs7921327	aldo-keto reductase family 1, member C3 (3-alpha hydroxysteroid dehydrogenase, type II); catalyzes the reduction of prostaglandin (PG) D2, PGH2 and phenanthrenequinone (PQ), and the oxidation of 9alpha,11beta-PGF2 to PGD2; role in controlling cell growth and/or differentiation	allergic diseases, prostate and breast cancer
AKR1C4	10p15-p14	rs3829125	aldo-keto reductase family 1, member C4 (chlordecone reductase; 3-alpha hydroxysteroid dehydrogenase, type I; dihydrodiol dehydrogenase 4); catalyzes the bioreduction of chlordecone, a toxic organochlorine pesticide, to chlordecone alcohol in liver	
UCP3	11q13	rs1800849	uncoupling protein 3 (mitochondrial, proton carrier; member of the family of mitochondrial anion	

		rs2075577	carrier proteins (MACP); UCPs separate oxidative phosphorylation from ATP synthesis with energy dissipated as heat, also referred to as the mitochondrial proton leak; UCPs facilitate the transfer of anions from the inner to the outer mitochondrial membrane and the return transfer of protons from the outer to the inner mitochondrial membrane	
OGG1	3p26.2	rs125701 rs2304277	8-oxoguanine DNA glycosylase; responsible for the excision of 8-oxoguanine, a mutagenic base byproduct which occurs as a result of exposure to reactive oxygen; OGG1 targeted to mitochondria reduces the activation of caspase-9	squamous cell carcinoma, GI cancer
PPARG	3p25	rs1175541 rs1801282 rs2938392	peroxisome proliferator-activated receptor gamma; member of the peroxisome proliferator-activated receptor (PPAR) subfamily of nuclear receptors; PPARs form heterodimers with retinoid X receptors (RXRs) and these heterodimers regulate transcription of various genes; regulator of adipocyte differentiation; growth inhibition and apoptosis	obesity, diabetes, atherosclerosis; B-ALL, neuroblastoma
TXNRD2	22q11.21	rs4646310 rs6518591 rs9306230	thioredoxin reductase 2; a dimeric NADPH-dependent FAD containing enzyme that catalyzes the reduction of the active site disulfide of thioredoxin and other substrates; member of a family of pyridine nucleotide-disulfide oxidoreductases; key enzyme in the regulation of the intracellular redox environment; oxidative stress; role in redox- regulated cell signaling	
GPX1	3p21.3	rs1800668	glutathione peroxidase 1; glutathione peroxidase family; detoxification of hydrogen peroxide, one of the most important antioxidant enzymes in humans; protects from CD95-induced apoptosis; its overexpression delays endothelial cell growth and increases resistance to toxic challenges	breast cancer
GPX2	14q24.1	rs10133054 rs10133290 rs12172810 rs17880380 rs1800669 rs2071566 rs2296327 rs2737844 rs4902345	glutathione peroxidase 2 (gastrointestinal); member of the glutathione peroxidase family; responsible for the majority of the glutathione-dependent hydrogen peroxide-reducing activity in the epithelium of the gastrointestinal tract; role of the ileal glutathione peroxidases in preventing inflammation in the GI tract	Doxorubicin resistance in sarcoma
GPX3	5q23	rs1946234 rs2042235 rs8177404 rs8177426 rs8177447 rs869975	glutathione peroxidase 3 (plasma); catalyzes the reduction of hydrogen peroxide, organic hydroperoxide, and lipid peroxides by reduced glutathione and functions in the protection of cells against oxidative damage	prostate cancer
GPX4	19p13.3	rs3746165 rs4807542 rs757228 rs8178977	glutathione peroxidase 4 (phospholipid hydroperoxidase); catalyzes the reduction of hydrogen peroxide, organic hydroperoxide, and lipid peroxides by reduced glutathione and functions in the protection of cells against oxidative damage; selenium-containing enzyme and the UGA codon is translated into a selenocysteine; overexpression induces an increase in COX-2 activity	breast cancer, colon cancer
SOD1	21q22.1; 21q22.11	rs2070424	superoxide dismutase 1, soluble (amyotrophic lateral sclerosis 1 (adult)); binds copper and zinc ions and is one of two isozymes responsible for destroying free superoxide radicals in the body	fam. amyotrophic lateral sclerosis
SOD2	6q25.3	rs1799725	superoxide dismutase 2, mitochondrial; member of the iron/manganese superoxide dismutase family;	cardiomyopathy, motor neuron

		rs5746081	one of the major cellular defences against oxidative stress; p53 is able to repress SOD2 gene expression; an overexpression of superoxide dismutase 2 decreases p53-mediated induction of apoptosis and decreases p53-gene expression at the promoter level; role in chemosensitivity in AML in Down syndrome	disease, pancreatic cancer
SOD3	4p15.3-p15.1	rs2855262	superoxide dismutase 3, extracellular; member of the superoxide dismutase (SOD) protein family; protect the brain, lungs, and other tissues from oxidative stress	
NOS2A	17q11.2-q12	rs2297518 rs9282801	nitric oxide synthase 2A (inducible, hepatocytes); nitric oxide synthase which is expressed in liver and is inducible by a combination of lipopolysaccharide and certain cytokines	astrocytic glioma, thyroid tumors
NOS3	7q36	rs1799983 rs3918226	nitric oxide synthase 3 (endothelial cell); produces nitric oxide; NO mediates vascular smooth muscle relaxation, apoptosis, and various cytostatic and cytotoxic effects, may increase growth rate, vascular density, and invasiveness of cancer	retinoblastoma, ALL, invasive breast cancer

APOPTOSIS

Sequential activation of caspases plays a central role in the execution-phase of cell apoptosis. Caspases exist as inactive proenzymes which undergo proteolytic processing at conserved

Gene	**Location**	**SNP**	**Group and function of protein**	**Related disease**
FAS	10q24.1	rs1324551 rs1468063 rs2234768	Fas (TNF receptor superfamily, member 6), role in regulation of programmed cell death; pathogenesis of various malignancies and diseases of the immune system	B-precursor ALL, osteosarcoma
FASLG	1q23	rs929087	Fas ligand (TNF superfamily, member 6); nteraction of FAS with this ligand is critical in triggering apoptosis of some types of cells such as lymphocytes	lupus; AML, retinoblastoma
CASP3	4q34	rs1049216 rs1405938 rs3087455 rs6948	caspase 3, apoptosis-related cysteine peptidase; member of the cysteine-aspartic acid protease (caspase) family; cleaves and activates caspases 6, 7 and 9, and the protein itself is processed by caspases 8, 9 and 10	Alzheimer`s; B-precursor ALL
CASP8	2q33-q34	rs2293554 rs2349070	caspase 8, apoptosis-related cysteine peptidase, cysteine-aspartic acid protease (caspase) family; involved in the programmed cell death induced by Fas and various apoptotic stimuli; may interact with Fas-interacting protein FADD; **important role in chemoresistance against genotoxic drugs**	Huntington`s disease; medulloblastoma, neuroblastoma
CASP9	1p36.3-p36.1	rs1052576 rs2020898 rs2020902	caspase 9, apoptosis-related cysteine peptidase, cysteine-aspartic acid protease (caspase) family; processed by caspase APAF1; one of the earliest steps in the caspase activation casc.	medulloblastoma
CASP10	2q33-q34	rs3900115	caspase 10, apoptosis-related cysteine peptidase; member of the cysteine-aspartic acid protease (caspase) family; cleaves and activates caspases 3 and 7, and the protein itself is processed by caspase 8; active role for caspase-10 in cytotoxic **drug-induced tumor cell death**	autoimm. lympho-prolif. syndrome; leukemia
BCR	22q11; 22q11.23	rs12233352 rs140504	breakpoint cluster region; reciprocal translocation between chromosomes 22 and 9 produces the Philadelphia chromosome (CML); function of the normal BCR gene product is not clear; has serine/threonine kinase activity and is a GTPase-activating protein for p21rac	CML
APAF1	12q23	rs1007573 rs1866477 rs2278361 rs2288729	apoptotic peptidase activating factor 1; cytoplasmic protein that initiates apoptosis; forms an oligomeric apoptosome which binds and cleaves caspase 9 preproprotein, releasing its mature, activated form, which stimulates the subsequent caspase cascade that commits the cell to apoptosis	GI cancer, leukemia
AHRR	5p15.3	AHRR-10	aryl-hydrocarbon receptor repressor; Calcium-binding protein required for T-cell receptor-, Fas-,	AML

		rs10078	glucocorticoid-induced cell death; mediates Ca(2+)- regulation signals along death pathway	
TP73L	3q28	rs1345186 rs17514215 rs3856775 rs6789961 rs6790167 rs7613791 rs7653848 rs9840360 TP73L-46 TP73L-47 TP73L-52	tumor protein p73-like; sequence specific DNA binding transcriptional activator or repressor; may be required in conjunction with TP73/p73 for initiation of TP53/p53 dependent apoptosis in response to genotoxic insults and the presence of activated oncogenes; involved in **Notch signaling;** regulation of epithelial morphogenesis; **tumor suppressor gene**	craniopharyngioma, neuroblastoma
TP53I3	2p23.3	rs10170774 rs2303287 rs4149371 rs4149372 rs7603220	tumor protein p53 inducible protein 3; similar to oxidoreductases, which are enzymes involved in cellular responses to oxidative stresses and irradiation; induced by the tumor suppressor p53 and is thought to be involved in p53-mediated cell death	Ewing sarcoma, glioma, breast, lung cancer
BAK1	6p21.3	rs210135 rs210145 rs513349	BCL2-antagonist/killer 1; BCL2 protein family (act as anti- or pro-apoptotic regulators that are involved in a wide variety of cellular activities); functions to induce apoptosis; interacts with the tumor suppressor P53	
BIRC2	11q22	rs1943781	baculoviral IAP repeat-containing 2; member of a family of proteins that inhibits apoptosis by binding to TNF receptor-associated factors TRAF1 and TRAF2, probably by interfering with activation of ICE-like proteases	
BIRC3	11q22	rs3460 rs3758841	baculoviral IAP repeat-containing 3; member of a family of proteins that inhibits apoptosis by binding to TNF receptor-associated factors TRAF1 and TRAF2, probably by interfering with activation of ICE-like proteases	desmoid tumors
TNFRSF1A	12p13.2	rs1800692 rs887477	tumor necrosis factor receptor superfamily, member 1A; one of the major receptors for the tumor necrosis factor-alpha; can activate NF-kappaB, mediate apoptosis, and function as a regulator of inflammation	neuroblastoma, malignant bone tumors
TNFRSF10A	8p21	rs2235126 rs4871857	tumor necrosis factor receptor superfamily, member 10a; member of the TNF-receptor superfamily; activated by tumor necrosis factor-related apoptosis inducing ligand (TNFSF10/TRAIL), and thus transduces cell death signal and induces cell apoptosis	leukemia
PPP1R13L	19q13.32	rs6966	protein phosphatase 1, regulatory (inhibitor) subunit 13 like; plays a central role in regulation of apoptosis and transcription via its interaction with NF-kappa-B and p53/TP53 proteins; blocks transcription of HIV-1 virus by inhibiting the action of both NF-kappa-B and SP1. Also inhibits p53/TP53 function, possibly by preventing the association between p53/TP53 and ASPP1 or ASPP2, and therefore suppressing the subsequent activation of apoptosis	HIV; breast and lung cancer, ALL

ATP-BINDING CASSETTE (ABC) TRANSPORTER AND RELATED PROTEINS

These are transmembrane proteins that function in the transport of substrates across extra- and intracellular membranes, including metabolic products, lipids, sterols, and drugs. They play a critical role in drug metabolism and multidrug resistance. The ABC superfamily is divided into seven distinct subfamilies, e.g. ABC1, White.

Gene	Loc.	SNP	Group and function of protein	Disease

ABCA1	9q31.1	rs2230806 rs2230808 rs2297404 rs2777801 rs4149313 rs7031748	ATP-binding cassette, sub-family A (ABC1), member ; functions as a cholesteral efflux pump in the cellular lipid removal pathway	Tangier's disease, HDL defects
ABCA5	17q24.3	rs15886	ATP-binding cassette, sub-family A (ABC1), member 5; neither the substrate nor the function known	colon tumors
ABCA6	17q24.3	rs9282552 rs9282553	ATP-binding cassette, sub-family A (ABC1), member 6; may play a role in macrophage lipid homeostasis	
ABCA7	19p13.3	rs3752241 rs3764651 rs9282559	ATP-binding cassette, sub-family A (ABC1), member 7; predominantly in myelo-lymphatic tissues with the highest expression in peripheral leukocytes, thymus, spleen, and bone marrow; suggests a role in lipid homeostasis in cells of the immune system	
ABCB1	7q21.1	rs1211152 rs2235074 rs9282564	ATP-binding cassette, sub-family B (MDR/TAP), member 1; involved in **multidrug resistance**; ATP-dependent drug efflux pump for xenobiotic compounds with broad substrate specificity; responsible for decreased drug accumulation in multidrug-resist. cells; transporter in blood-brain barrier	colon tumors
ABCB11	2q24	rs3770603 rs853785	ATP-binding cassette, sub-family B (MDR/TAP), member 11; involved in **multidrug resistance**; major canalicular bile salt export pump in man	hepatocellular carcinoma
ABCC2	10q24	ABCC2-10 rs2273697 rs3740066 rs3740074 rs717620	ATP-binding cassette, sub-family C (CFTR/MRP), member 2; involved in **multidrug resistance**; expressed in the canalicular part of the hepatocyte; functions in biliary transport	Dubin-Johnson s., MTX toxicity
ABCC4	13q32	rs2274406 rs3765535 rs4148472	ATP-binding cassette, sub-family C (CFTR/MRP), member 4; involved in **multidrug resistance**; may play a role in cellular detoxification as a pump for its substrate, organic anions	
ABCG8	2p21	rs6544718 rs9282572 rs9282575	ATP-binding cassette, sub-family G (WHITE), member 8 (sterolin 2)	
ATP1B2	17p13.1	rs1624085 rs1641512 rs1641535	ATPase, Na+/K+ transporting, beta 2 polypeptide; belongs to the family of Na+/K+ and H+/K+ ATPases beta chain proteins (subfamily of Na+/K+ -ATPases); integral membrane protein responsible for establishing + maintaining electrochemical gradients of Na + K ions across plasma membran	

SOLUTE CARRIER FAMILY

The solute carrier (SLC) group of membrane transport proteins include over 300 members organized into 47 families. The SLC group include examples of transport proteins that are a) facilitated transporter (allow solutes to flow downhill with their electrochemical gradients) b) secondary active transporter (allow solutes to flow uphill against their electrochemical gradient by coupling to transport of a second solute that flows downhill with its gradient such that the overall free energy change is still favorable).

