Series Editor: William W. Huang, MD, MPH

Genetic Pathways, Part 2

Alyssa Daniel, MD

Dr. Daniel is from is from the Department of Dermatology, Wake Forest University, Winston-Salem, North Carolina.
The author reports no conflict of interest.

Gene	Gene function	Loss of function	Disease Association	Inheritance	Clinical findings
Adenomatous polyposis coli *(APC)*	Encodes for the APC protein, which associates with β-catenin; β-catenin regulates downstream transcription factors causing growth and differentiation	Mutated *APC* cannot associate with β-catenin, and unregulated β-catenin causes excessive proliferation of cells	Gardner syndrome	AD	Colonic polyposis with 100% malignant transformation by age 50 y, epidermoid cysts with areas of localized pilomatricomas, congenital hypertrophy of the retinal pigment epithelium
Folliculin *(FLCN)*	Encodes for the FLCN protein; restrains cell growth, possibly through the mTOR signaling pathway	Increased proliferation of cells and cell survival	Birt-Hogg-Dubé syndrome	AD	Fibrofolliculomas, trichodiscomas, collagenomas, oral fibromas, pulmonary cysts with spontaneous pneumothorax, renal cell carcinoma, medullary thyroid carcinoma, colon cancer
MutS homolog 2 (*MSH2*) MutL homolog 1 (*MLH1*)	Mismatch repair genes	Leads to incorrect matching of bases during DNA replication	Muir-Torre syndrome	AD	Hereditary nonpolyposis colorectal cancer, laryngeal carcinoma, sebaceous neoplasms/carcinomas, keratoacanthomas
Neurofibromin 1 *(NF1)*	Encodes for neurofibromin, a GAP-related protein; negatively regulates Ras family oncogenes	Upregulated Ras family oncogenes lead to an enhanced phenotype that has been associated with many tumors and cancers	Neurofibromatosis type I (von Recklinghausen disease)	AD	>6 café au lait macules/patches, >2 neurofibromas, axillary freckling, Lisch nodules, bony defects (eg, sphenoid wing dysplasia, thinning of long cortical bones), optic gliomas, MPNSTs, pheochromocytomas, CNS tumors, JXGs, JMML
Neurofibromin 2 (merlin) *(NF2)*	Encodes for merlin, an ERM-related protein that mediates contact inhibition of growth	Lack of inhibition leads to excessive signaling from the extracellular matrix	Neurofibromatosis type II (bilateral vestibular schwannomas [Wishart])	AD	Bilateral acoustic neuromas, hearing loss, meningiomas, schwannomas, juvenile subcapsular cataracts; fewer café au lait macules/patches than neurofibromatosis type I, no Lisch nodules

continued on next page

(continued)

Gene	Gene function	Loss of function	Disease Association	Inheritance	Clinical findings
Patched 1 *(PTCH1)*	Encodes for PTCH1, a transmembrane protein receptor for SHh; in its unbound state, *PTCH1* acts to inhibit the activity of smoothened, a 7-transmembrane protein receptor that activates GLI, a transcription factor	If *PTCH1* is mutated, it can no longer inhibit smoothened, which then is constitutively active allowing GLI to act at the nucleus	Basal cell nevus syndrome (Gorlin syndrome)	AD	Numerous early-onset BCCs, palmar pits, odontogenic keratocysts of the mandible, medulloblastomas, meningiomas, ovarian and cardiac fibromas, calcification of the falx cerebri, agenesis of the corpus callosum
Phosphatase and tensin homolog *(PTEN)*	Encodes for the PTEN enzyme, which regulates levels of phosphatidylinositol (3,4,5)-trisphosphate and negatively regulates the Akt/PKB pathway	A mutation in Akt/PKB causes *PTEN* to act unregulated; the Akt/PKB pathway is important in cell survival and apoptosis	Bannayan-Riley-Ruvalcaba syndrome, Cowden syndrome	AD	Hemangiomas and lipomas are common; macrocephaly, genital lentigines, mental retardation, trichilemmomas, oral papillomas, sclerotic fibromas, acral papules, fibroadenomas and adenocarcinomas of the breast and thyroid, GI polyps
Serine/threonine kinase 11 (*STK11* [also known as *LKB1*])	*STK11/LKB1* is a primary upstream mediator of AMPK, which serves as an inhibitor of cell proliferation	Inactive AMPK leads to proliferation of cells with no inhibition	Peutz-Jeghers syndrome	AD	Pigmented macules on the mucosae and fingers; GI polyps (most common in the small bowel); GI adenocarcinomas; ovarian sex cord-stromal tumors; tumors of the breast, pancreas, and endometrium
Tuberous sclerosis 1 *(TSC1)*	Encodes for hamartin, a GAP-related protein; functions to negatively regulate Rab/Rheb proto-oncogenes.	Upregulated Rab/Rheb leads to stimulation of cells to go through G_1/S stages unregulated and prevents them from entering G_0 resting stage; also important in mTOR signaling pathway, which integrates upstream mediators and regulates growth and development, cell proliferation, and motility	Tuberous sclerosis (Bourneville disease)	AD	Hypopigmented macules (also called ash-leaf macules), facial angiofibromas, collagenomas, periungual/gingival fibromas, dental enamel pits; hypopigmented macules are the earliest sign and can be seen in infancy

