Syndromes Associated with Pigment Alterations

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Birthmarks and other skin discoloration

Amount/location of melanin pigment
Origin and destinations of melanocytes from the neural crest

- Explains CNS, ocular, and auditory findings in melanocytic disorders
- Explains pigmentary findings in “neurocristopathies”
Neurofibromatosis 1: pigmentary findings

- ≥6 CALMs typically develop by age 1-2 y
- Intertriginous “freckling” in ~80%, usually by age 6-8 y
- Lisch nodules usually by late childhood
- JXGs by age 2-3 in 15-30%
  - Consider NF1 if also CALMs
Neurofibromatosis 1: neurofibromas

- Plexiform in >25%, superficial lesions usually apparent by age 3-5 y
- Cutaneous neurofibromas around puberty
Cellular proliferation

SHP2

SOS1

RAS GDP

RAS GTP

NF1 (RAS GTPase-activating protein)

RAF

Cellular proliferation
Mosaicism in NF1: pay attention to CALM distribution
Multiple CALM in children presenting to NF1 referral clinic (n=110)

**NF1**
- Mean age = 1 y
- Distinct, regular borders
- Uniform pigmentation

**Not NF1**
- Mean age = 6 y
- Irregular, smudgy borders
- Less homogeneous pigmentation

Nunley et al Arch Derm 2009
‘Typical’ CALM

• 1-5: None dx with NF1
• ≥6: ~75% dx with NF1

‘Atypical’ CALM

• 1-5: None dx with NF1
• ≥6: ~10% dx with NF1
Many ‘irregular’ CALM, *not* NF1
Nevus anemicus: clue to diagnosis of NF1

- >50% of pediatric NF1 patients in recent prospective series (n_total=219)
- Favor the mid chest
  - More evident after stroking
- Assoc. with macrocephaly
- Not described in other syndromes with CALM

Hernandez-Martin et al Ped Derm 2015
Marque et al JAAD 2013
Cellular proliferation

SHP2

SOS1

RAS GDP

RAS GTP

SPRED1

NF1-like

SPRED1

NEurofibromin

Stowe et al. Genes Devel 2012

RAS

GDP

GTP

RAF

MEK

ERK

Cellular proliferation
Legius (NF1-like) syndrome

- Autosomal dominant disorder due to *SPRED1* defects
  - Recognized in 2007, >300 patients reported
  - ~2% of patients who meet NF1 criteria
  - ~70% of familial CALM ± freckling *without* neurofibromas or *NF1* mutation

References:
- Brems et al Hum Mut 2012
- Denayer et al Hum Mut 2011
- Muram et al J Child Neurol 2010
- Messiaen et al JAMA 2009
- Spurlock et al & Pasmack et al J Med Genet 2009
- Brems et al Nat Genet 2007
NF1-like (Legius) syndrome

- Clinical findings
  - ✔ >5 café-au-lait spots
  - ✔ Flexural freckling (~50%)
  - ✔ ± Macrocephaly, developmental delay, ADHD
  - ❌ No neurofibromas, optic gliomas, Lisch nodules
  - ± Lipomas, hypopigmented macules, hemangiomas/vascular malformations

Often meet classic NF1 criteria

Denayer et al Hum Mut 2011
Messiaen et al JAMA 2009
Spurlock et al & Pasmack et al J Med Genet 2009
Brems et al Nat Genet 2007
Yet another NF1 mimic: constitutional mismatch repair deficiency syndrome

- **Homozygous/biallelic** mutations in mismatch repair genes (eg *MLH1*, *MSH2*, *MSH6*, *PMS2*)
  - ? also *somatic* NF1 mutations
  - HNPCC ± Muir-Torre in *heterozygotes*

- **Skin features**
  - NF1-like: *multiple CALMs > axillary freckling, neurofibromas*
  - ± hypopigmented macules

- **Extracutaneous features**
  - CNS gliomas, leukemia, colorectal cancer
Don’t want to wait to find out if it’s NF1…

• ~97% of affected individuals meet clinical criteria for NF1 by age 8 y
  -but-
• Analysis of the NF1 and/or SPRED1 genes
  – Comprehensive testing now available in cost-effective panels
  – ≥95% sensitive
Cellular proliferation