Gene	Location		Group and function of protein	Related disease
SLC2A1	1p35-p31.3	rs1770810	solute carrier family 2 (facilitated glucose transporter), member 1; enhanced expression in neoplasie signifies increased glucose uptake and glycolytic metabolism / response to **tissue hypoxia**	

SLC2A4	17p13	rs5435	solute carrier family 2 (facilitated glucose transporter), member 4; functions as an insulin-regulated facilitative glucose transporter	NIDDM
SLC4A2	7q35-q36	rs10245199 rs13240966 rs6464120	solute carrier family 4, anion exchanger, member 2 (erythrocyte membrane protein band 3-like; plasma membrane anion exchange protein of wide distribution	
SLC6A3	5p15.3	rs2652511 rs460700 rs6347 rs6413429	solute carrier family 6 (neurotransmitter transporter, dopamine), member 3; sodium- and chloride-dependent transporter; neurotransmitter/sodium symporter activity; amine transporter; terminates the action of dopamine by its high affinity sodium-dependent reuptake into presynaptic terminals	
SLC6A18	5p15.33	SLC6A18-13	solute carrier family 6, member 18; Sodium- and chloride-dependent transporter; having neurotransmitter/sodium symporter activity; amine transporter; terminates the action of dopamine by its high affinity sodium-dependent reuptake into presynaptic terminals	
SLC19A1	21q22.3	rs1051266 rs1051298	solute carrier family 19 (folate transporter), member 1; transport of **folate** compounds into mammalian cells can occur via receptor-mediated or carrier-mediated mechanisms; functional coordination between these 2 mechanisms is propably the method of folate uptake in certain cell types; MTX actively transported by the carrier-mediated uptake system	leukemia
SLC23A1	5q31.2-q31.3	rs10063949 rs4257763 rs6596471 SLC23A1-05	solute carrier family 23 (nucleobase transporters), member 1; Sodium/ascorbate cotransporter; one of the two required transporters for tissue-specific uptake of vitamin C	
SLC23A2	20p13	rs1110277 rs12479919 rs1715364 rs1715365 rs1776964 rs4813725 rs4987219 rs6084957	solute carrier family 23 (nucleobase transporters), member 2; Sodium/ascorbate cotransporter; one of the two required transporters for tissue-specific uptake of vitamin C	
SLC30A1	1q32-q41	rs2278651	solute carrier family 30 (zinc transporter), member 1; family of zinc transporters; cell growth promoting	prostate cancer
SLC30A4	15q21.1	rs1153829	solute carrier family 30 (zinc transporter), member 4; probably involved in zinc transport out of the cytoplasm, may be by sequestration into an intracellular compartment	
SLC39A2	14q11.2	rs2234636 rs945352	solute carrier family 39 (zinc transporter), member 2; mediates zinc uptake; zinc uptake may be mediated by a Zn(2+)-HCO(3)(-) symport mechanism and can function in the presence of albumin; may also transport other divalent cations; may be important in contact inhibition of normal epithelial cells and loss of its expression may play a role in tumorigenesis	

PROTEIN-PROTEIN INTERACTION

Cell adhesion is a key physiol. event tightly coupled to other major cellular processes coordinating morphogenesis and histogenesis. Cell-to-cell and cell-to-extracellular matrix adhesion play a critical role in pathogenesis of cancer. The largest cell adhesion molecule superfamily is that related to N-CAM, the members of which characteristically contain immunoglobulin domains. Cadherins constitute another important superfamily with different properties.

Gene	Loc.	SNP	Group and function of protein	Disease

SELE	1q22-q25	rs5361	selectin E (endothelial adhesion molecule 1); responsible for the accumulation of blood leukocytes at sites of inflammation by mediating the adhesion of cells to the vascular lining; organ selectivity in **metastatic progress** involves the binding of the circulating cancer cells to endothelial E-selectin	gastric cancer; ALL, colon cancer
TGM1	14q11.2	rs2229463 rs2855006	transglutaminase 1 (K polypeptide epidermal type I, protein-glutamine-gamma-glutamyltransferase); catalyzes the cross-linking of proteins and con-jugation of polyamines to protein; responsible for cross- linking epidermal proteins during formation of stratum corneum; **cell-cell adherens**	
EFNB3	17p13.1-p11.2	rs3744262 rs3744263	ephrin-B3; member of the ephrin gene family, largest subfamily of receptor protein-tyrosine kinases; important in brain development as well as in its maintenance, especially forebrain function; **axon guidance**	neuroblastoma
MET	7q31	MET-26 rs11762213 rs13223756 rs41736	Hepatocyte growth factor receptor; encodes tyrosine-kinase activity; **oncogene; Axon guidance; cytokine-cytokine interaction**	melanoma, hepatoblastoma
ARVCF	22q11.21	rs2240716	armadillo repeat gene deletes in velocardiofacial syndrome; member of the **catenin family**; plays an important role in the formation of adherens junction complexes, which are thought to facilitate communication between the inside and outside environments of a cell; may have a function as a nuclear protein	Velo-Cardio-Facial syndrome (ARVCF)
NINJ1	9q22	rs1127851 rs1127857	ninjurin 1; homophilic cell adhesion molecule that promotes **axonal growth**; may play a role in nerve regeneration and in the formation and function of other tissues; **cell adhesion, protein binding**	
NPAT	11q22-q23	rs228589	nuclear protein, ataxia-telangiectasia locus; involved in the **maintenance of tight junction** by regulating the activity of CDC42, thereby playing a central role in apical polarity of epithelial cells	
RGS17	6q25.3	rs2295231 rs3870366	regulator of G-protein signalling 17; member of the regulator of G-protein signaling family	
RGS6	14q24.3	rs2238280 rs2238284 rs3784058	regulator of G-protein signalling 6; members of the RGS (regulator of G protein signaling) family have been shown to modulate the functioning of G proteins by activating the intrinsic GTPase activity of the alpha (guanine nucleotide-binding) subunits	Mantle cell leukemia

FOLATE PATHWAY

Folate is necessary for the production and maintenance of new cells. This is especially important during periods of rapid cell division and growth such as infancy and pregnancy. Folate is needed to replicate DNA. Therefore folate metabolism is a target for cancer treatment. There are two major drug groups: folate antagonists (e.g., methotrexate) and thymidylate synthase inhibitors (e.g., 5-fluorouracil). The administration of these drugs in cancer chemotherapy can cause a state of severe folate depletion with sometimes life-threatening toxicities. Some recent studies suggest that inherited variability (polymorphisms) in proteins in folate metabolism may modify the effectiveness and toxicity of these antifolate drugs. This may explain why some patients respond to the drugs and others do not – or why some patients experience side effects and toxicity.

Gene	Location	SNP	Group and function of protein	Related disease
MTHFR	1p36.3	rs12121543 rs1801133 rs2066470	5,10-methylenetetrahydrofolate reductase (NADPH); methylation, synthesis and repair of DNA; **tumor suppressor gene; MTX resistance** in pediatric patients with ALL	ALL; lung cancer
MTRR	5p15.3-p15.2	rs10380 rs1802059 rs2287779	5-methyltetrahydrofolate-homocysteine methyltransferase reductase; involved in the reductive regeneration of cobalamin cofactor required for the maintenance of methionine synthase in a functional state; methionine is an essential amino acid required for protein synthesis and one carbon	ALL; MTX resistance (ALL)

		rs2287780 rs8659 rs9332	metabolism	
MTHFD2	2p13.1	rs1667627	methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 2, methenyltetrahydrofolate cyclohydrolase; nuclear-encoded mitochondrial bifunctional enzyme with methylenetetrahydrofolate dehydrogenase and methenyltetrahydrofolate cyclohydrolase activities	
DHFR	5q11.2-q13.2	DHFR-07 rs865646	Dihydrofolate reductase; converts dihydrofolate into tetrahydrofolate, a methyl group shuttle required for the de novo synthesis of purines, thymidylic acid, certain amino acids	anemia; osteosarkoma, leukemia
MTR	1q43	rs1805087 rs2275565 rs2275566	5-methyltetrahydrofolate-homocysteine methyltransferase; catalyzes the final step in methionine biosynthesis	lymphoma
TYMS	18p11.32	rs1059394 rs2790 rs699517	thymidylate synthetase; uses the 5,10-methylenetetrahydrofolate (methylene-THF) as a cofactor to maintain the dTMP (thymidine-5-prime monophosphate) pool critical for **DNA replication and repair;** possible target for cancer chemotherapeutic agents; may be the primary site of action for 5-fluorouracil, 5-fluoro-2-prime-deoxyuridine, some folate analogs	leukemia, glioblastoma
ALDH1L1	3q21.2	rs1127717 rs2305230 rs9282690	aldehyde dehydrogenase 1 family, member L1; catalyzes the conversion of 10-formyltetrahydrofolate, NADP, and water to tetrahydrofolate, NADPH, and carbon dioxide; responsible for formate oxidation in vivo; deficiencies in this gene can result in an accumulation of formate and subsequent methanol poisoning.	
GGH	8q12.3	rs1031552 rs719235	gamma-glutamyl hydrolase (conjugase, folylpolygammaglutamyl hydrolase; catalyzes the hydrolysis of folylpoly-gamma-glutamates and antifolylpoly-gamma-glutamates by the removal of gamma-linked polyglutamates and glutamate	

JAK-STAT SIGNALING PATHWAY

The **JAK-STAT signaling pathway** takes part in the regulation of cellular responses to cytokines and growth factors. Employing Janus kinases (JAKs) and Signal Transducers and Activators of Transcription (STATs), the pathway transduces the signal carried by these extracellular polypeptides to the cell nucleus, where activated STAT proteins modify gene expression. Although STATs were originally discovered as targets of Janus kinases, it has now become apparent that certain stimuli can activate them independent of JAKs. The pathway plays a central role in principal cell fate decisions, regulating the processes of cell proliferation, differentiation and apoptosis. It is particularly important in hematopoiesis. In response to cytokines and growth factors, STAT family members are phosphorylated by the receptor associated kinases, and then form homo- or heterodimers that translocate to the cell nucleus where they act as transcription activators.

Gene	**Location**	**SNP**	**Group and function of the protein**	**Related disease**
IL2	4q26-q27	rs2069762 rs2069763	interleukin 2; secreted cytokine that is important for the proliferation of T and B lymphocytes	melanoma, neuroblastoma
IL3	5q31.1	rs40401	interleukin 3 (colony-stimulating factor, multiple); potent growth promoting cytokine; supporting the proliferation of a range of hematopoietic cell types; cell growth, differentiation,apoptosis; neurotrophic activity	ALL
IL4	5q31.1	rs2070874 rs2243248 rs2243250 rs2243268 rs2243290	interleukin 4; pleiotropic cytokine produced by activated T cells; interleukin 4 receptor also binds to IL13 (overlapping functions); STAT6, a signal transducer and activator of transcription, has been shown to play a central role in mediating the immune regulatory signal of this cytokine	Hodgkin lymphoma, ALL
IL4R	16p12.1-p11.2	rs1801275 rs1805011	interleukin 4 receptor; encodes the alpha chain of the interleukin-4 receptor, a type I transmembrane protein that can bind interleukin 4 and interleukin 13 to regulate IgE production	atopy; ALL, medulloblastoma

		rs1805012 rs1805015 rs1805016 rs2057768 rs3024544 rs8832		
IL6	7p21	rs1800795 rs1800797	interleukin 6 (interferon, beta); produced by macrophages, fibroblasts, endothelial cells and activated T-helper cells; acts in synergy with IL-1 and TNF-(in many immune responses, including T-cell activation; IL-6 is the primary inducer of the acute-phase response in liver and enhances the differentiation of B-cells and their consequent production of immunoglobulin; glucocorticoid synthesis is also enhanced by IL-6	AML, ALL
IL6R	1q21	rs8192284	Interleukin 6 receptor; Interleukin 6 (IL6) is a potent pleiotropic cytokine that regulates cell growth and differentiation and plays an important role in immune response. induces the maturation of B cells into immunoglobulin-secreting cells	multiple myeloma, autoimmune diseases
IL7R	5p13	rs1494555 rs7737000	interleukin 7 receptor; the function of this receptor requires the interleukin 2 receptor, gamma chain (IL2RG); critical role in the V(D)J recombination during lymphocyte development; controls accessibility of TCR gamma locus by STAT5 and histone acetylation; blocks apoptosis during differentiation and activation of T lymph.	severe combined immuno-deficiency (SCID); ALL
IL10	1q31-q32	rs1800871 rs1800890 rs1800896 rs3021094 rs3024491 rs3024496 rs3024509	interleukin 10; a cytokine produced primarily by monocytes and lymphocytes; has pleiotropic effects in immunoregulation and inflammation; down-regulates the expression of Th1 cytokines, MHC class II Ags, and costimulatory molecules on macrophages; enhances B cell survival, proliferation, and antibody production; can block NF-kappa B activity	ALL
IL10RA	12q14	rs2229114 rs9610	interleukin 10 receptor, alpha; mediate the immunosuppressive signal of interleukin 10, and thus inhibits the synthesis of proinflammatory cytokines; promote survival of progenitor myeloid cells through the insulin receptor substrate-2/PI 3-kinase/AKT pathway. Activation of this receptor leads to tyrosine phosphorylation of JAK1 and TYK2	
IL12A	3q25.33-q26	rs582537	interleukin 12A (natural killer cell stimulatory factor 1, cytotoxic lymphocyte maturation factor 1, p35); subunit of a cytokine that acts on T and natural killer cells; required for the T-cell-independent induction of interferon (IFN)-gamma, and is important for the differentiation of both Th1 and Th2 cells; the responses of lymphocytes to this cytokine are mediated by the activator of transcription protein STAT4	
IL12B	5q31.1-q33.1	rs3212227 rs730690	interleukin 12B (natural killer cell stimulatory factor 2, cytotoxic lymphocyte maturation factor 2, p40); cytokine that acts on T and natural killer cells; expressed by activated macrophages that serve as an essential inducer of Th1 cells development; important for sustaining a sufficient number of memory/effector Th1 cells	multiple sclerosis, asthma; neuroblastoma
IL13	5q31.1-q33.1	rs1295686 rs1800925 rs1881457 rs20541	interleukin 13; immunoregulatory cytokine produced primarily by activated Th2 cells; involved in B-cell maturation and differentiation; up-regulates CD23 and MHC class II expression, and promotes IgE isotype switching of B cells; down-regulates macrophage activity, thereby inhibits the production of pro-inflammatory cytokines and chemokines	asthma; Hodgkin's disease, pediatric brain tumors
IL15	4q31	rs1057972 rs10833 rs1493013	interleukin 15; induces the activation of JAK kinases, as well as the phosphorylation and activation of transcription activators STAT3, STAT5, and STAT6	ALL

