

RESIDENT ROUNDS: PART II

Hereditary Syndromes Associated With Increased Risk of Keratinocyte Carcinomas

Erin X. Wei MD, Jose E. Ollague MD, and Jonathan Weiss MD
Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL

INTRODUCTION

These tables review the inheritance patterns, involved genes, and clinical findings of the many hereditary syndromes associated with an increased risk of keratinocyte carcinomas. While these genodermatoses present with complex clinical pictures, often affecting multiple organ systems, the identification of an increased risk of skin cancers is crucial. Patient and family education regarding primary prevention, as well as frequent full body skin examinations, can significantly decrease morbidity and improve the prognosis of these patients.

TABLE 1.

Syndromes Associated With Basal Cell Carcinomas			
Syndrome	**Inheritance**	**Gene**	**Clinical Findings**
Nevoid basal cell carcinoma syndrome (Gorlin syndrome, basal cell nevus syndrome)	AD	PTCH1 PTCH2 SUFU	BCCs (early onset; before age 20 years) Odontogenic keratocysts, polyostotic bone cysts Palmar or plantar pits Ectopic calcifications of falx cerebri Frontal bossing Congenital skeletal abnormalities: bifid, fused, splayed, or missing ribs; fused, or wedged vertebrae Cardiac or ovarian fibromas Medulloblastomas Other congenital malformations (cleft lip/palate, polydactyly, cataracts, coloboma, microphthalmia, pectus deformity) Lymphomesenteric cysts
Rombo syndrome	AD	Unknown	BCCs (age 30-40 years) Milia Atrophoderma vermiculatum Acrocyanosis Trichoepitheliomas Hypotrichosis
Bazex-Dupré-Christol syndrome	XD	Unknown (mapped to Xq24-q27)	Multiple BCCs (2nd to 3rd decade) Hypotrichosis Follicular atrophoderma (dorsal hands/feet, face, extensor surfaces) Milia Prominent columella, “pinched nose” Hypohidrosis
Brooke-Spiegler syndrome	AD	CYLD	Cylindromas (scalp, forehead, trunk, pubic area) Trichoepitheliomas (peri-nasal) Spiradenomas BCCs
Schöpf-Schulz-Passarge syndrome	AR	WNT10A	Ectodermal dysplasia (hypotrichosis, hypodontia, anonychia, and trachyonychia) Hidrocystomas (eyelids) Palmoplantar hyperkeratosis Hyperhidrosis BCCs

Syndrome	Inheritance	Gene	Clinical Findings
Multiple hereditary infundibulocystic BCC	AD	Unknown	Multiple BCCs (infundibulocystic type)
Cartilage-hair hypoplasia syndrome	AR	RMRP	Short stature Metaphyseal dysostosis Fine and hypopigmented hair Defective cell-mediated immunity (sensitive to varicella) Increased risk for non-Hodgkin lymphoma BCCs

AD, autosomal dominant; AR, autosomal recessive; BCC, basal cell carcinoma; XD, X-linked dominant

TABLE 2.

Syndromes Associated With Squamous Cell Carcinomas

Syndromes of Multiple Keratoacanthomas

Syndrome	Inheritance	Gene	Clinical Findings
Multiple keratoacanthomas of Ferguson-Smith (multiple self-healing squamous epitheliomas)	AD	TGFBR1	Multiple KAs (3rd decade) Predilection to sun-exposed areas Spontaneous resolution with scarring KAs spare mucosa
Generalized eruptive keratoacanthomas of Grzybowski	Sporadic	Unknown	Numerous (100s-1000s) 2mm-3mm "miliary" KAs Spontaneous resolution with scarring KAs involve mucosa (may cause ectropion, eclabium, masked facies) Chronic course
Multiple familial keratoacanthomas of Witten and Zak	AD	Unknown	Multiple KAs (childhood) KAs with features of both Ferguson-Smith and Grzybowski variants (though tend to spare mucosa)
Muir-Torre syndrome	AD	MLH1 MSH2 MSH6	Multiple KAs Sebaceous neoplasms Increased risk of colon, breast, genitourinary tract, hematologic malignancies BCCs with sebaceous differentiation