NRAS

BRAF

V600E

MEK

NRAS

Small CMN

Acquired nevi

Melanoma subset

CMN = congenital melanocytic nevi

Neurofibromin

Large/giant CMN

Neurocutaneous melanocytosis

Melanoma subset

Small CMN

Acquired nevi

Melanoma (superficial spreading)

PTEN

PI3K

PIP2

PIP3

AKT

Cell proliferation/
survival

Cellular proliferation

CMN = congenital melanocytic nevi
Large ‘classic’ CMN, their ‘satellites’, and neurocutaneous melanocytosis (NCM): activating NRAS mutation Q61K/R

Kinsler et al J Invest Derm 2013
CMN: patchy distribution without midline demarcation
CMN-type SLN (nevus spilus-type CMN): activating NRAS mutation Q61H in nevi and hyperpigmented background

SLN = speckled

Kinsler et al J Invest Derm 2014
Multiple small/medium-sized CMN

Scattered

Clustered with background hyperpigmentation
High risk for NCM

Large/giant CMN + many (>10-20) ‘satellites’

Less risk for NCM

Large CMN without ‘satellites’

Large CMN-type SLN without ‘satellites’

Screening MRI of brain + spine
- Ideally at age <6 months
- Traditionally with + without contrast…
- ~5-20% +
- Neuro-developmental follow-up

Many (≥3; but usually >10-20) small/medium CMN without ‘mother ship’
PTPN11
SOS1
RAS
GDP
RAS
GTP
RAF
MEK
GDF
RAS

Costello
HRAS

Noonan
KRAS, NRAS

Noonan with multiple lentigines (LEOPARD)

Cardiofaciocutaneous
BRAF>KRAS

Cellular proliferation
CFC & Noonan  
Noonan with multiple lentigines (LEOPARD)  

- Lentigines, CALM, nevi
- Acanthosis nigricans
- Woolly/curlly/loose anagen hair
- Keratosis pilaris (atrophyicans)

- Risk of rhabdomyosarcoma, bladder cancer

Mosaic mutations in nonepidermolytic epidermal nevi

- FGFR3
- FGFR2
- PIK3CA
- HRAS
- NRAS
- KRAS
- multiple genes
- ??

~35%
Mosaic activating mutations

**NEVUS SEBACEOUS**

- **HRAS** in ~95%
  - Almost all G13R
  - Also in tumors
- **KRAS** in 5%
- Each in Schimmelpenning syndrome

Cell proliferation/survival

Groesser et al Nat Genet 2012
Speckled lentiginous nevus (nevus spilus): activating **HRAS** mutation

Sarin et al JAMA Derm 2013
Groesser et al J Invest Derm 2013
Sarin et al J Invest Derm 2014
Speckled lentiginous nevus (nevus spilus) + nevus sebaceus: phacomatosis pigmentokeratotica

HRAS mutation in both types of lesions
A simple mechanism – not really “twin spots”

• Mosaisicism for a single heterozygous mutation in a pluripotent progenitor cell
  – ‘Mother’ cell to more than one tissue type
different birthmarks/other manifestations

• *Not* complex postzygotic recombination
It depends on the cell type/tissue affected….

Melanocytes $\rightarrow$ melanocytic nevi

Keratinocytes $\rightarrow$ epidermal nevi

Adnexae $\rightarrow$ sebaceous nevi
woolly hair nevi

Kinsler et al J Invest Derm 2013
Lim et al Hum Molec Genet 2014
Levinsohn J Invest Derm 2014
Bone ➔ elevated serum FGF23 levels, hypophosphatemia and osteomalacia

CNS ➔ neurodevelopmental problems

Muscle ➔ risk of rhabdomyosarcoma

It depends on the cell type/tissue affected....