		rs2254514 rs2857261		
IL15RA	10p15-p14	rs2228059 rs2296135 rs2296141 rs3136614	interleukin 15 receptor, alpha; cytokine receptor that specifically binds IL15 with high affinity; enhances cell prolif. and expression of apoptosis inhibitor BCL2L1/ BCL2-XL/ BCL2	leukemia
JAK3	19p13.1	rs3008 rs3212711 rs3212752	Janus kinase 3; expressed in immune cells and transduces a signal in response to its activation via tyrosine phosphorylation by interleukin receptors	SCID, ALL
PIM1	6p21.2	rs10507 rs12197850 rs1757000 rs262933	pim-1 oncogene; encodes a protein kinase; required for IL6-induced activation of androgen receptor-mediated transcription in prostate cancer; plays a role, most likely by phosphorylation, in promoting complex formation between NuMA, HP1beta, dynein and dynactin, a complex that is necessary for mitosis	prostate cancer
IFNG	12q14	rs1861494	interferon, gamma; produced by lymphocytes activated by specific antigens or mitogens; antiviral activity, potent activator of macrophages, antiproliferative effects on transformed cells, can potentiate the antiviral and antitumor effects of the type I interferons	Ewing`s, leukemia
IFNGR1	6q23-q24	rs11914 rs3799488	interferon gamma receptor 1; encodes the ligand-binding chain (alpha) of the heterodimeric gamma interferon receptor; . IFNGR2 encodes the non-ligand-binding partner of the heterodimeric receptor	
IFNGR2	21q22.11	rs1059293	interferon (alpha, beta and omega) receptor 2; a type I integral membrane protein; belongs to the type II cytokine family of receptors; forms part of the interferon gamma receptor and is thought to interact with GAF, JAK1, and/or JAK2 in the interferon gamma signal transduction pathway	
IFNAR2	21q22.11	rs2236757 rs3153 rs7279064	interferon (alpha, beta and omega) receptor 2; type I membrane protein that forms one of the two chains of a receptor for interferons alpha and beta; binding and activation of the receptor stimulates Janus protein kinases, which in turn phosphorylate several proteins, including STAT1 and STAT2	
STAT1	2q32.2	rs2066804	signal transducer and activator of transcription 1, 91kDa; activated by various ligands including interferon-alpha, interferon-gamma, EGF, PDGF and IL6; mediates the expression of a variety of genes, which is thought to be important for cell viability in response to different cell stimuli and pathogens	Wilm`s tumor, follicular lymphoma
LEPR	1p31	rs1137100 rs1137101 rs1887285 rs7602	leptin receptor; cytokine receptor family; increases the expression of vascular endothelial growth factor and its receptor type two (VEGF-R2); **oncogene**	mammary tumor, gastric cancer

PI3K/PTEN/AKT PATHWAY

The serine/threonine kinase Akt/PKB pathway is a new target for molecular therapeutics, as it functions as a cardinal nodal point for transducing extracellular (growth factor and insulin) and intracellular (receptor tyrosine kinases, Ras and Src) oncogenic signals. Alterations of the Akt pathway have been detected in a number of human malignancies.

Gene	Location		Group and function of protein	Related disease
PTEN	10q23.3	rs1903858 rs701848	phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase; phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase; tumor suppressor that is mutated in a large number of cancers at high frequency; **tumor suppressor gene**	pediatric brain tumors and other
BCL2L1	20q11.21	rs1484994 rs1994251	BCL2-like 1, BCL-2 protein family, regulate outer mitochondrial membrane channel (VDAC) opening; **tumor suppressor gene**	Wilms tumor, ALL

		rs3181073		
STK11	19p13.3	rs741764	serine/threonine kinase 11, serine/threonine kinase family; regulates cell polarity and functions as a **tumor suppressor**	Peutz-Jeghers syndrome
AKT1	14q32.32	rs2498799	v-akt murine thymoma viral oncogene homolog 1; serine-threonine protein kinase; inactive in serum-starved primary and immortalized fibroblasts; activated by platelet-derived growth factor through phosphatidylinositol 3-kinase; critical mediator of growth factor-induced neuronal survival; survival factors can suppress apoptosis in a transcription-independent manner by activating the serine/threonine kinase AKT1, which then phosphorylates and inactivates components of the apoptotic machinery; **signal transducer; oncogene**	medulloblastoma
BAX	19q13.3-q13.4	rs4645887 rs905238	BCL2-associated X protein; BCL2 protein family (act as anti- or pro-apoptotic regulators); interacts with, and increases the opening of the mitochondrial voltage-dependent anion channel which leads to the loss in membrane potential and the release of cytochrome c; expr. regulated by P53; involved in P53-mediated apoptosis; **signal transducer, oncogene**	basal cell carcinoma, Wilms tumor, ALL

APC PATHWAY AND WNT/-CATENIN SIGNALING PATHWAY

The adenomatous polyposis coli gene (*APC*) encodes a key tumor suppressor involved in negative regulation of the canonical Wnt/-catenin signaling cascade. Mutations of *APC* have been detected in sporadic cancers and in the germline of familial adenomatous polyposis (FAP) patients. APC interacts with many components of the Wnt/-catenin signaling pathway, including AXIN, GSK-3 and -catenin, but the key tumor suppressor function of APC involves destabilization of free -catenin. Loss of functional APC leads to nuclear accumulation of -catenin, which binds to members of the T-cell factor/lymphoid enhancer factor (TCF/LEF) family of transcription factors such as TCF4. Formation of a TCF4/-catenin complex results in transcriptional activation of target genes, such as *MYC* and cyclin D1, which are involved in early transformation of the colonic epithelium.

Gene	Location	SNP	Group and function of protein	Related disease
APC	5q21-q22	rs2229992 rs2909786 rs41115 rs459552 rs866006	adenomatosis polyposis coli; cell adhesion, tyrosine phosphorylation; tumor suppressor protein that includes among its many intracellular functions one of nuclear export; **tumor suppressor gene**	adenomatosis polyposis coli; colon, endometrial carcinoma
AXIN2	17q23-q24	rs11867417 rs11868547 rs2240308 rs3923087 rs4128941 rs4541111 rs7210356	Axin-related protein, Axin2, presumably plays an important role in the regulation of the stability of beta-catenin in the Wnt signaling pathway; deregulation of beta-catenin is an important event in the genesis of a number of malignancies; **defective mismatch repair; tumor suppressor gene**	neuroblastoma, colorectal cancer
CDH1	16q22.1	rs1801026 rs1801552 rs9282650	cadherin 1, type 1, E-cadherin (epithelial); classical cadherin from the cadherin superfamily; calcium dependent cell-cell adhesion glycoprotein comprised of five extracellular cadherin repeats, a transmembrane region and a highly conserved cytoplasmic tail; loss of function is thought to contribute to progression in cancer by increasing proliferation, invasion, and/or metastasis; the ectodomain of this protein mediates bacterial adhesion to mammalian cells and the cytoplasmic domain is required for internalization	gastric, breast, colorectal, thyroid, ovarian cancer; Ewing sarcoma, leukemia
CASR	3q13	rs1042636 rs1965357 rs2270916 rs2270917	calcium-sensing receptor (hypocalciuric hypercalcemia 1, severe neonatal hyperparathyroidism); sensor for parathyroid and kidney to determine the extracellular calcium concentration and thus helps to maintain a stable calcium concentration; CaSR-mediated secretion of Wnt5a inhibits Wnt signaling	familial hypocalciuric hypercalcemia; colon cancer

		rs2279802 rs3749208 rs4678045		
LRP5	11q13.4	rs312016 rs3736228 rs491347 rs607887	low density lipoprotein receptor-related protein 5: involved in the Wnt/beta catenin signaling pathway, probably by acting as a coreceptor together with Frizzled for Wnt	osteosarcoma
CTNNB1	3p21	rs11129895 rs11564437 rs11564452 rs11564465 rs1880481 rs2371452 rs2953 rs3864004 rs4135385 rs4533622 rs5743395 rs9813198 rs9883073	catenin (cadherin-associated protein), beta 1, 88kDa; adherens junction protein; critical for the establishment and maintenance of epithelial layers; adherens junctions regulate normal cell growth and behavior and plays a role in tumor cell metastasis; **signal transducer, oncogene**	prostate cancer, ALL, medulloblastoma
LRP6	12p11-p13	rs2075241 rs3782528	low density lipoprotein receptor-related protein 6; essential for the Wnt/beta catenin signaling pathway, probably by acting as a coreceptor together with Frizzled for Wnt; specific high-affinity receptor for DKK1 and DKK2, but not DKK3	leukemia
FZD7	2q33	rs1207955 rs12474408 rs13034206 rs4673222	Member of the 'frizzled' gene family (encode 7-transmembrane domain proteins that are receptors for Wnt signaling proteins); may downregulate APC function and enhance beta-catenin-mediated signals; **oncogene**	esophageal carcinomas, colon tumors
RAC1	7p22	rs2303364	ras-related C3 botulinum toxin substrate 1 (rho family, small GTP binding protein Rac1); RAS superfamily of small GTP-binding proteins; control of cell growth, cytoskeletal reorganization, and the activation of protein kinases; **oncogene**	Brain tumors, alveolar rhabdomyosarcoma

RECEPTOR TYROSINE KINASE PATHWAY AND RAS/MAPK/ERK PATHWAY

The receptor tyrosine kinases (RTKs) are a major type of cell-surface receptors. The ligands for RTKs are soluble or membrane-bound peptide/protein hormones including nerve growth factor (NGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), and insulin. Binding of a ligand to this type of receptor stimulates the receptor's intrinsic protein-tyrosine kinase activity, which subsequently stimulates a signal-transduction cascade leading to changes in cellular physiology and/or patterns of gene expression. RTK signaling pathways have a wide spectrum of functions including regulation of cell proliferation and differentiation, promotion of cell survival, and modulation of cellular metabolism. Following activation of the RTK pathway, several signal transduction pathways can be activated: Ras-MAP kinase pathway, the ERK pathway, the JNK/SAPK pathway, the p38/HOG pathway, and the STAT pathway (see there).

The **MAPK/ERK pathway** is a signal transduction pathway that couples intracellular responses to the binding of growth factors to cell surface receptors. This pathway is very complex and includes many protein components. In many cell types, activation of this pathway promotes cell division.

Ras is a key regulator of cell growth in all eukaryotic cells. The Ras signal transduction pathway responds to diverse extracellular stimuli, including peptide growth factors, cytokines, and hormones. Activating mutations in Ras are prevalent in about 30% of all human cancers.

Gene	Location	SNP	Group and function of protein	Related disease

MYC	8q24.21	rs3891248	v-myc myelocytomatosis viral oncogene homolog (avian); Helix-loop-helix protein; multifunctional, nuclear phosphoprotein that plays a role in cell cycle progression, apoptosis and cellular transformation; functions as a transcription factor that regulates transcription of specific target genes; **oncogene; nuclear transcription factor**	Burkitt`s lymphoma, leukemia, lymphoma
CAV1	7q31.1	CAV1-23 rs10257125 rs1049334 rs1049337 rs2215448 rs6950798 rs8713	caveolin 1, caveolae protein, 22kDa; main component of the caveolae plasma membranes found in most cell types; links integrin subunits to the tyrosine kinase FYN, an initiating step in coupling integrins to the **Ras-ERK pathway** and promoting cell cycle progression; **tumor suppressor gene;** negative regulator of the **Ras-p42/44 MAP kinase cascade**	Ewing family of tumors
RAB15	14q23.3	rs2277502 rs3742599 rs3825644	RAB15, member RAS onocogene family; may act in concert with RAB3A in regulating aspects of synaptic vesicle membrane flow within the nerve terminal; **nuclear transcription factor**; regulator of cell proliferation, differentiation, transformation; association with apoptotic cell death; **oncogene**	
FOS	14q24.3	rs1063169 rs4645856 rs7101	v-fos FBJ murine osteosarcoma viral oncogene homolog; Fos gene family consists of 4 members: FOS, FOSB, FOSL1, and FOSL2; leucine zipper proteins that can dimerize with proteins of the JUN family, thereby forming the transcription factor complex AP-1; regulators of cell proliferation, differentiation, and transformation; associated with apoptotic cell death; **oncogene, nuclear transcription factor**	ALL
RHOA	3p21.3	rs3448	ras homolog gene family, member A; regulates a diverse set of biological activities including actin organization, cell motility, cell polarity, gene transcription and cell-cycle progression; **oncogene; nuclear transcription factor**	hepatocellular, colorectal cancer, astrozytoma
EGF	4q25	rs2237051 rs4444903 rs971696	epidermal growth factor (beta-urogastrone); profound effect on the differentiation of specific cells in vivo and is a potent mitogenic factor for a variety of cultured cells of both ectodermal and mesodermal origin; membrane-bound molecule which is proteolytically cleaved to generate the 53-amino acid peptide hormone that stimulates cells to divide	nephroblastoma
EGFR	7p12	rs1140475 rs2017000 rs2293347	Epidermal growth factor receptor; receptor also for other members of the EGF family, as TGF-alpha, amphiregulin, betacellulin, heparin-binding EGF-like growth factor, GP30 and vaccinia virus growth factor; involved in the control of cell growth and differentiation; **oncogene**	Squamous cell carcinoma of the lung
TNIP1	5q32-q33.1	rs2277940 rs736775	TNFAIP3 interacting protein 1; extracellular signal regulated kinase1/2 (ERK1/2), an important factor in signal transduction, controls cell growth, differentiation, and death; this protein binds to human ERK2; **EGF/MEK/ERK2 signal transduction pathway**	
TGFB1	19q13.2; 19q13.1	rs1800469 rs1800471	transforming growth factor, beta 1 (Camurati-Engelmann disease); multifunctional peptide that controls proliferation, differentiation, and other functions in many cell types; acts as a negative autocrine growth factor; dysregulation of TGFB activation and signaling may result in apoptosis	ALL
CD14	5q22-q32; 5q31.1	rs2569190	CD14 molecule; surface protein preferentially expressed on monocytes/macrophages; binds lipopolysaccharide binding protein and recently has been shown to bind apoptotic cells; Toll-like receptor signaling pathway; Hematopoietic cell lineage; Regulation of actin cytoskeleton	leukemia
TGFBR1	9q22	rs334358 rs868	transforming growth factor, beta receptor I (activin A receptor type II-like kinase, 53kDa); serine/threonine protein kinase; forms a heteromeric complex with type II TGF-beta receptors when	Loeys-Dietz aortic aneurysm syndrome

