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Genetic Pathways, Part 1

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The author reports no conflict of interest.

Gene	Gene Function	Loss of Function	Disease Association	Inheritance	Clinical Findings
ATP-binding cassette, sub-family A, member 12 *(ABCA12)*	Encodes for a membrane protein in epidermal lamellar granules/bodies that is involved in energy-dependent lipid transport	Improper formation of lamellar granules/bodies and incomplete/lack of secretion of glucosylceramide (essential epidermal lipid) leading to abnormal formation of the lipid bilayer, resulting in hyperkeratosis and abnormal barrier function	Harlequin ichthyosis	AR	Thick collodion membrane present at birth, deep fissures, ectropion, eclabion, PDA, thyroid aplasia; high neonatal mortality; treatment with retinoids; ichthyosiform erythroderma seen later in childhood
ATPase, Ca^{2+} transporting, cardiac muscle, slow twitch 2 *(ATP2A2)*	Encodes SERCA2, which causes Ca^{2+} influx into the endoplasmic reticulum	Abnormal intracellular signaling results in acantholysis in the stratum spinosum	Darier disease (keratosis follicularis)	AD	Crusted keratotic papules in a seborrheic distribution, keratotic papules on the hands, white oral papules, red-white nails with V-shaped nicking
ATPase, Ca^{2+} transporting, type 2C, member 1 *(ATP2C1)*	Encodes hSPCA1, which is important for influx of Ca^{2+} into the Golgi	Inadequate Ca^{2+} stores in the endoplasmic reticulum cause acantholysis secondary to incomplete processing of Ca^{2+}-dependent desmosomal proteins and apoptosis of epidermal cells	Hailey-Hailey disease (benign familial pemphigus)	AD	Flaccid blisters and erosions on the neck and intertriginous areas
Ectodysplasin A *(EDA)*; ectodysplasin A receptor *(EDAR)*; EDAR-associated death domain *(EDARADD)*	*EDA* encodes for the ligand ectodysplasin A and binds to *EDAR*; *EDARADD* is an intracellular adaptor protein that assists in transducing the signal from the activated receptor to the nucleus needed to activate transcription factor NF-κβ	Loss of function leads to abnormal signaling and decreased transcription of NF-κβ	Hypohidrotic ectodermal dysplasia	XLR (*EDA*), AD/AR (*EDAR*), AR (*EDARADD*)	Sparse hair, hypodontia, peg teeth, hyperpyrexia, decreased sweating

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GNAS complex locus *(GNAS1)*	Encodes the α subunit of G proteins; associates with GPCRs and stimulates adenylate cyclase	Gain of function with mutation, overexpression in tissues where adenylate cyclase acts as a second messenger (organs with hormonal control and bone)[a]	McCune-Albright syndrome	Sporadic	Large café au lait patches and polyostotic fibrous dysplasia, precocious puberty
Inhibitor of κ light polypeptide gene enhancer in B-cells, kinase γ *(IKBKG)*/NF-κβ essential modulator *(NEMO)*	Subunit of a kinase that activates NF-κβ, a transcription factor important for altering expression of a number of genes	Failure to activate NF-κβ leads to TNF-α–induced apoptosis	Incontinentia pigmenti	XLD mosaicism	Lethal in males; 4 disease stages: (1) inflammatory/vesicular, (2) verrucous, (3) hyperpigmented, (4) hypopigmented/atrophic; skin lesions follow Blaschko lines; alopecia, nail dystrophy, peg teeth, seizures, eye abnormalities
			Hypohidrotic ectodermal dysplasia with immunodeficiency	XLR	Affects male neonates born to women with incontinentia pigmenti; ectodermal dysplasia
Porcupine homolog *(Drosophila)* (*PORCN*)	Encodes a putative O-acyltransferase involved in palmitoylation and Wnt secretion in the endoplasmic reticulum; Wnt is a morphogen important in fetal development; Wnt is involved in regulating cell-to-cell interactions during embryogenesis and in some cancers; Wnt binds to frizzled receptor (GPCR), which activates Dvl; Dvl blocks the β-catenin destruction complex, leading to accumulation of β-catenin; β-catenin acts as a transcription factor in the nucleus for target genes	Dysfunctional and decreased Wnt signaling leads to increased destruction of β-catenin, gene is expressed in the ectoderm, mesoderm, and endoderm	Focal dermal hypoplasia (Goltz syndrome)	XLD mosaicism	Telangiectasia, hypopigmentation, hyperpigmentation, dermal atrophy, raspberrylike papillomas in the perioral/anal regions, lobster claw deformities, hypodontia, ocular defects