Kinsler et al J Invest Derm 2013
Lim et al Hum Molec Genet 2014
Levinsohn J Invest Derm 2014
Nevus ‘depigmentosus’

• Evident in 1:150 neonates & ~1:30 children/adults, vs 1:20,000 prevalence of tuberous sclerosis

• Typically no associated extracutaneous abnormalities

• ND ~5-fold more common in epileptic children

Karabiber et al J Child Neurol 2002
Di Lernia Ped Derm 1999
Lee et al JAAD 1999
Tuberous sclerosis: pigmentary findings

Hypopigmented macules: Polygonal > ‘ash leaf’ >> confetti

‘Confetti’ macules of hypopigmentation
Tuberous sclerosis complex revised dx criteria

TS1 — hamartin  
TS2 — tuberin

Mucocutaneous

Major features
- Hypomelanotic macules ≥5 mm size (≥3)
- Angiofibromas (≥3) or fibrous cephalic plaque
- Ungual fibromas
- Shagreen patch

Minor features
- Confetti macules
- Intraoral fibromas (≥2)

Extracutaneous

Major features
- Multiple retinal hamartomas
- Cortical dysplasias
- Subependymal nodules or giant cell astrocytoma
- Cardiac rhabdomyomas
- Lymphangiomyomatosis
- Renal angiomyolipomas

Minor features
- Retinal achromic patch
- Dental enamel pits (≥3)
- Multiple renal cysts
- Nonrenal hamartomas
Piebaldism: $KIT$ mutations

Familial progressive hyper- and hypopigmentation: *KITLG* mutations

Amyere et al J Invest Derm 2011
Cuell et al Clin Exp Derm 2015
WAARDENBURG SYNDROME

- White Forelock
- Heterochromia Irides
- Dystopia Canthorum and Broad Root of the Nose
- Arm anomalies
- Deafness
- Hirschsprung disease
- Congenital Depigmentation

- Connective Tissues of the Head and Neck
- Components of Branchial Arch Muscles
- Adrenal Medulla
- Sensory and Autonomic Ganglia
- Melanocytes
- Gut Enteric Neural Plexus

Diagram showing various anomalies associated with Waardenburg Syndrome.
The lines of Blaschko

- Pathways of epidermal cell migration during embryonic development

- Dermatoses following Blaschko’s lines reflect mosaicism
  - Involve primarily epidermal structures (including melanocytes and appendages)
  - Genotypes of keratinocytes and underlying fibroblasts may differ

Happle & Assim J Am Acad Derm 2001
Hypopigmentation along Blaschko’s lines

 Courtesy, A. Torrelo MD
Hypopigmentation along Blaschko’s lines

- Reflects clone of cells with decreased pigment production potential
  - Lighter streaks evident at birth or appear in infancy/early childhood

- Possible extracutaneous abnormalities
  - CNS (developmental delay [often mild], seizures) > musculoskeletal (e.g. scoliosis, hemi-overgrowth) > ocular, cardiac, other (e.g. precocious puberty) Pavone et al Medicine 2016
  - Usually evident within the first year of life
  - How often?
    - >80% at pediatric neurology centers – obvious referral bias!!!
    - ~30% at an Italian pediatric center Pavone et al Neurol Sci 2015/2006
    - Likely <10% in the general population, where often overlooked in healthy children with fair skin
BEWARE of ‘Hypomelanosis of Ito’

BEWARE Google of ‘HOI’
Then what should we call it?

Descriptive term, **not a specific syndrome**

- Linear nevoid hypopigmentation
- Hypopigmentation along Blaschko’s lines (‘HABL’)
- Linear hypomelanosis in narrow bands
- Linear hypomelanosis of the Ito type
- Blaschkoid dyspigmentation
Clinical evaluation

• History and physical examination
  – Findings (if any) direct further evaluation

• If healthy with normal growth/development, don’t need to go looking
  – Consider ophtho exam if generalized or facial

• For parents
  – Reassurance when child is healthy (especially if >1 y)
  – Explanation, depending on interest/medical sophistication

• For older kids
  – Beautiful ‘natural body art’ ….
Genetic evaluation

- Even if extracutaneous issues, usually no affect on management – but may give insight into overall diagnosis
- Chromosomal mosaicism detectable via standard cytogenetic analysis
  - ~1/3 in lymphocytes
  - Additional ~1/4 in lesional fibroblasts only
  - Likely higher yield: analyze melanocytes or keratinocytes; array-CGH
- Types of abnormalities
  - Numerical (e.g. trisomy 18 or 20, triploidy) or structural
  - Tetrasomy 12p = Pallister-Killian syndrome
    - Intellectual disability, seizures, facial dysmorphism
  - ~90% overlap with locations of pigmentary genes
    - e.g. 15q, site of P (OCA2) gene

Taibjee et al Br J Derm 2004
Taibjee et al Clin Exp Derm 2009
Costa et al Mol Cytogenet 2015
Alesi et al Am J Med Genet 2017
Nevoid hypo-/hyperpigmentation – mutations in specific genes?