		rs928180	bound to TGF-beta, transducing the TGF-beta signal from the cell surface to the cytoplasm;	
PAK6	15q14	rs11636097 rs2242119 rs2242120 rs900055 rs936216	p21(CDKN1A)-activated kinase 6; protein that shares a high degree of sequence similarity with p21-activated kinase (PAK) family members; PAK kinases are implicated in the regulation of a number of cellular processes, including cytoskeleton rearrangement, apoptosis and the MAP kinase signaling pathway; this protein interacts with androgen receptor (AR), which is a steroid hormone-dependent transcription factor that is important for male sexual differentiation and development; highly expressed in testis and prostate tissues; shown to cotranslocate into the nucleus with AR in response to androgen; **oncogene**	
RET	10q11.2	rs1800858 rs1800860	multiple endocrine neoplasia and medullary thyroid carcinoma 1, Hirschsprung disease; Cadherin-superfamily: receptor tyrosine kinases, which are cell-surface molecules that transduce signals for	Hirschsprung disease, MEN, medullary thyroid CA
PDGFB	22q12.3-q13.1; 22q13.1	rs11704525	platelet-derived growth factor beta polypeptide (simian sarcoma viral (v-sis) oncogene homolog; member of the platelet-derived growth factor family; mitogenic factors for cells of mesenchymal origin; **oncogene; Akt-pathway**	astrocytoma, osteosarcoma
ERBB2	17q21.1	rs1058808 rs1810132	v-erb-b2 erythroblastic leukemia viral oncogene homolog 2; member of the epidermal growth factor (EGF) receptor family of receptor tyrosine kinases; activation of downstream signalling pathways; **oncogene**	breast, ovarian, lung, and stomach cancer

ANGIOGENESIS

Tumors induce capillary growth into the tumor by secreting various growth factors, e.g. VEGF for initiation and PDGF for maintenance of blood vessels. Blood vessels supply the tumors with required nutrients and serve as a waste pathway. Angiogenesis is necessary for transition from a small harmless cluster of cells to a large tumor, which metastasizes.

Gene	Location	SNP	Group and function of protein	Related disease
VCAM1	1p32-p31	rs1041163 rs2392221 rs3176879	vascular cell adhesion molecule 1; mediates leukocyte-endothelial cell adhesion and signal transduction; involved in tumor progression, angiogenesis, met. process; inflamm. processes	GI tumors,astrocytoma
ARNT	1q21	rs1027699 rs1889740 rs2228099 rs2256355 rs2864873 rs7517566	aryl hydrocarbon receptor nuclear translocator; forms a complex with the ligand-bound Ah receptor, and is required for receptor function; beta subunit of a heterodimeric transcription factor, hypoxia-inducible factor 1 (HIF1)	vascular tumors in liver
VEGF	6p12	rs1005230 rs25648 rs3025039	vascular endothelial growth factor A; **member of the PDGF/VEGF growth factor family;** acts on endothelial cells and has various effects, including mediating increased vascular permeability, inducing angiogenesis, vasculogenesis and endothelial cell growth, promoting cell migration, and inhibiting apoptosis	diabetic retinopathy; pediatric brain tumors
RGS5	1q23.1	rs15049	regulator of G-protein signalling 5; expression of this single gene in pericytes controls the shape and function of the **tumor vasculature**; potential target in immunotherapeutic strategies; **signal transduction**	ductal carcinoma in situ of the breast

IMMUNE REGULATION

The **immune system** is a collection of mechanisms within an organism that protects against disease by identifying and killing pathogens and tumor cells. When normal cells turn into cancer cells, some of the antigens on their surface change. These cells constantly shed bits of protein from their surface into the circulatory system. Shed antigens prompt action from immune defenders, including cytotoxic T cells, natural killer cells, and macrophages. Patrolling cells of the immune system provide continuous bodywide surveillance, catching and eliminating cells that undergo malignant transformation. Tumors develop when this immune surveillance breaks down or is overwhelmed.

Gene	Location	SNP	Group and function of protein	Related disease
CD4	12pter-p12	rs3213427	CD4 molecule; accessory protein for MHC class-II antigen/T-cell receptor interaction; may regulate T-cell activation; induces the aggregation of lipid rafts	leukemia, Hodgkin lymphoma
CD40	20q12-q13.2	rs1535045 rs3765459	CD40 molecule, TNF receptor superfamily member 5; essential in mediating a broad variety of immune and inflammatory responses including T cell-dependent immunoglobulin class switching, memory B cell development, and germinal center formation	leukemia, thyroid cancer
CD86	3q21	rs1129055 rs9282641	CD86 molecule; type I membrane protein; member of the IG superfamily; expressed by antigen-presenting cells; ligand for two proteins at the cell surface of T cells, CD28 antigen and cytotoxic T-lymphocyte-associated protein 4; binding with CD28 antigen is a costimulatory signal for activation of T-cells; binding with cytotoxic T-lymphocyte-associated protein 4 negatively regulates T-cell activation, diminishes immune response	leukemia
CD80	3q13.3-q21	rs1385520 rs2228017 rs9282638	CD80 molecule; provides a costimulatory signal necessary for T cell activation and survival; provides (together with CD86) the necessary stimuli to prime T cells against antigens presented by antigen-presenting cells	leukemia
CD81	11p15.5	rs708155 rs810225	CD81 molecule; member of the transmembrane 4 superfamily (cell-surface proteins that are characterized by the presence of four hydrophobic domains; mediate signal transduction events that play a role in the regulation of cell development, activation, growth and motility); promotes muscle cell fusion and supports myotube maintenance; may be involved in signal transduction; localized in the **tumor-suppressor gene region**	neuroblastoma
IL1A	2q14	rs17561 rs2071374	interleukin 1, alpha; member of the interleukin 1 cytokine family; involved in various immune responses, inflammatory processes, hematopoiesis; produced by monocytes and macrophages as proprotein, proteolytically processed and released in response to cell injury, and thus induces apoptosis	rheum. arthritis, Alzheimer's disease; Ependymoma
IL1B	2q14	rs1071676 rs1143627 rs1143634 rs16944 rs3136558	member of the interleukin 1 cytokine family; produced by activated macrophages as a proprotein, which is proteolytically processed to its active form by caspase 1, important mediator of the inflammatory response; involved in cell proliferation, differentiation, apoptosis	inflammatory pain hypersensitivity; astrocytomas
IL1RN	2q14.2	rs380092 rs419598 rs454078	interleukin 1 receptor antagonist; member of the interleukin 1 cytokine family; inhibits the activities of interleukin 1, alpha (IL1A) and interleukin 1, beta (IL1B), and modulates a variety of interleukin 1 related immune and inflammatory responses	osteoporotic fractures; gastric cancer, astrocytoma
IL8	4q13-q21	rs2227306 rs2227549 rs4073	interleukin 8; member of the CXC chemokine family; one of the major mediators of the inflammatory response; functions as a chemoattractant, and is also a potent angiogenic factor; **Toll-like receptor signaling pathway**	bronchiolitis; leukemia
IL8RA	2q35	rs2854386	interleukin 8 receptor, alpha; member of the G-protein-coupled receptor family; inhibits embryonic oligodendrocyte precursor migration in developing spinal cord	leukemia, melanoma
IL8RB	2q35	rs1126579	interleukin 8 receptor, beta; member of the G-protein-coupled receptor family; mediates neutrophil migration to sites of inflammation; binds also to chemokine (C-X-C motif) ligand 1 (CXCL1/MGSA), a protein with melanoma growth stimulating activity; angiogenic effects of IL8 in intestinal microvascular endothelial cells are found to be mediated by this receptor	melanoma

CD3EAP	19q13.3	rs3212986	CD3e molecule, epsilon associated protein; DNA-dependent RNA polymerase catalyzes transcription of DNA into RNA; component of RNA polymerase I which synthesizes ribosomal RNA precursors; Isoform 1 involved in UBTF-activated transcription; Isoform 2 component of preformed T-cell receptor (TCR) complex	
TNF	6p21.3	rs1799964 rs1800629 rs1800630 rs3093661	tumor necrosis factor; **member of the tumor necrosis factor (TNF) superfamily**; multifunctional proinflammatory cytokine; mainly secreted by macrophages; functions through its receptors TNFRSF1A/TNFR1 and TNFRSF1B/TNFBR; wide spectrum of processes (cell proliferation, differentiation, apoptosis, lipid metabolism, and coagulation); autoimmune diseases, insulin resistance, and cancer	ALL
LTA	6p21.3	rs3093546 rs909253	Lymphotoxin alpha; **member of the tumor necrosis factor family**; a cytokine produced by lymphocytes; mediates a large variety of inflammatory, immunostimulatory, and antiviral responses; involved in the formation of secondary lymphoid organs; plays a role in apoptosis	diabetes mellitus; non-Hodgkin's lymphoma
SLAMF1	1q22-q23	rs1061217 rs164283 rs2295612	signaling lymphocytic activation molecule family member 1; T-cell receptor activity	diabetes, lupus erythematodes
RNASEL	1q25	rs11072 rs486907	ribonuclease L (2',5'-oligoisoadenylate synthetase-dependent); component of the interferon-regulated 2-5A system that functions in antiviral and antiproliferative roles of interferons	prostate cancer, neuroblastoma
NCF2	1q25	rs2274064 rs2296164 rs699244	neutrophil cytosolic factor 2 (65kDa, chronic granulomatous disease, autosomal 2); subunit of the multi-protein complex known as NADPH oxidase found in neutrophils; this oxidase produces a burst of superoxide which is delivered to the lumen of the neutrophil phagosome; role in myelopoiesis	chronic granulomatous disease
PTGS1 PTGS2	9q32-q33.3, 1q25.2-q25.3	rs5788 rs20417 rs4648276 rs5275 rs5277 rs689466	prostaglandin-endoperoxide synthase 1 and 2 (prostaglandin G/H synthases and cyclooxygenases); key (iso)enzymes in prostaglandin biosynthesis; prostanoid biosynthesis involved in inflammation and mitogenesis; angiogenesis in endothelial cells; cell-cell signaling; tissue homeostasis	retinoblastomas, brain tumors, sarcomas
MSR1	8p22	rs414580 rs971594	macrophage scavenger receptor 1; macrophage-specific trimeric integral membrane glycoprotein; implicated in many macrophage-associated processes including atherosclerosis, Alzheimer's disease, and host defense	Alzheimer`s; leukemia
CTSB	8p22	rs1065712	cathepsin B; lysosomal cysteine proteinase; involved in the proteolytic processing of amyloid precursor protein (APP); Antigen processing and presentation	Alzheimer`s; brain tumors
CRP	1q21-q23	rs1205 rs1800947	C-reactive protein, pentraxin-related; member of the class of acute phase reactants; role in complement binding to foreign and damaged cells and enhances phagocytosis by macrophages; important role in innate immunity	
CSF1R	5q33-q35	rs10079250 rs2228422 rs3829987	colony stimulating factor 1 receptor, formerly McDonough feline sarcoma viral (v-fms) oncogene homolog; member of the CSF1/PDGF receptor family of tyrosine-protein kinases; controls the production, differentiation, and function of macrophages; mediates most if not all of the biological effects of this cytokine	myeloid malignancy
CSF2 CSF3	5q31.1; 17q11.2-q12	rs25882 rs1042658 rs2227338	colony stimulating factor 2 (granulocyte-macrophage); cytokine that controls the production, differentiation, and function of granulocytes and macrophages	AML
CFH	1q32	rs1065489	complement factor H; regulator of Complement Activation (RCA) gene cluster	HUS