continued on next page

(continued)

Gene	Gene function	Loss of function	Disease Association	Inheritance	Clinical findings
Tuberous sclerosis 2 *(TSC2)*	Encodes for tuberin, which cofunctions with hamartin	May disrupt cytoskeletal-mediated adhesion; mutations in *TSC2* are more common than in *TSC1*	Tuberous sclerosis (Bourneville disease)	AD	Hypopigmented macules, facial angiofibromas, collagenomas, periungual/gingival fibromas, dental enamel pits; hypopigmented macules are the earliest sign and can be seen in infancy

Abbreviations: AD, autosomal dominant; mTOR, mammalian target or rapamycin; GAP, GTPase-activating protein; Ras, retrovirus-associated sequence; MPNSTs, malignant peripheral nerve sheath tumors; CNS, central nervous system; JXGs, juvenile xanthogranulomas; JMML, juvenile myelomonocytic leukemia; ERM, ezrin/radixin/moesin; SHh, sonic hedgehog; GLI, glioma-associated oncogene; BCC, basal cell carcinoma; Akt, v-akt murine thymoma viral oncogene homolog; PKB, protein kinase B; GI, gastrointestinal; AMPK, adenosine monophosphate–activated kinase; Rab, Ras-related protein in brain; Rheb, Ras homolog enriched in brain; G_1, gap 1; S, synthesis; G_0, gap zero.

Practice Questions

1. **A 6-month-old male infant presented to your dermatology clinic with an ash-leaf macule on the right back. What is the most common gene defect seen in this condition?**
   a. tuberin
   b. merlin
   c. neurofibromin
   d. smoothened
   e. hamartin

2. **Bilateral acoustic neuromas are associated with what gene mutation?**
   a. *NF1* (neurofibromin 1)
   b. *NF2* (neurofibromin 2)
   c. *PTCH1* (patched 1)
   d. *TSC1* (tuberous sclerosis 1)
   e. *TSC2* (tuberous sclerosis 2)

3. **Which of the following would least likely be seen in neurofibromatosis types 1 or 2?**
   a. angiofibromas
   b. café au lait macules
   c. gliomas
   d. Lisch nodules
   e. neurofibromas

4. **What protein is the patched 1 gene a receptor for?**
   a. fused
   b. glioma-associated oncogene
   c. smoothened
   d. sonic hedgehog
   e. suppressor of fused

5. **A 20-year-old woman presented to your dermatology clinic with a history of numerous basal cell carcinomas. On physical examination, it was noted that she had numerous palmar pits. What finding could be noted on a radiograph of the head?**
   a. congenital hypertrophy of the retinal pigment epithelium
   b. collagenomas
   c. cysts of the mandible
   d. lisch nodules
   e. angiomas

Fact sheets and practice questions will be posted monthly. Answers are posted separately on www.cutis.com.