Familial Cancer Syndromes with Dermatologic Manifestations

Alina Goldenberg, MD, Antoine Amado, MD & Sharon E. Jacob, MD (Updated July 2015)*

DISORDER	INHERITANCE	GENE DEFECT	CLINICAL MANIFESTATIONS	NEOPLASMS
Bannayan-Riley-Ruvalcaba	AD	PTEN	Pigmented macules on glans penis, macrocephaly, hemagiomas, hamartomas, lipomas	Non-medullary thyroid carcinoma
Bazex-Dupré-Christol Syndrome	XLD	Unknown	Follicular atrophoderma, hypohidrosis, hypotrichosis	BCC
Beckwith-Widemann Syndrome	Imprinting/Sporadic	IGF2, p57 (KIP2)	Hemangiomas, facial nevus flammeus, ear lobe indentation, posterior helical ear pit, macroglossia	Hepatoblastoma, neuroblastoma, Wilms tumor, rhabdomyosarcoma
Birt-Hogg-Dube Syndrome	AD	FLCN (folliculin)/BHD	Fibrofolliculomas, trichodiscomas, acrochordons, lipomas, intestinal polyposis	Renal cell carcinoma (oncocytoma and papillary), medullary carcinoma of the thyroid
Brooke-Fordyce Syndrome	AD	CYLD1	Trichoepitheliomas, cylindromas of	Cylindrocarcinoma, adenocarcinoma of salivary gland, trichoepitheliomas may degenerate into BCC
(Epithelioma Adenoides Cystica)	AD	CYLD	Poncet-Spiegler, surface telangiectasias	
Brooke Spiegler Syndrome			Spiradenomas, trichoepitheliomas, cylindromas	Benign tumors rarely become malignant, increased risk of salivary gland tumors (benign and malignant)
Carney Complex (NAME & LAMB Syndromes)	AD	PRKAR 1A, CNC	NAME: nevi, atrial myxoma, myxoid neurofibromas, ephelides; LAMB: lentigines, atrial myxomas, blue nevi; pigmented nodular adrenocortical disease, psammomatous melanotic schwannomas	Testicular tumors (Sertoli, Leydig tumors), pituitary growth; Hormone secreting-tumors, thyroid tumors
Costello Syndrome (Faciocutaneoskeletal syndrome)	AD	HRAS/PTEN	Coarse facial features, curly/fine hair, loose/soft skin, palmo-plantar creases, perinasal/perianal papillomata	Rhabdomyoscarcoma, neuroblastoma, transitional cell carcinoma of bladder
Cowden Disease (Multiple Hamartoma Syndrome)	AD	PTEN/Killin	Acral keratoses, trichilemmomas, oral papillomas, sclerotic fibromas, intestinal polyposis	Breast carcinoma, follicular thyroid carcinoma, colon hamartomas
Dyskeratosis Congenita	AD	TERC, TERT, TINF2		SCC of the oral mucosa & rectum
(Zinsser-Engman-Cole Syndrome)	XLR (most common)	DKC1 (dyskerin)	Atrophy & reticular pigmentation of skin, nail dystrophy, leukoplakia, aplastic anemia	Cervical cancer
Gardner Syndrome	AD	APC	Epidermal inclusion cysts (EIC), fibromas, GI polyps, pilomatricomas, desmoids, CHRPE	Colorectal carcinoma
Gorlin Syndrome (Nevoid BCC Syndrome)	AD	PTCH 1 (patched-1)	Nevi (achrochordon-like), palmar and plantar pits, jaw cysts, bifid ribs, calcification of falx cerebri	BCC, ovarian fibromas medulloblastomas, fibrosarcomas
HLRCC Syndrome	AD	LRCC, FH	Cutaneous & uterine leiomyomas	Leiomyosarcoma, papillary RCC
Howel Evans Syndrome (Tylosis with esophageal cancer)	AD	TOC (envoplakin), RHBDF2	Palmoplantar keratoderma (PPK)	Esophageal carcinoma
Huriez Syndrome	AD	TYZ, HRZ	Scleroatrophy, keratoderma of palms and soles, nail hypoplasia	Cutaneous SCC
KID Syndrome (Keratitis, Icthyosis, Deafness)	AD	Connexin 26 (GJB2)	Ichthyosis, vascularized keratitis, stippled PPK, deafness	Malignant fibrous histiocytoma
Legius Syndrome	AD	SPRED1	Same as NF1	Juvenile myelomonocytic leukemia
Maffucci Syndrome (Multiple enchondromatosis)	sporadic	PTHrP	Hemangiomas, subcutaneous calcifications, dyschondrodysplasia, enchondromas, Olliers syndrome	Chondrosarcoma, angiosarcoma
MEN I Syndrome (Wermer Syndrome)	AD	MEN I (menin)	Facial angiofibromas, collagenomas, CALMs, migratory necrolytic erythema (secondary to glucagonoma), lipomas	Carcinoid tumors, mengigioma, ependymoma, pancreatic islet cell tumors, parathyroid cancer, pituitary adenoma, adrenocortical adenomas, insulinomas
MEN IIa Syndrome (Sipple Syndrome)	AD	RET	Cutaneous macular or lichen amyloidosis	Medullary thyroid carcinoma, parathyroid hyperplasia, pheochromocytoma
MEN IIb/III	AD	RET	CALMs, marfanoid habitus, mucosal neuromas, GI, ganglioneuromatosis (megacolon)	Medullary thyroid carcinoma, pheochromocytoma
Muir-Torre Syndrome	AD	hMSH2, MLH1	Sebaceous adenomas, keratoacanthomas	Colorectal carcinoma, sebaceous carcinoma, GU cancer (transitional cell)
Nail-patella syndrome	AD	LMX1B	Triangular lunulae, absent or hypoplastic patella; glaucoma/Lester iris	Rare reported colorectal carcinoma
Neuroblastoma	AD	KIF1B	CALMs	NMSC, neuroblastoma
Neurofibromatosis I (Von Recklinghausen Disease)	AD	NF1	CALMs, axillary freckling, sphenoid wing dysplasia, plexiform fibromas, hamartomas (Lisch nodules)	Neurofibrosarcoma, astrocytomas, carcinoid pheochromocytoma, rhabdomyosarcoma, NF + JXG assoc w/ CML