		rs1329423 rs2274700 rs2300430 rs800292		
MPO	17q23.1	rs2071409	Myeloperoxidase; heme protein synthesized during myeloid differentiation that constitutes the major component of neutrophil azurophilic granules	Prognosis in AML
NFKBIE	6p21.1	rs2282151 rs483536 rs513688 rs730775	nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, epsilon; B cell receptor signaling	
CYBB	Xp21.1	rs4422908 rs5964125 rs5964149 rs5964151 rs6610650	cytochrome b-245, beta polypeptide (chronic granulomatous disease); composed of cytochrome b alpha (CYBA) and beta (CYBB) chain; component of the microbicidal oxidase system of phagocytes; angiogenesis	CGD; AML
CTLA4	2q33	rs11571315 rs11571316 rs11571317 rs231775 rs3087243 rs4553808 rs5742909	cytotoxic T-lymphocyte-associated protein 4; member of the immunoglobulin superfamily; transmits an inhibitory signal to T cells	autoimmune diseases
IRF1	5q31.1	rs839 rs9282763	interferon regulatory factor 1; member of the interferon regulatory transcription factor (IRF) family; serves as activator of interferons alpha and beta transcription, required for double-stranded RNA induction of these genes; transcription activator of genes induced by interferons alpha, beta, and gamma; plays a role in regulating apoptosis and tumor suppression	AML, medulloblastoma
IRF3	19q13.3	rs2304204 rs2304206 rs7251	interferon regulatory factor 3; member of the interferon regulatory transcription factor (IRF) family; found in an inactive cytoplasmic form that upon serine/threonine phosphorylation forms a complex with CREBBP; this complex translocates to the nucleus and activates the transcription of interferons alpha and beta, as well as other interferon-induced genes	
VIL2	6q25.2-q26	rs3123109 rs901369	villin 2 (ezrin); functions as a protein-tyrosine kinase substrate in microvilli; leukocyte transendothelial migration; regulation of actin cytoskeleton	
ICAM1	19p13.3-p13.2	rs281432 rs3093032 rs5030390 rs5498	intercellular adhesion molecule 1 (CD54), human rhinovirus receptor; typically expressed on endothelial cells and cells of the immune system; binds to integrins of type CD11a / CD18, or CD11b / CD18; also exploited by Rhinovirus as a receptor	non-Hodgkin lymphomas
TLR2	4q32	rs3804099 rs3804100 rs4696480	toll-like receptor 2; member of the Toll-like receptor (TLR) family; role in pathogen recognition and activation of innate immunity; recognizes pathogen-associated mol. patterns that are expressed on infectious agents; mediates production of cytokines for development of effective immunity; host response to Gram-pos. bacteria and yeast via stimul. of NF-kappaB	ALL
CX3CR1	3p21/3p21.3	rs3732378	chemokine (C-X3-C motif) receptor 1; fractalkine (FKN, CX3CL1), operating through the receptor	colorectal cancer

		rs3732379	CX3CR1, effective chemoattractant and adhesion receptor for NK cells and monocytes, important constituents of the innate immune response; over-expression of CX3CL1 by tumor cells enhances antitumor responses	
CCR2	3p21.31	rs1799864 rs1799865 rs3138042	chemokine (C-C motif) receptor 2; encodes two isoforms of a receptor for monocyte chemoattractant protein-1, a chemokine which specifically mediates monocyte chemotaxis; involved in monocyte infiltration in inflammatory diseases such as rheumatoid arthritis as well as in the inflammatory response against tumors	rheum. arthritis; hepato-cellular carcinoma, leukemia
CCR3	3p21.3	rs3091312 rs4987053	chemokine (C-C motif) receptor 3; family 1 of the G protein-coupled receptors; binds and responds to a variety of chemokines, including eotaxin (CCL11), eotaxin-3 (CCL26), MCP-3 (CCL7), MCP-4 (CCL13), and RANTES (CCL5); expressed in eosinophils and basophils; plays role in accumul. and activation of eosinophils + other inflamm. cells in allergic airway	leukemia, osteosarcoma
CCR5	3p21.31	rs1799987 rs1800024 rs2734648	chemokine (C-C motif) receptor 5; member of the beta chemokine receptor family; seven transmembrane protein similar to G protein-coupled receptors; expressed by T cells and macrophages; important co-receptor for macrophage-tropic virus, including HIV, to enter host cells; ligands of this receptor include monocyte chemoattractant protein 2 (MCP-2), macrophage inflammatory protein 1 alpha (MIP-1 alpha) and beta (MIP-1 beta)	HIV infection resistance; leukemia
CCL5	17q11.2-q12	rs2107538 rs2280789	chemokine (C-C motif) ligand 5; one of several CC cytokine genes clustered on the q-arm of chrom. 17; chemoattractant for blood monocytes, memory T helper cells and eosinophils; causes the release of histamine from basophils and activates eosinophils; one of the major HIV-suppressive factors produced by CD8+ cells	HIV; cutaneous lymphoprolif. disorders, lung cancer
NFKB1	4q24	rs230496 rs230532 rs230547 rs3774932 rs3774937 rs4648059	nuclear factor of kappa light polypeptide gene enhancer in B-cells 1 (p105); Rel protein-specific transcription inhibitor and the 50 kD protein is a DNA binding subunit of the NF-kappa-B (NFKB) protein complex; activated by various intra- and extra-cellular stimuli such as cytokines, oxidant-free radicals, ultraviolet irradiation, and bacterial or viral products; involved in immune response, acute phase reactions, apoptosis	inflammatory diseases
MASP1	3q27-q28	rs1001073 rs12635264 rs13089330 rs13094773 rs1533593 rs3105782 rs3733001 rs3774268 rs3864099 rs4376034 rs696405 rs698079 rs698090 rs698105 rs710459 rs7609662	mannan-binding lectin serine peptidase 1 (C4/C2 activating component of Ra-reactive factor); member of the peptidase S1 family; triggers the activation of complement cascade by activating the C4 and C2 components; it activates the C4 component by cleaving the alpha-chain of C4	glioma
BPI	20q11.23-q12	rs1131847	bactericidal/permeability-increasing protein; a lipopolysaccharide binding protein; associated with human neutrophil granules; has bactericidal activity on gram-negative organisms	

P2RX7	12q24	rs3751144	purinergic receptor P2X, ligand-gated ion channel, 7; family of purinoceptors for ATP; functions as a ligand-gated ion channel and is responsible for ATP-dependent lysis of macrophages through the formation of membrane pores permeable to large molecules	
MX1	21q22.3	rs1050008 rs2070229 rs2072683 rs2280807 rs455599 rs458582 rs469270 rs469304 rs469390	myxovirus (influenza virus) resistance 1, interferon-inducible protein p78 (mouse); responsible for a specific antiviral state against influenza virus infection; member of dynamin family and family of large GTPases	
FUT2	19q13.3	rs603985	fucosyltransferase 2 (secretor status included); creates a soluble precursor oligosaccharide FuC-alpha ((1,2)Galbeta-) called the H antigen which is an essential substrate for the final step in the soluble A and B antigen synthesis pathway	
BCL6	3q27	rs1464645 rs1474326 rs3172469 rs3774306 rs3774309	B-cell CLL/lymphoma 6 (zinc finger protein 51); zinc finger transcription factor; sequence-specific repressor of transcription, has been shown to modulate the transcription of START-dependent IL-4 responses of B cells; plays an important role in lymphomagenesis; required for germinal center formation and antibody affinity maturation; **oncogene**	diffuse large-cell lymphoma (DLCL), Non-Hodgin lymph.
PLA2G2A	22q13.1	rs2236771	phospholipase A2, group IIA (platelets, synovial fluid); hydrolyze the sn-2 fatty acid acyl ester bond of phosphoglycerides, releasing free fatty acids and lysophospholipids; they play an important role in a variety of cellular processes, including the digestion and metabolism of phospholipids as well as the production of precursors for inflammatory reactions.	
PLA2G6	22q13.1	rs132987 rs2016755 rs4376 rs84473	A2 phospholipase; catalyzes the release of fatty acids from phospholipids; The encoded protein may play a role in phospholipid remodelling, arachidonic acid release, leukotriene and prostaglandin synthesis, fas-mediated apoptosis, and transmembrane ion flux in glucose-stimulated B-cells	
ALOX5	10q11.2	rs1369214 rs1565096 rs1565097 rs2029253 rs4986832 rs4987105 rs892691	arachidonate 5-lipoxygenase; member of the lipoxygenase gene family and plays a dual role in the synthesis of leukotrienes from arachidonic acid: mutations in the promoter region of this gene lead to a diminished response to antileukotriene drugs used in the treatment of asthma and may also be associated with atherosclerosis and several cancers	
MBL2	10q11.2-q21	rs10082466 rs1031101 rs10824793 rs11003124 rs11003125 rs12264958 rs1838066 rs2099902 rs7096206 rs930508	mannose-binding lectin (protein C) 2, soluble (opsonic defect); recognizes mannose and N-acetylglucosamine on bacterial pathogens; can activate the classical complement pathway	

RPA4	Xq21.33	rs2642219	replication protein A4, 34kDa; required for simian virus 40 DNA replication in vitro; participates in a very early step in initiation; single-stranded DNA-binding protein	
RAG1	11p13	rs2227973	recombination activating gene 1; RAG1 and RAG2 act together to activate immunoglobulin V-D-J recombination; RAG1 is involved in recognition of the DNA substrate	
ARHGDIB	12p12.3	rs2075267 rs921	Rho GDP dissociation inhibitor (GDI) beta; regulates the GDP/GTP exchange reaction of the Rho proteins by inhibiting the dissociation of GDP from them, and subsequent binding	
XBP1	22q12.1; 22q12	rs2097461 rs2239815 rs2267131 rs3788409	X-box binding protein 1; transcription factor that regulates MHC class II genes by binding to a promoter element referred to as an X box; binds to an enhancer in the promoter of the T cell leukemia virus type 1 promoter; may increase expression of viral proteins by acting as the DNA binding partner of a viral transactivator; essential for hepatocyte growth, the differentiation of plasma cells, the immunoglobulin secretion, and the unfolded protein response (UPR)	
SCARB1	12q24.31	rs3924313 rs4765181 rs4765621 rs865716 rs989892	scavenger receptor class B, member 1; receptor for different ligands such as phospholipids, cholesterol ester, lipoproteins, phosphatidylserine and apoptotic cells; probable receptor for HDL; facilitates the flux of free and esterified cholesterol between the cell surface and extracellular donors and acceptors, such as HDL, apoB-containing lipoproteins and modified lipoproteins; probably involved in the **phagocytosis of apoptotic cells**, via its phosphatidylserine binding activity; receptor	brain tumor
CARD15/ NOD2	16q21	rs1077861 rs2066843 rs2066850 rs2067085 rs748855	caspase recruitment domain family, member 15; Nod1/Apaf-1 family; two caspase recruitment (CARD) domains and six leucine-rich repeats (LRRs); primarily expressed in the peripheral blood leukocytes; plays a role in the immune response to intracellular bacterial lipopolysaccharides (LPS) by recognizing the muramyl dipeptide (MDP) derived from them and activating the NFKB protein	Crohn disease, Blau syndrome

METABOLISM

All tissues, including tumors, need to follow a simple plan to survive and grow. They need to take up energy substrates, metabolize these substrates to produce ATP (cellular energy currency), and remove metabolic wastes. The way in which different tissues accomplish these tasks varies, especially in tumors. Most tumor cells are dividing rapidly and consequently they need a constant supply of substrates for energy production. Different tumors use different energy substrates including: fatty acids/ketone bodies, amino acids, carbohydrates, and lactate. Although tumors have been shown to use all the above substrates for energy production, the two preferential substrates for tumors appear to be glutamine and glucose. Which substrate or substrates are used depends on the specific tumor and its microenvironment.

Gene	Location	SNP	Group and function of protein	Related disease
ENPP1	6q22-q23	rs1044498 rs1044582	ectonucleotide pyrophosphatase/phosphodiesterase 1; member of the ecto-nucleotide pyrophosphatase/phosphodiesterase (ENPP) family; cleaves a variety of substrates, including phosphodiester bonds of nucleotides and nucleotide sugars and pyrophosphate bonds of nucleotides and nucleotide sugars; **purine metabolism**	'idiop.' infantile arterial calcification; breast cancer
TYR	11q14-q21	rs1393350 rs1800422	tyrosinase (oculocutaneous albinism IA); copper-containing oxidase that functions in the formation of pigments such as melanins and other polyphenolic compounds; catalyzes the rate-limiting conversions of tyrosine to DOPA, DOPA to DOPA-quinone and possibly 5,6-dihydroxyindole to indole-5,6 quinone; **tyrosine metabolism**	melanoma
LPL	8p22	rs1059507 rs263 rs316 rs325 rs326 rs327	lipoprotein lipase; functions as a homodimer, and has the dual functions of triglyceride hydrolase and ligand/bridging factor for receptor-mediated **lipoprotein uptake**	craniopharyngioma

		rs328		
EPHX2	8p21-p12	rs1042032 rs1126452	epoxide hydrolase 2, cytoplasmic; member of the epoxide hydrolase family; binds to specific epoxides and converts them to the corresponding dihydrodiols	familial hypercholesterolemia
LIPC	15q21-q23	rs1077834 rs1800588 rs1869145 rs1968687 rs1968689 rs2242064 rs2242066 rs3825776 rs6074 rs6083	lipase, hepatic; encodes hepatic triglyceride lipase, which is expressed in liver; has the dual functions of triglyceride hydrolase and ligand/bridging factor for receptor-mediated **lipoprotein uptake**	
CTSH	15q24-q25	rs3129	cathepsin H; lysosomal cysteine proteinase important in the overall degradation of lysosomal proteins; composed of a dimer of disulfide-linked heavy and light chains, both produced from a single protein precurso; belongs to the peptidase C1 protein family; can act both as an aminopeptidase and as an endopeptidase	prostate tumors
CBS	21q22.3	rs12613 rs234706 rs397589 rs6586282	cystathionine-beta-synthase; involved in the transsulfuration pathway; first step of this pathway, from homocysteine to cystathionine, is catalyzed by this protein; **transsulfuration pathway; drug sensitivity**	Homocystinuria; leukemia in Down syndrome
CTH	1p31	rs473334 rs515064 rs559062 rs6413471 rs663465 rs663649	cystathionase (cystathionine gamma-lyase); converts cystathione derived from methionine into cysteine; **trans-sulfuration pathway; glycine, serine and threonine metabolism**	cystathioninuria; leukemia
BHMT	5q13.1-q15	rs567754 rs585800 rs617219	Betaine-homocysteine methyltransferase; cytosolic enzyme that catalyzes the conversion of betaine and **homocysteine** to dimethylglycine and methionine	hyperhomocyst(e)inemia;
GSK3B	3q13.3	rs10934500 rs10934503 rs1381841 rs1574154 rs1719888 rs1719889 rs1719895 rs1732170 rs17810235 rs2873950 rs334555 rs334558 rs334559 rs3732361 rs3755557	glycogen synthase kinase 3 beta; proline-directed serine-threonine kinase that was initially identified as a phosphorylating and inactivating **glycogen synthase**; involved in energy metabolism, **neuronal cell development**, and body pattern formation	