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Serine peptidase inhibitor, Kazal type 5 *(SPINK5)*	Encodes for LEKTI, a serine protease inhibitor	Uncontrolled proteolytic activity leads to degradation of lamellar body lipid processing enzymes	Netherton syndrome	AR	Ichthyosis linearis circumflexa, trichorrhexis invaginata, severe atopic dermatitis, elevated IgE
Transglutaminase 1 *(TGM1)*	Catalyzes the formation of γ-glutamyl lysine isopeptide bonds between proteins, calcium dependent	Incomplete cross-linking of structural proteins (involucrin, SPRP, loricrin, keratin, desmosomal proteins), dysfunctional insoluble protein envelope	Lamellar ichthyosis	AR	Collodion membrane present at birth, erythroderma replaced by brown platelike scale in a mosaic pattern (involves flexures) with minimal scale, ectropion and eclabion
			Nonbullous congenital ichthyosiform erythroderma	AR	Collodion membrane present at birth, fine scaling with erythema prominent on flexures, growth retardation

Abbreviations: AR, autosomal recessive; PDA, patent ductus arteriosus; SERCA2, sarcoendoplasmic reticulum $Ca2^{+}$-ATPase; AD, autosomal dominant; hSPCA1, human secretory pathway $Ca2^{+}$-ATPase 1; NF-κβ, nuclear factor κβ; XLR, X-linked recessive; GPCRs, G protein–coupled receptors; TNF-α, tumor necrosis factor α; XLD, X-linked dominant; LEKTI, lympho-epithelial Kazal-type-related inhibitor; SPRP, small proline-rich peptide.

[a]Mutation is related to gain of function.

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Practice Questions

1. **Which keratinization disorder is characterized by drastically lower levels of lamellar bodies?**
   a. Harlequin ichthyosis
   b. ichthyosis vulgaris
   c. lamellar ichthyosis
   d. nonbullous congenital ichthyosiform erythroderma
   e. X-linked ichthyosis

2. **Mutation of this enzyme leads to uncontrolled proteolytic activity causing degradation of lamellar body lipid processing enzymes:**
   a. FALDH (fatty aldehyde dehydrogenase)
   b. LEKTI (lympho-epithelial Kazal-type-related inhibitor)
   c. PEX7 (perioxsomal biogenesis factor 7)
   d. PHYH (phytanoyl-CoA hydroxylase)
   e. NSDHL (NAD[P] dependent steroid dehydrogenase-like)

3. **A 30-year-old man presented for evaluation of abnormal nails. Physical examination revealed a red streak with distal V-shaped nicking. Numerous keratotic papules on the hands and chest and oral papules also were noted. The gene responsible for these findings encodes a Ca^{2+}-ATPase responsible for a Ca^{2+} influx into what cellular structure?**
   a. cytoplasm
   b. endoplasmic reticulum
   c. Golgi
   d. nucleus
   e. ribosome

4. **A female neonate aged 2 weeks presented with linear and whorled vesicles on the thighs and trunk. The delivery was uncomplicated. The patient was afebrile, but her mother said she has been "doing well" at home. On pathology, what do you expect to see?**
   a. apoptosis of epidermal cells
   b. cell-poor blister
   c. molding and margination of chromatin as well as multinucleated giant cells
   d. numerous pseudohyphae
   e. spongiosis of epidermal cells

5. **A young child presents with linear atrophic plaques with fat herniation and raspberrylike oral papillomas. What signal transduction pathway is altered in this syndrome?**
   a. *ABCA12* (ATP-binding cassette, sub-family A, member 12)
   b. adenylate cyclase
   c. β-catenin
   d. LEKTI (lympho-epithelial Kazal-type-related inhibitor)
   e. nuclear factor κ light chain enhancer of activated B cells

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

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