Syndromes of Pigmentary Disorder With Increased Risk of SCCs

Syndrome	Inheritance	Gene	Clinical Findings
Oculocutaneous albinism	AR	*Type 1a/1b:*TYR *Type 2:* OCA2/P-gene *Type 3:*TYRP1 *Type 4:* SLC45A2	*Type 1a:* no melanin in skin/hair/eyes, nystagmus, strabismus, poor visual acuity *Type 1b:* little or no pigment at birth, develop pigment over time; milder ocular involvement *Type 2:* variable pigmentary dilution; light brown hair/skin *Type 3:* cream to light tan skin, beige to light brown hair and blue-green to brown irides, nystagmus, reduced retinal pigment *Type 4:* light brown hair/skin, nystagmus, poor visual acuity
Hermansky-Pudlak syndrome	AR	8 subtypes; most common are *Type 1:* HPS1 *Type 2:* AP3B1	Oculocutaneous albinism Hemorrhagic diathesis Pulmonary fibrosis Granulomatous colitis Renal failure Cardiomyopathy Neutropenia and immunodeficiency (Type 2) Predisposition to SCCs
Chédiak-Higashi syndrome	AR	LYST/CHS1	Oculocutaneous albinism Immunologic deficiency with recurrent infections Silvery metallic hair Easy bruising Progressive neurologic deterioration Predisposition for SCCs "Accelerated phase": pancytopenia, lymphohistiocytic infiltration of reticuloendothilial system

Griscelli syndrome	AR	MYO5 RAB27A MLPH	Pigmentary dilution (variable) Silvery metallic hair Immunodeficiency with recurrent pyogenic infections Pancytopenia Neurologic abnormalities Predisposition for SCCs
Syndromes of Chronic Wounds With Increased Risk of SCCs			
Syndrome	**Inheritance**	**Gene**	**Clinical Findings**
Dystrophic epidermolysis bullosa	AD, AR	COL7A1	Severe widespread bullae with atrophic scarring Mitten deformity Milia Nail dystrophy Esophageal/oral strictures Multiple SCCs
Junctional Epidermolysis bullosa	AR	Laminin 5 Integrin α6β4 COL17A1	Severe widespread bullae Poor healing with exuberant granulation tissue Dental enamel defects Anonychia Scarring alopecia Increased risk of SCCs Pyloric atresia (with integrin α6β4 mutation)
Syndrome of Predisposition to Viral Transformation With Increased Risk of SCCs			
Syndrome	**Inheritance**	**Gene**	**Clinical Findings**
Epidermodysplasia verruciformis	Sporadic, AR	EVER1 EVER2	Increased susceptibility to HPV infection Red-brown macules on face, trunk, papules, hand resembling flat warts Malignant transformation in 50% of individuals (HPV 5, HPV 8)
Syndromes of Defective DNA Repair With Increased Risk of SCCs			
Syndrome	**Inheritance**	**Gene**	**Clinical Findings**
Xeroderma pigmentosum	AR	Nucleotide excision repair (multiple genes identified)	Photosensitivity Ocular findings (photophobia, keratitis, corneal opacification, vascularization) Progressive deafness Increased risk of SCCs
Fanconi anemia	AR	DNA repair (multiple genes identified)	Diffuse hyperpigmentation Multiple café-au-lait macules Hypoplastic radii and thumbs Pancytopenia Increased risk of SCCs, solid organ cancers, leukemia
Dyskeratosis congenita	XR, AD, AR	Telomere maintenance (multiple genes identified)	Poikiloderma Nail dystrophy (ie, pterygium, atrophy) Premalignant leukoplakia Frictional bullae Palmoplantar hyperhidrosis Bone marrow failure Increased risk of mucosal SCCs, Hodgkin's lymphoma, acute myeloid leukemia
Rothmund-Thomson syndrome	AR	RECQL4	Poikiloderma Normal intelligence Alopecia Cataracts Hypoplastic radii, thumbs, ulnae Increased risk of SCCs and osteosarcoma
Bloom syndrome	AR	BLM/RECQL3	Poikiloderma High-pitched voice Short stature Normal intelligence Immune deficiency; decreased IgM and IgA; respiratory and gastrointestinal infections Decreased fertility Increased risk of SCCs, leukemia, lymphoma, gastrointestinal malignancies

Syndrome	Inheritance	Gene	Clinical Findings
Werner syndrome	AR	WRN/RECQL2	Short stature/thin limbs Premature graying of hair Central obesity Beaked nose Micrognathia High-pitched voice Mottled hyperpigmentation Sclerodermoid changes Cataracts Diabetes Premature atherosclerosis Chronic leg ulcers Increased risk of SCCs, sarcomas, osteosarcomas

AD, autosomal dominant; AR, autosomal recessive; HPV, human papilloma virus; KA, keratoacanthoma; SCC, squamous cell carcinoma; XR, X-linked recessive.

DISCLOSURES

The authors have no relevant conflicts of interest to disclose.

AUTHOR CORRESPONDENCE

Jonathan Weiss MD
E-mail:..... jweiss@med.miami.edu