		rs4072520 rs4624596 rs4688046 rs6438553 rs7617372 rs7620750 rs9873477 rs9878473		
CETP	16q21	rs1801706 rs289717 rs820299	cholesteryl ester transfer protein, plasma; cholestery ester transfer protein (CETP) transfers cholesteryl esters between lipoproteins; **lipid metabolism**	atherosclerosis
LDLR	19p13.3	rs1003723 rs14158 rs5925 rs5930	low density lipoprotein receptor (familial hypercholesterolemia); bound at cell membrane and taken into the cell ending up in lysosomes where the protein is degraded and cholesterol is made available for repression of microsomal enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase (rate-limiting step in cholesterol synthesis); **lipid metabolism**	familial hypercholesterolemia
APOA2	1q21-1q23	rs5082 rs5085 rs6413453	apolipoprotein A-II, second most abundant protein of the high density lipoprotein particles; defects in this gene may result in apolipoprotein A-II deficiency or **hypercholesterolemia**	ganglioneuroblastoma
APOB	2p24-p23	rs1042034 rs1367117 rs1469513 rs1800481 rs3791981	apolipoprotein B (including Ag(x) antigen); main apolipoprotein of chylomicrons and low density lipoproteins (LDL); remnant lipoproteins (RLP) are TG-rich lipoproteins, which are produced by hydrolysis of VLDL and chylomicrons; they can induce proliferation of smooth muscle cells via activation of mitogen-activated **protein kinase (MAPK)** and EFGR transactivation, along with the involvement G protein-coupled receptor (GPCR)-dependent protein kinase C (PKC); **lipid metabolism**	gallstones; prostate and gallbladder cancer
APOE	19q13.2	rs440446	apolipoprotein E; a main apoprotein of the chylomicron, binds to a specific receptor on liver cells and peripheral cells; essential for the normal catabolism of triglyceride-rich lipoprotein constituents; **lipid metabolism**	type III hyperlipoproteinemia
LCAT	16q22.1	rs1109166 rs4986970 rs5923	lecithin-cholesterol acyltransferase; encodes the extracellular cholesterol esterifying enzyme, lecithin-cholesterol acyltransferase; esterification of cholesterol is required for cholesterol transport; **metabolism of plasma lipoproteins**	fish-eye disease, LCAT deficiency
ALOX15	17p13.3	rs2664593 rs7220870	arachidonate 15-lipoxygenase; converts arachidonic acid to 15S- hydroperoxyeicosatetraenoic acid; acts on C-12 of **arachidonate as well as on linoleic acid**	
CBR1	21q22.13	rs1005695 rs2156406 rs25678	carbonyl reductase 1; one of several monomeric, NADPH-dependent oxidoreductases having wide specificity for carbonyl compounds; **Arachidonic acid metabolism**	
SOAT2	12q13.13	rs17123210 rs2280698 rs2280699	sterol O-acyltransferase 2; member of a small family of acyl coenzyme A: cholesterol acyltransferases; membrane-bound enzyme localized in the endoplasmic reticulum that produces intracellular cholesterol esters from long-chain fatty acyl CoA and cholesterol; implicated in cholesterol absorption in the intestine and in the assembly and secretion of apolipoprotein B-containing lipoproteins such as VLDL; **Bile acid biosynthesis**	
NR1H4	12q23.1	NR1H4-18	nuclear receptor subfamily 1, group H, member 4; receptor for bile acids such as chenodeoxycholic	

		rs35724	acid, lithocholic acid and deoxycholic acid; represses the transcription of the cholesterol 7-alpha-hydroxylase gene (CYP7A1) and activates the intestinal bile acid-binding protein (IBABP); activates the transcription of bile salt export pump ABCB11 by directly recruiting histone methyltransferase CARM1 within its gene locus; **Bile acid biosynthesis**	
CBR3	21q22.2	rs881712	carbonyl reductase 3; catalyzes the reduction of a large number of biologically and pharmacologically active carbonyl compounds to their corresponding alcohols; monomeric NADPH-dependent oxidoreductase; **Arachidonic acid metabolism**	
ALAD	9q33.1	rs1139488 rs1805313 rs8177806	aminolevulinate, delta-, dehydratase; catalyzes the condensation of 2 molecules of delta-aminolevulinate to form porphobilinogen; second step in the **porphyrin and heme biosynthetic pathway**	acute hepatic porphyria
LMO2	11p13	rs3740616 rs3740617 rs3781577	LIM domain only 2 (rhombotin-like 1); central and crucial role in **hematopoietic development**	ALL
COL18A1	21q22.3	rs2236451 rs2236467 rs7499	collagen, type XVIII, alpha 1; one of the multiplexins, extracellular matrix proteins that contain multiple triple-helix domains (collagenous domains) interrupted by non-collagenous domains; may play an important role in retinal structure and in neural tube closure; **collagen synthesis**	Knobloch syndrome
SEC14L2	22q12.2	rs1010324 rs2267154 rs2267155 rs757660	SEC14-like 2 (S. cerevisiae); cytosolic protein which belongs to a family of lipid-binding proteins including Sec14p, alpha-tocopherol transfer protein, and cellular retinol-binding protein; stimulates squalene monooxygenase which is a downstream enzyme in the cholesterol biosynthetic pathway; **cholesterol biosynthetic pathway**	
HFE	6p21.3	rs1572982 rs1799945 rs707889	Hemochromatosis; membrane protein that is similar to MHC class I-type proteins and associates with beta2-microglobulin (beta2M); functions to regulate **iron absorption** by regulating the interaction of the transferrin receptor with transferrin	hereditary haemochromatosis
TFRC	3q29	rs3817672	transferrin receptor (p90, CD71); mediates cellular **uptake of iron; hematopoietic cell lineage**	sarcomas, leukemia, lymph.
MPDU1	17p13.1-p12	rs4227	mannose-P-dolichol utilization defect 1; may be involved in the **synthesis of the sugar** donor Dol-P-Man which is required in the synthesis of N-linked and O-linked oligosaccharides and for that of GPI anchors	
HADHA	2p23	rs1049987 rs2289019 rs7260	hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A thiolase/enoyl-Coenzyme A hydratase (trifunctional protein), alpha subunit; catalyzes the last three steps of mitochondrial beta-oxidation of long chain fatty acids; **Fatty acid metabolism**	LCHAD deficiency
SAT2	17p13.1	rs13894 rs858520	spermidine/spermine N1-acetyltransferase 2; enzyme which catalyzes the acetylation of polyamines; **urea cycle and metabolism of amino groups**	
MAOA	Xp11.3	rs6323	monoamine oxidase A; degrades amine neurotransmitters, such as dopamine, norepinephrine, and serotonin; **Metabolism of amino groups**	MAO deficiency
ALOX12	17p13.1	rs1126667	arachidonate 12-lipoxygenase	atheriosclerosis, essential thrombocythemia

HORMONES, THEIR RECEPTORS AND RELATED GENES

A hormone is achemical messenger that carries a signal from one cell (or group of cells) to another via the blood. In general, hormones regulate the function of their target cells, which are cells that express a receptor for the hormone. Many of the responses to hormone signals can be described as serving to regulate metabolic activity of an organ or tissue. **Hormonal tumorigenesis** may be highly tissue and species-specific. It is unclear whether hormones act as a carcinogen or as a promoter. Tumorigenesis with hormones appears only in vivo, while chemical carcinogens may also act in vitro. Hormones cause tumors in target organs only. It appears that it is unnecessary for hormones to be metabolized before causing tumorigenesis. Evidence that hormones may have an additive effect is absent, while chemicals do act additively. Hormones are unknown to act as mutagens while chemical carcinogens do. There appears to be much dissimilarity in the action of hormones and chemical carcinogens in tumorigenesis.

Gene	Loc.	SNP	Group and function of protein	Disease
OPRD1	1p34.3-p36.1	rs204076 rs760589	opioid receptor, delta 1; inhibits neurotransmitter release by reducing calcium ion currents and increasing potassium ion conductance; highly stereoselective; receptor for enkephalins	
OPRM1	6q24-q25	rs1799971 rs562859 rs607759 rs9282821	opioid receptor, mu 1; inhibits neurotransmitter release by reducing calcium ion currents and increasing potassium ion conductance; receptor for beta-endorphin	neuroblastoma
GRPR	Xp22.2-p22.13	rs4986945 rs4986946	gastrin-releasing peptide receptor; regulates numerous functions of the gastrointestinal and central nervous systems, including release of gastrointestinal hormones, smooth muscle cell contraction, and epithelial cell proliferation and is a potent mitogen for neoplastic tissues	autism
SSTR3	22q13.1	rs229569 rs86582	somatostatin receptor 3; member of the superfamily of receptors; acts at many sites to inhibit the release of many hormones and other secretory proteins; effects probably mediated by a family of G	
AR	Xq11.2-q12	rs1204038 rs1337080 rs1337082 rs2361634	androgen receptor (dihydrotestosterone receptor; testicular feminization; spinal and bulbar muscular atrophy; Kennedy disease); functions as a steroid-hormone activated transcription factor; stimulates transcription of androgen responsive genes	prostate cancer, astrocytoma
RXRA	9q34.3	rs1536475 rs1805352	retinoid X receptor, alpha; member of the steroid and thyroid hormone receptor superfamily of transcriptional regulators; Retinoid X receptors (RXRs) and retinoic acid receptors (RARs) are nuclear receptors that mediate the biological effects of retinoids by involvement in retinoic acid-mediated gene activation	
GC	4q12-q13	rs7041	group-specific component (vitamin D binding protein); albumin gene family; multifunctional protein found in plasma, ascitic fluid, cerebrospinal fluid and on the surface of many cell types; binds to vitamin D and its plasma metabolites and transports them to target tissues	von Recklinghausen neuro-fibromatosis
SHBG	17p13-p12	rs6257 rs6259 rs727428 rs858517	sex hormone-binding globulin; androgen transport protein, but may also be involved in receptor mediated processes; each dimer binds one molecule of steroid; specific for 5-alpha-dihydrotestosterone, testosterone, and 17-beta-estradiol; regulates the plasma metabolic clearance rate of steroid hormones by controlling their plasma concentration	
ESR1	6q25.1	rs1801132 rs2071454 rs2077647 rs2228480 rs2273206 rs3798577 rs3798758 rs488133 rs9340770	estrogen receptor 1; ligand-activated transcription factor composed of several domains important for hormone binding, DNA binding, and **activation of transcription**	Glioma, fibromatosis
ESR2	14q23.2	rs3020450	estrogen receptor 2 (ER beta); member of the family of estrogen receptors and superfamily of	fibromatosis

		rs4986938	nuclear receptor transcription factors; upon binding to 17beta-estradiol or related ligands, the encoded protein forms homo- or hetero-dimers that interact with specific DNA sequences to activate **transcription**	
DIO1	1p33-p32	rs1883454 rs2235544	deiodinase, iodothyronine, type I; selenoprotein that deiodinates prohormone thyroxine to bioactive T3; unclear underexpression in tumours	hypothyroidism
PGR	11q22-q23	rs1042838 rs1042839 rs10895068 rs1870019 rs474320 rs481775 rs492457 rs516693 rs529359 rs543215 rs561650 rs565186 rs568157 rs572483 rs613120 rs660541 rs9282823	progesterone receptor; member of the steroid receptor superfamily; central role in the reproductive events associated with the establishment and maintenance of pregnancy	
CALCR	7q21.3	rs1801197 rs2074122	calcitonin receptor; activity mediated by G proteins which activate adenylyl cyclase; couples to heterotrimeric guanosine triphosphate-binding protein that is sensitive to cholera toxin	osteosarcoma
CGA	6q12-q21	rs4986869 rs6155 rs6631 rs932742	glycoprotein hormones, alpha polypeptide; glycoprotein hormones alpha chain family; alpha subunit of four human glycoprotein hormones chorionic gonadotropin (CG), luteinizing hormone (LH), follicle stimulating hormone (FSH), and thyroid stimulating hormone (TSH)	
HTR1B	6q13	rs130058 rs6296	5-hydroxytryptamine (serotonin) receptor 1B; one of the several different receptors for 5-hydroxytryptamine; serotonin functions as a neurotransmitter, a hormone, and a mitogen	NHL
HTR1D	1p36.3-p34.3	rs605367 rs6300 rs676643	5-hydroxytryptamine (serotonin) receptor 1D; role in maintenance of neuron- and neurotransmitter-associated functions; contributes to homeostasis of serotonergic neurons; **oncogene**	osteosarcoma
LEP	7q31.3	rs2167270	leptin (obesity homolog, mouse); secreted by white adipocytes; mutations in this gene are linked to severe and morbid obesity	severe obesity
PTH	11p15.3-p15.1	rs177706 rs6254 rs6256	parathyroid hormone; secreted by parathyroid cells; elevates blood Ca2+ level by dissolving the salts in bone and preventing their renal excretion	familial hypopara-thyroidism
DRD1	5q35.1	rs5326	dopamine receptor D1; stimulates adenylyl cyclase and activates cyclic AMP-dependent protein kinases; regulates neuronal growth and development, mediates some behavioral responses, and modulate dopamine receptor D2-mediated events; **Calcium signaling pathway; Neuroactive ligand-receptor interaction; Gap junction**	
DRD2	11q23	rs1079597	dopamine receptor D2; encodes the D2 subtype of the dopamine receptor; this G-protein coupled	Myocl dystonia, schizophrenia

		rs1799978	receptor inhibits adenylyl cyclase activity	
DRD4	11p15.5	rs4987059 rs916457	dopamine receptor D4; G-protein coupled receptor which inhibits adenylyl cyclase; associated with various behavioral phenotypes, including autonomic nervous system dysfunction, ADHD	Schizophrenia, Parkinson disease
GHR	5p13-p12	GHR-113 GHR-21 rs1858136 rs2940913 rs2940930 rs2940944 rs2972392 rs2972395 rs2972418 rs2972419 rs2972780 rs4451056 rs6179 rs6180 rs6873545 rs6878512 rs6897530 rs7712701 rs7732059 rs7735889	growth hormone receptor; activation of an intra- and intercellular signal transduction pathway leading to growth	Laron syndrome; neuro-fibromatosis
VDR/ NR1I1	12q13.11	rs2239185 rs757343	vitamin D (1,25- dihydroxyvitamin D3) receptor; functions as receptor for secondary bile acid lithocholic acid; belongs to family of trans-acting transcriptional regulatory factors; shows sequence similarity to steroid and thyroid hormone receptors; some downstream targets are involved in mineral metabolism; involved in **immune response** and cancer	vitamin D-resistant rickets; Leukemia

BIOSYNTHESIS OF STEROIDS

In carcinogenesis hormonal steroids are believed to act as tumour promoters by modulating oncogene expression. It is postulated that the hormonal steroids act on cells in which the initiating carcinogen has either induced mutations in protooncogenes normally hormonally regulated or has induced changes in gene architecture, aligning protooncogenes to hormone-responsive elements, thus placing these genes under nonphysiological hormonal control.