- Mosaic \textit{MTOR} mutations
  - Hypo- and hyperpigmentation along Blaschko’s lines + asymmetric megalencephaly/cortical dysplasia
  - 3 children with mosaicism for p.Thr1977Ile

Mirzaa et al JAMA Neurol 2016
DDx of Blaschko-linear leukoderma “plus”

Goltz syndrome

Lichen sclerosus

Munro acne nevus

Lichen striatus

Epidermal nevus
IP Stage 4: “Chinese characters” on calves
Which is the “normal” skin, light or dark?
Hyperpigmentation along Blaschko’s lines ("Linear and whorled nevoid hypermelanosis")

- Reflects clone of cells with *increased* pigment production potential
- Term lacks stigma of HOI
- Can have associated extracutaneous abnormalities
  - CNS, musculoskeletal, ocular
  - Similar frequencies (15-30%) as HOI at peds derm centers
  - 75% (18/24) of patients with pigmentary mosaicism + CNS manifestations in Indian series had *hyperpigmentation*

Nehal et al Arch Derm 1996
Di Lernia Pediatr Derm 2007
Cohen et al Ped Derm 2014
DDx of hyperpigmentation along Blaschko’s lines

Incontinentia pigmenti, stage 3

LP pigmentosus

Female “carrier” of hypohidrotic ectodermal dysplasia

Linear atrophoderma of Moulin
Epidermal nevi with subtle elevation

+ lipomatosis

PIK3CA

+ woolly hair nevus

HRAS
Heterochromia of the scalp hair

Restano et al. JAAD 2001
Lines of Blaschko, broader bands

‘Pigmentary mosaicism’ alone

McCune-Albright syndrome
($G_s\alpha$ activation; $GNAS$)

• ‘Coast of Maine’ irregular/geographic borders
  – *Darker color* (café but no lait)
  – Distribution does *not* correlate with sites of bone lesions
  – Difficult to identify mutation in skin samples

• Polyostotic fibrous dysplasia
  – Favors proximal femur, skull base
  – Craniofacial: asymmetry or lump by early childhood
  – Limb: pain, limp, pathologic fractures, scoliosis
  – Skeletal survey x-rays to screen

• Endocrine activation, e.g. precocious puberty, hyperthyroidism

Boyce & Collins, Gene Rev 2015
Becker’s nevus: mosaic beta-actin (ACTB) mutations

- Rare breast hypoplasia, scoliosis, musculo-skeletal anomalies
- Increased acne and TV

Nevus spilus: mosaic HRAS mutations

Cai et al J Invest Derm 2017
‘Segmental pigmentation disorder’

- **Terminology**
  - Coined by Metzker *et al* in 1983 and re-introduced by Hogeling and Frieden in 2010
  - AKA “flag-like” hypo-/hypermelanotic nevus

- **Features**
  - Usually apparent in infancy, esp. if darker skin
  - Hyper- or hypopigmented
  - Favors trunk
  - Typically no association with developmental delay or extracutaneous abnormalities

Metzker *et al* Acta Derm Ven 1983
Hogeling & Frieden Br J Derm 2010
‘Segmental pigmentation disorder’

- Midline demarcation more often ventrally (~80%) than dorsally (~20%)
  - May extend a few cm past the midline
- Often less well-defined laterally

Hogeling & Frieden Br J Derm 2010
Hypomelanosis - mosaic trisomy 13q:
• Leaf-like, pear-shaped, oblong “floral ornaments”
• Telangiectatic macules
• Thick eyebrows, long eyelashes
• CNS, eye, craniofacial & digital anomalies

Patterned dyspigmentation