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Neurofibromatosis II	AD	NF2 (merlin)	CALM, peripheral schwannomas, neurofibromas, posterior subcapsular lenticular opacity/cataracts	Meningiomas, spinal schwannomas, multiple gliomas
Peutz-Jeghers Syndrome	AD	STK11/ LKB1	Lentigines, melanoplakia, GI polyps, risk intussusception	Small bowel carcinomas > colon > stomach; ovarian, breast carcinomas
Tuberous Sclerosis	AD	TSC1 (hamartin), TSC2 (tuberin)	Poliosis, adenoma sebaceum, shagreen patch, periungual fibromas (Koenen tumors), "ash-leaf" spots, confetti macules, Shagreen patches, seizures, retinal phakomas, enamel pits	Renal carcinoma, cardiac rhabdomyomas, molluscum fibrosum pendulum, pulmonary lymphangiomyoma (PLAM), angiomyolipomas, renal cysts and RCC
Acrodermatitis Enteropathica	AR	SCL3qA4, ZIP4	Paronychia, photophobia, periorificial eczema	Sarcomas
Ataxia Telangiectasia (Louis-Barr Disease)	AR	ATM	Cerebellar ataxia, telangiectasia, CALM, sinopulmonary infections, progeroid, athymia	Leukemias, Lymphomas, breast carcinoma
Bloom Syndrome	AR	BLM, RECQ3 SCX_	Facial telangiectasia, CALM, photosensitivity, short stature, infertility	Non-Hodgkin lymphoma, carcinoma of the colon> esophagus
Chediak-Higashi Syndrome	AR	LYST, CHS1	Incomplete albinism, oral ulcers, staphylococcal infections, silver hair	Lymphoma-like acceleration phase
Cockayne Syndrome	AR	CSA/ ERCC8, CSB/ ERCC6	hotodermatitis, optic atrophy, mental retardation, "salt & pepper" retinitis pigmentosa, cachectic dwarfism	Skin cancer ONLY with XP-CS complex
Fanconi Anemia	AR	FANCD1	Hyper/hypopigmentation, CALM, hypoplastic anemia, mental retardation,	Myelomonocytic leukemia, SCC of the skin, Breast cancer (FA-D1=BRCA2)
Rothmund-Thompson Syndrome (Poikiloderma Congenitale)	AR	RECQL4	Poikiloderma, keratoses, nail dystrophy, cataracts, photosensitivity, EPS	Osteosarcomas, nonmelanoma skin cancer
Werner Syndrome (Adult Progeria)	AR	WRN, RECQ3	Premature aging, scleroderma-like skin, hyperkeratosis, telangiectasia, atherosclerosis, cataracts, high pitched voice	Thyroid carcinoma, fibrosarcoma, osteosarcomas, meningioma, melanoma
Xeroderma Pigmentosum	AR	XP-A to XP-G and XPV	Dermatoheliosis, lentigines, AKs, keratoacanthomas, photosensitivity, MR	BCC, SCC, melanomas, leukemia, 10-20X risk of internal malignancy: sarcoma, GI/ lung CA
Familial Melanoma (Dysplastic Nevus)	Polygenic	CDKN2A and CDK4	Atypical moles, GI tumors	Pancreatic carcinoma, melanoma
Schimmelpenning Syndrome (Epidermal Syndrome)	Sporadic AD	Unknown	CALM, sebaceous epithelioma, cutaneous hemangioma, coloboma, CNS abnormalities, conjunctival lipodermoids	Wilms tumor, nephroblastoma, rhabdomyosarcoma, astrocytoma
Wiskott-Aldrich Syndrome	XLR	WASP CD43 sialophorin	Atopy (eczema), thrombocytopenia (purpura), and recurrent pyogenic infections (impetigo, cellulitis,abscesses).	Lymphoma, leukemia
X-linked dyskeratosis congenital	XLR	DKC1	Nail dystrophy, mucosal leukoplakia, pigmented changes	Head /neck/cutaneous SCC, gastrointestional and hematologic malignancies
X-linked agammaglobulinemia	XLR	BTK	Cellulitis/impetigo, atopic dermatitis, dermatomyositis-like syndrome	Colorectal adenocarcinoma

Abbreviations:

APC: adenomatous polyposis coli
CHRPE: congenital hypertrophied retinal pigmented epithelium
FH: fumarate hydratase
GU: genitourinary
LYST: lysosomal trafficking regulator
MEN: multiple endocrine neoplasia
SCC: squamous cell carcinoma
XP-CS: Xeroderma pigmentosum-cockayne syndrome
BCC: basal cell carcinoma
CX26: conexin 26
EPS: elastosis perforans serpiginosa
FLCL: folliculin
GJB2: gap junction protein B2
PTC: patched gene
SCX_: sister chromatid exchange
ZIP4: zinc transporter
CALM: café au lait macules
ERCC: excision-repair cross-complementing
DKC1: dyskerin
GI: gastrointestinal
HLRCC: hereditary leiomyomatosis & renal cell cancer
PTHR 1: parathyroid hormone-related protein
TERC: telomerase RNA component

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Note: In the course of creating this chart, the authors have used reliable, up-to-date sources. Readers are encouraged to confirm the information periodically, however, as some variables evolve over time.