Gene	Loc.	SNP	Group and function of protein	Disease
HMGCR	5q13.3-q14	rs2241402 rs2303151	3-hydroxy-3-methylglutaryl-Coenzyme A reductase; HMG-CoA reductase is the rate-limiting enzyme for cholesterol synthesis	medulloblastoma
HSD3B1	1p13.1	rs10754400 rs1998182 rs2064902 rs4659182 rs6428830 rs6667572	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 1; carcinogenesis by altering the balance between cell proliferation and apoptosis	breast cancer
HSD3B2	1p13.1	rs12411115 rs1361530 rs1417608	hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomeras; carcinogenesis by altering the balance between cell proliferation and apoptosis	prostate cancer

		rs4659175		
HSD17B1	17q11-q21	rs2676530 rs597255 rs676387	hydroxysteroid (17-beta) dehydrogenase 1; favors the reduction of estrogens and androgens; has 20-alpha-HSD activity	
HSD17B2	16q24.1-q24.2	rs1424151 rs723012	hydroxysteroid (17-beta) dehydrogenase 2; capable of catalyzing the interconversion of testosterone and androstenedione, estradiol and estrone	
HSD17B4	5q21	rs17145464 rs2451818 rs246965 rs2546210 rs32659 rs3797372 rs384346 rs7737181	hydroxysteroid (17-beta) dehydrogenase 4; enzyme involved in peroxisomal fatty acid beta-oxidation; first identified as a 17-beta-estradiol dehydrogenase	gonadal stroma tumour
NQO1	16q22.1	rs10517 rs689452 rs689453	NAD(P)H dehydrogenase, quinone; member of the NAD(P)H dehydrogenase (quinone) family; encodes a cytoplasmic 2-electron reductase; prevents the one electron reduction of quinones that results in the production of radical species; serves as a quinone reductase in connection with conjugation reactions of hydroquinons involved in detoxification pathways as well as in biosynthetic processes such as the vitamin K-dependent gamma-carboxylation of glutamate	tardive dyskinesia, Alzheimer's disease; leukemia
BZRP/ TSPO	22q13.31	rs113515 rs3937387 rs6971	translocator protein (18kDa); key factor in the flow of cholesterol into mitochondria to permit the initiation of steroid hormone synthesis	hepatic encephalopathy

INSULIN SIGNAL TRANSMISSION

Signaling through the insulin pathway is critical for the regulation of intracellular and blood glucose levels. According to the current state of knowledge, it can be assumed that nutritive carbohydrates can be regarded as a risk factor for various tumor diseases.

Gene	Location	SNP	Group and function of protein	Related disease
INSR	19p13.3-p13.2	INSR-59 rs1035940 rs1035942 rs1051690 rs1799817 rs2860175 rs3745545 rs3745551 rs3815901 rs8110533 rs891087 rs919275	insulin receptor; binding of insulin to the insulin receptor (INSR) stimulates glucose uptake; insulin is a potent growth factor	medulloblastoma
IGF1	12q22-q23	rs2162679 rs2373721 rs4764883 rs5742629	insulin-like growth factor 1 (somatomedin C); somatomedins, or insulin-like growth factors (IGFs), comprise a family of peptides that play important roles in mammalian growth and development; mediates many of the growth-promoting effects of growth hormone	leukemia

		rs5742665 rs5742667 rs5742694 rs5742714 rs978458		
IGF2	11p15.5	rs2230949 rs3213216 rs3213221 rs3213223 rs734351	insulin-like growth factor 2 (somatomedin A); member of the insulin family of polypeptide growth factors, involved in development and growth	eating disorders; leukemia
IRS1	2q36	rs1366757 rs1801278 rs9282766	insulin receptor substrate 1; IRS-1 is a major insulin receptor substrate which may play an important role in insulin signal transmission; may mediate the control of various cellular processes by insulin; overexpressed in skeletal muscle,and adipocytes	medulloblastoma
IGF2R	6q26	rs1570070 rs1803989 rs2282140 rs629849 rs998074 rs998075	insulin-like growth factor 2 receptor; receptor for both, insulin-like growth factor 2 (IGF2) and mannose 6-phosphate (M6P); functions in the intracellular trafficking of lysosomal enzymes, the activation of transforming growth factor beta, and the degradation of IGF2	brain tumors, neuroblastoma
IGF2AS	11p15.5	rs1003483 rs3741211 rs3741212	insulin-like growth factor 2 antisense; function unknown	Wilm`s tumor
IGFBP1	7p13-p12	rs4619	insulin-like growth factor binding protein 1; member of the insulin-like growth factor binding protein (IGFBP) family; encodes a protein with an IGFBP domain and a thyroglobulin type-I domain; binds both insulin-like growth factors (IGFs) I and II and circulates in the plasma	ALL
IGFBP2	2q33-q34	rs1106037 rs2270360 rs2372848	insulin-like growth factor binding protein 2, 36kDa; regulator of somatic growth and cellular proliferation; major IGFBP of the spinal fluid expressed by multiple neural tissues, highly expressed in infancy and older age adult; involved in control and regulation of neuroblastoma growth and invasion	leukemia, neuroblastoma
IGFBP3	7p13-p12	rs2471551	insulin-like growth factor binding protein 3; member of the insulin-like growth factor binding protein (IGFBP) family and encodes a protein with an IGFBP domain and a thyroglobulin type-I domain; forms a ternary complex with insulin-like growth factor acid-labile subunit (IGFALS) and either insulin-like growth factor (IGF) I or II; in this form, it circulates in the plasma, prolonging the half-life of IGFs and altering their interaction with cell surface receptors	AML
IGFBP5	2q33-q36	rs1978346 rs2241193	insulin-like growth factor binding protein 5; complexing with IGF1 and IGF2; binding to bone cells (skeletal growth factor); role in growth and differentiation of neuroblastoma cells; may influence extrinsic apoptotic pathways via a differential modulation of downstream cell survival and cell death pathways	neuroblastoma
IGFBP6	12q13	rs12821902 rs822688	insulin-like growth factor binding protein 6; member of the insulin-like growth factor binding protein (IGFBP) family; expressed in fibroblasts, in prostatic and ovarian cells, predominantly found in CSF and serum	
IGF1R	15q26.3	rs2137680 rs2175795 rs2229765	insulin-like growth factor 1 receptor; binds insulin-like growth factor with a high affinity; plays a critical role in transformation events; cleavage of the precursor generates alpha and beta subunits; highly overexpressed in most malignant tissues where it functions as an anti-apoptotic agent by enhancing cell survival	leukemia, Wilm`s tumor

		rs3743259 rs3743260 rs907806 rs9282715	
IGFALS	16p13.3	rs2745205	insulin-like growth factor binding protein, acid labile subunit
ROS1	6q22	rs1998206 rs2243 rs2243377 rs497186 rs498251 rs574664 rs581235	v-ros UR2 sarcoma virus oncogene homolog 1 (avian); subfamily of tyrosine kinase insulin receptor genes; highly-expressed in a variety of tumor cell lines; type I integral membrane protein with tyrosine kinase activity; may function as a growth or differentiation factor receptor; **oncogene**

DRUG METABOLISM (CYTOCHROME P450)

These are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. In drug metabolism, cytochrome P450 is probably the most important element of oxidative metabolism (a part of phase I metabolism). Many drugs may increase or decrease the activity of various CYP isozymes in a phenomenon known as enzyme induction and inhibition. This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interaction are especially important to take in account when using drugs of vital importance to the patient, drugs with important side effects and drugs with small therapeutic window.

Gene	Loc.	SNP	Group and function of protein	Disease
CYP1A1	15q22-q24	CYP1A1-91 rs2198843 rs2472299 rs2606345 rs4646421	cytochrome P450, family 1, subfamily A, polypeptide 1; induced by some polycyclic aromatic hydrocarbons (PAHs) (some found in cigarette smoke)	lung cancer, leukemia
CYP1B1	2p21	rs10175368 rs10916 rs162549 rs162555 rs162556 rs162562 rs1800440	cytochrome P450, family 1, subfamily B, polypeptide 1; estrogen metabolism: metabolizes procarcinogens such as polycyclic aromatic hydrocarbons and 17beta-estradiol	congential glaucoma, prostate cancer
CYP2C19	10q24.1-q24.3	rs4244285 rs4986894	cytochrome P450, family 2, subfamily C, polypeptide 19; metabolizes many xenobiotics, including the anticonvulsive drug mephenytoin, omeprazole, diazepam and some barbiturates	
CYP2E1	10q24.3-qter	rs2070673 rs2070676 rs8192766	cytochrome P450, family 2, subfamily E, polypeptide 1; induced by ethanol, the diabetic state, and starvation; metabolizes both endogenous substrates such as ethanol, acetone, and acetal, as well as exogenous substrates including benzene, carbon tetrachloride, ethylene glycol, and nitrosamines (cigarette smoke)	hepatic cirrhosis, diabetes; ALL

CYP3A4	7q21.1	CYP3A4-57	cytochrome P450, family 3, subfamily A, polypeptide 4; metabolism of approximately half the drugs which are are used today; role in the metabolism of CPT-11 (irinotecan); also metabolizes some steroids and carcinogens	
CYP3A7	7q21-q22.1	rs12360	cytochrome P450, family 3, subfamily A, polypeptide 7; hydroxylates testosterone and dehydroepiandrosterone 3-sulphate, involved in the formation of estriol during pregnancy	
CYP7B1	8q21.3	CYP7B1-06 rs1376772 rs1451868 rs3779870	cytochrome P450, family 7, subfamily B, polypeptide 1; catalyzes the first reaction in the cholesterol catabolic pathway of extrahepatic tissues, which converts cholesterol to bile acids; role in total bile acid synthesis, involved in development of atherosclerosis, neurosteroid metabolism, sex hormone synthesis	leukemia
CYP17A1	10q24.3	rs10883782 rs284849 rs4919682 rs4919687 rs619824 rs743572	cytochrome P450, family 17, subfamily A, polypeptide 1; both 17alpha-hydroxylase and 17,20-lyase activities; key enzyme in the steroidogenic pathway that produces progestins, mineralocorticoids, glucocorticoids, androgens, and estrogens	pseudohermaphroditism, adrenal hyperplasia
CYP19A1	15q21.1	CYP19A1-30 rs10046 rs1004983 rs1004984 rs1065779 rs12907866 rs2304463 rs2414096 rs2445765 rs2446405 rs2470144 rs4646 rs6493494 rs700518 rs727479 rs730154 rs749292 rs767199	cytochrome P450, family 19, subfamily A, polypeptide 1; catalyzes the last steps of estrogen biosynthesis, three successive hydroxylations of the A ring of androgens	
CYP24A1	20q13	rs2245153 rs2248359 rs2259735 rs2296241 rs751087	cytochrome P450, family 24, subfamily A, polypeptide; initiates the degradation of 1,25-dihydroxyvitamin D3, the physiol. active form of vitamin D3, by hydroxyl. of the side chain	
AHR	7p15	rs2066853 rs2074113 rs7796976	aryl hydrocarbon receptor; ligand-activated transcription factor involved in regulation of biological responses to planar aromatic hydrocarbons; regulates xenobiotic-metabolizing enzymes such as cytochrome P450	
GSTP1	11q13	rs1799811 rs947894	glutathione S-transferase pi; family of enzymes that play a role in detoxification by catalyzing the conjugation of many hydrophobic and electrophilic compounds with reduced glutathione; metabolism of xenobiotics by cyt P450	drug resistance
DHDH	19q13.3	rs2270939	dihydrodiol dehydrogenase (dimeric); catalyzes the NADP(+)-linked oxidation of trans-dihydrodiols of	

		rs4987162	aromatic hydrocarbons to the corresponding catechols	

OTHER DRUG METABOLISM, (DE)TOXIFICATION

Drug metabolism is the biochemical modification or degradation of drugs, usually through specialized enzymatic systems. Lipophilic chenical compounds are converted in more polar products. Drug metabolism can result in intoxication or detoxication. Several major enzymes and pathways are involved in drug metabolism, and can be divided into Phase I and Phase II reactions.

Gene	Loc.	SNP	Group and function of protein	Disease
ANKK1	11q23.1	rs1800497	ankyrin repeat and kinase domain containing 1; member of an extensive family of proteins involved in signal transduction pathways; functionally related with dopamine receptor; changes in ANKK1 activity may provide an alternative explanation for previously described associations between the DRD2 Taq1A RFLP and neuropsychiatric disorders	addiction
UGT1A8	2q37	rs1042640	UDP glucuronosyltransferase 1 family, polypeptide A8; enzyme of the glucuronidation pathway that transforms small lipophilic molecules, such as steroids, bilirubin, hormones, and drugs, into water-soluble, excretable metabolites (involved in cellular defense against toxic, carcinogenic, and pharmacologically active electrophilic compounds)	colon cancer
ALDH2	12q24.2	rs2238151	aldehyde dehydrogenase 2 family (mitochondrial); belongs to the aldehyde dehydrogenase family of proteins; second enzyme of the major **oxidative pathway of alcohol metabolism**; two major liver	alcohol intoxication; cyclo-phosphamide metabolism
GSTA4	6p12.1	rs367836 rs405729 rs4986947 rs543613	glutathione S-transferase A4; Cytosolic and membrane-bound forms of glutathione S-transferase are encoded by two distinct supergene families; detoxification of lipid peroxidations; linked to a number of degenerative diseases including Parkinson's disease, Alzheimer's disease, cataract formation, and atherosclerosis	
GSTZ1	14q24.3	rs1046428	glutathione transferase zeta 1 (maleylacetoacetate isomerase); member of the glutathione S-transferase (GSTs) super-family which encodes multifunctional enzymes important in the detoxification of electrophilic molecules, including carcinogens, mutagens, and several therapeutic drugs, by conjugation with glutathione; this enzyme also plays a significant role in the catabolism of phenylalanine and tyrosine (defects may lead to severe metabolic disorders including alkaptonuria, phenylketonuria and tyrosinaemia)	alkaptonuria, phenylketonuria and tyrosinaemia
COMT	22q11.21-q11.23	rs4646312 rs4680 rs6269 rs7290221	catechol-O-methyltransferase; catalyzes the transfer of a methyl group from S-adenosylmethionine to catecholamines, including the neurotransmitters dopamine, epinephrine, and norepinephrine; results in one of the major degradative pathways of the catecholamine transmitters; important in the metabolism of catechol drugs used in the treatment of hypertension, asthma, and Parkinson disease	
ADH1C		rs17526590 rs2009181 rs2241894 rs283411 rs698	alcohol dehydrogenase 1C (class I), gamma polypeptide; member of the alcohol dehydrogenase family; metabolize a wide variety of substrates, including ethanol, retinol, other aliphatic alcohols, hydroxysteroids, and lipid peroxidation products	digestive tract cancer
EPHX1	1q42.1	rs1051740 rs1051741 rs2234922 rs2260863 rs2671272 rs2854455 rs2854456	epoxide hydrolase 1, microsomal (xenobiotic); activation and detoxification of exogenous chemicals such as polycyclic aromatic hydrocarbons	ALL, colorectal cancer

		rs2854461 rs3738043		
AMACR	5p13	rs10941112 rs2278008 rs2287939 rs3195676 rs34677 rs34689 rs6863657 rs840409	alpha-methylacyl-CoA racemase; required for the **synthesis of bile acids** from cholesterol and for the degradation of branched-chain fatty acids (of dietary origin); implicated in the bioactivation of non-steroidal anti-inflammatory drugs of the ibuprofen type; recessively inherited deficiency of AMACR in humans causes adult-onset sensory motor neuropathy and, possibly, a more severe infantile liver dysfunction	recessively inherited deficiency; prostate cancer, breast cancer
GSTM3	1p13.3	rs1537234 rs2234696 rs7483	Cytosolic and membrane-bound forms of glutathione S-transferase; mu class of enzymes; detoxification of electrophilic compounds, including carcinogens, therapeutic drugs, environmental toxins and products of oxidative stress, by conjugation with glutathione; Mutations of this class mu gene have been linked with a slight increase in a number of cancers, likely due to exposure with environmental toxins	ALL

DIFFERENT GROUPS AND FUNCTIONS, PATHWAY UNKNOWN

These are different genes, which could not be grouped in specific cancer pathways, though a releation to tumorigenesis has been found.

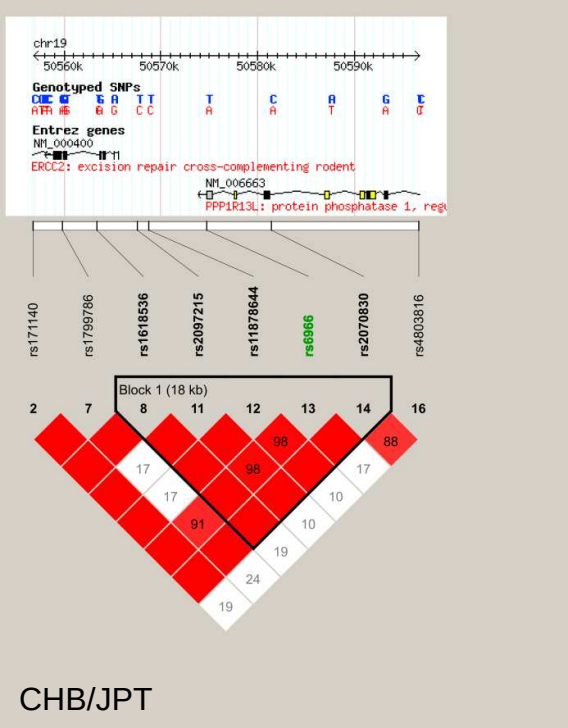
Gene	Loc.	SNP	Group and function of protein	Disease
EDN1	6p24.1	rs5369 rs5370	endothelin 1; belongs to the endothelin/sarafotoxin family; involved in **melanogenesis**	osteosarcoma; leukemia
RERG	12p12.3	RERG-03 RERG-29 rs10160846 rs1045733 rs1055151 rs17834986 rs2193174 rs2216225 rs3748302 rs6488766 rs715398 rs767201	RAS-like, estrogen-regulated, **growth inhibitor**; binds GDP/GTP; possesses intrinsic GTPase activity; higher affinity for GDP than for GTP; in cell lines overexpression leads to a reduction in the rate of proliferation, colony formation and in tumorigenic potential	
SFTPD	10q22.2-q23.1	rs2243639 rs721917	surfactant, pulmonary-associated protein D; contributes to the **lung's defense against inhaled microorganisms**; may participate in the extracellular reorganization or turnover of pulmonary surfactant; binds strongly maltose residues and to a lesser extent other alpha-glucosyl moieties	
LMOD1	1q32	rs2820312	leiomodin 1 (smooth muscle); **cytoskelatal protein binding, cell growth / maintenance**	Graves' disease, gastric cancer
MEST	7q32	rs2072574	mesoderm specific transcript homolog (mouse); member of the [alpha]/[beta] hydrolase fold family; may play a role in development	
MMP1	11q22.3	rs10488 rs2071230 rs5031036	matrix metallopeptidase 1 (interstitial collagenase); matrix metalloproteinase (MMP) family (involved in the **breakdown of extracellular matrix** in normal physiological processes, such as embryonic development, reproduction, and tissue remodeling, as well as in disease processes, such as arthritis	Ewing`s sarcoma, brain tumors, thyroid carcinoma

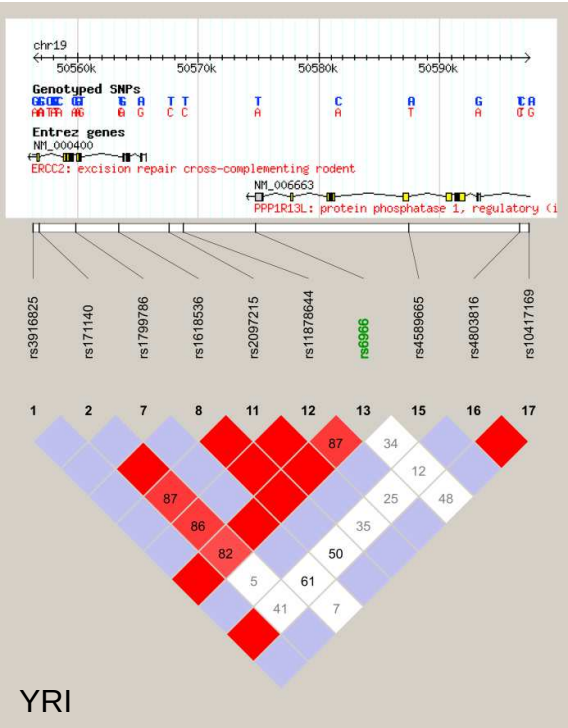
		rs5854	and metastasis); encodes enzyme which breaks down the interstitial collagens	
MYO5A	15q21	rs1058219 rs2242058 rs2290336	myosin VA (heavy chain 12, myoxin); processive actin-based motor that can move in large steps approximating the 36-nm pseudo-repeat of the **actin filament**; involved in melanosome transport; may also be required for some polarization process involved in **dendrite formation**	
MRPL39	21q21.3	BIC-21 rs12482371 rs1893650 rs2829801 rs2829803 rs4143370 rs4817027 rs767649 rs915860 rs928883	mitochondrial ribosomal protein L39; helps in protein synthesis within the mitochondrion	
OCA2	15q11.2-q12	rs1800404 rs1800407 rs1900758	oculocutaneous albinism II (pink-eye dilution homolog, mouse); believed to be an integral membrane protein involved in small molecule transport, specifically tyrosine - a **precursor of melanin**; one of the components of the mammalian pigmentary system	oculo-cutaneous albinism
ENG	9q33-q34.1	rs1330683 rs1330684	endoglin (Osler-Rendu-Weber syndrome 1); component of the transforming growth factor beta receptor complex as it binds TGFB1 and TGFB3 with high affinity	ALL
CSTF1	20q13.3	rs16979877 rs6064387 rs6064389 rs6099129	cleavage stimulation factor, 3' pre-RNA, subunit 1, 50kDa; involved in the polyadenylation and 3'end cleavage of pre-mRNAs; contains transducin-like repeats	
TFF1	21q22.3	rs2839488	trefoil factor 1; stable secretory protein expressed in gastrointestinal mucosa; may protect the mucosa from insults, stabilize the mucus layer, and affect healing of the epithelium; **regulator of cell proliferation**	
PHB	17q21	rs4987082	Prohibitin; negative regulator of cell proliferation and may be a tumor suppressor; inhibits DNA synthesis; unclear if the protein or the mRNA exhibits this effect; may play a role in regulating mitochondrial respiration activity and in aging; **tumor suppressor gene; regulator of cell proliferation**	sporadic breast cancer
TFF3	21q22.3	rs2236705	trefoil factor 3 (intestinal); stable secretory protein expressed in gastrointestinal mucosa; may protect the mucosa from insults, stabilize the mucus layer and affect healing of the epithelium; may have a role in promoting cell migration (motogen); **cell migration**	
KRT23	17q21.2	rs2269858 rs9257	keratin 23 (histone deacetylase inducible); member of the keratin family (intermediate filament proteins responsible for the structural integrity of epithelial cells and are subdivided into cytokeratins and hair keratins); **cell communication**	
PCTP	17q21-q24	rs12948867 rs2114443	phosphatidylcholine transfer protein; catalyzes the transfer of phosphatidylcholine between membranes; **cellular hemeostasis**	
GDF15	19p13.11	rs1059369	growth differentiation factor 15; member of the transforming growth factor-beta superfamily; regulates	

		rs1059519	tissue differentiation and maintenance; synthesized as precursor molecules that are processed at a dibasic cleavage site to release C-terminal domains containing a characteristic motif of 7 conserved cysteines in the mature protein; **tissue differentiation and maintenance**	
TCTA	3p21	rs6784820 rs6997	T-cell leukemia translocation altered gene; **unknown function** , may be a membrane associated protein	T-cell leukemia
ALS2CR12	2q33.1	rs1035142	amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 12; **unknown function**	amyotrophic lateral scler.
DNAJC18	5q31.2	rs4315920	DnaJ (Hsp40) homolog, subfamily C, member 18; heat shock protein binding	
WDR79	17p13.1	FLJ10385-06 FLJ10385-09 rs2287498 rs2287499	WD repeat domain 79; **unknown function**	
NICN1	3p21.31	rs8897	nicolin 1; nuclear protein, **unknown function**	
NUBP2	16p13.3	rs1065663 rs344357 rs344360	nucleotide binding protein 2 (MinD homolog, E. coli); **unclear function**	
FLJ45983	10p14	rs1149901 rs556960	FLJ45983 protein; **unknown function**	
SCUBE2	11p15.3	rs2003906 rs3751052 rs3751058	signal peptide, CUB domain, EGF-like 2; **unknown function**	
LOC112869	16p11.2	rs3194168	LOC112869 pseudogene; **unknown function**	
FAM82A	2p24.3	rs1367696 rs163077 rs163086	family with sequence similarity 82, member A; **unknown function**	
CG018	13q12-q13	rs1207953	hypothetical gene CG018; **unknown function**	
HSPB8	12q24.23	rs11038	small heat-shock protein	
KRAS	12p12.1	rs10505980 rs10842515 rs10842518 rs11047902 rs11047918 rs1137196 rs1137282 rs12226937 rs12228277 rs13096 rs17329025 rs17329424 rs17388148	member of the small GTPase superfamily	lung adenocarcinoma; mucinous adenoma; pancreas adn colorectal carcinoma

	rs2970532
	rs4246229
	rs4368021
	rs4623993
	rs6487461
	rs712
	rs7133640
	rs7973746
	rs9266
MGC20255	rs2241719

Supplemental Figure 1. Linkage Disequilibrium (LD) plots of the regions adjacent to rs6966 in *PPP1R13L* in HapMap Asian (CHB/JPT) and Yoruba African (YRI) populations
The SNP rs6966 is highlighted in green. Shading reflects differences in pairwise LD (white r^2 = low LD; red r^2 = near-perfect LD). Numbers in squires are estimates of pairwise coefficients (D′), expressed in percentages. Unreported values reflect D′ of 1.0 (100%).





Supplemental Figure 2. Linkage Disequilibrium (LD) plots of the regions adjacent to rs414580 in *MSR1* in HapMap Asian (CHB/JPT) and Yoruba African (YRI) populations
The SNP rs414580 is highlighted in green. Shading reflects differences in pairwise LD (white r^2 = low LD; red r^2 = near-perfect LD). Numbers in squires are estimates of pairwise coefficients (D′), expressed in percentages. Unreported values reflect D′ of 1.0 (100%).