Genetic Skin Disorders

Basic Dermatology Curriculum

Content for this module was developed by the Society for Pediatric Dermatology

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Module Instructions

- The following module contains a number of blue, underlined terms which are hyperlinked to the dermatology glossary, an illustrated interactive guide to clinical dermatology and dermatopathology.
- We encourage the learner to read all the hyperlinked information.
Goals and Objectives

- The purpose of this module is to help develop a clinical approach to the evaluation and initial management of patients presenting with genodermatoses.
- By completing this module, the learner will be able to:
  - Identify and describe the morphology of skin lesions typical of tuberous sclerosis, neurofibromatosis type 1, and Sturge-Weber Syndrome.
  - Summarize the clinical manifestations of these three genodermatoses.
  - Describe the clinical features and summarize the clinical findings of genetic disorders other than NF1 associated with café au lait macules.
Case One

Claire
Case One: History

- HPI: Claire is a 9 year old girl who presents for well child care with 6 light brown spots (each >5mm) that have grown with her since birth.
Case One: Physical Exam

- Oval uniformly pigmented light brown macules and patches with smooth borders
- Consistent with Café au lait (CAL) macules and patches
Case One: Question 1

How many CAL macules/patches (>5mm) would prompt referral to a geneticist for evaluation of possible Neurofibromatosis 1 (NF1)?

- a. ≥ 2
- b. ≥ 3
- c. ≥ 4
- d. ≥ 6
Case One: Question 1

Answer: d

How many CAL macules/patches (>5mm) would prompt referral to a geneticist for evaluation of possible NF1?

- a. ≥ 2
- b. ≥ 3
- c. ≥ 4
- d. ≥ 6

- In Caucasian children, > 3 may prompt evaluation
- Must also take into account family history and other associated symptoms
Café au Lait Spots (CALS)

- Discrete uniformly pigmented macules or patches, varying from light to dark brown with smooth or irregular borders.
- Histology: increased melanin content with giant melanosomes, no melanocyte proliferation.
- In newborns, having at least 1 CALM varies with ethnicity:
  - 18% of African American
  - 3% of Hispanic
  - 0.4% of Chinese
  - 0.3% of Caucasian
- > 3 CAL spots are noted in only 0.2-0.3% of school children without a genetic disorder.
Differential Diagnosis of CALS

Congenital melanocytic nevus: May have overlying hypertrichosis

Becker’s Nevus: Overlying hypertrichosis in teenager
Differential Diagnosis of CALS

Speckled Lentiginous Nevus
(Also referred to as nevus spilus)

Segmental Pigmentation Disorder
(Also referred to as pigmentary mosaicism)
Systemic Disorders Associated With CALS Other Than NF1

- **Neurofibromatosis Type 2**
  - CALS not essential for diagnosis, but may be noted
  - Associated with vestibular schwannomas and other neoplasms
- **McCune Albright Syndrome**
  - Patches usually large, have irregular borders and are located on sacrum, buttocks, and upper spine
  - Associated with endocrine abnormalities and fibrous dysplasia of bones
- **Legius Syndrome**
  - NF1-like syndrome due to SPRED1 gene mutation
Case One, Question 3

How is NF1 transmitted from parent to child?

a. Autosomal dominant
b. Autosomal recessive
c. X-linked dominant
d. X linked recessive
Case One, Question 3

**Answer: a**

How is NF1 transmitted from parent to child?

- a. Autosomal dominant
- b. Autosomal recessive
- c. X-linked dominant
- d. X linked recessive
Ask About Family History

- NF1 is autosomal dominant and there may be a family history of disease
  - Variable expressivity means individuals with the same mutation can have different phenotypes
- There are some families with multiple generations of > 6 CALS without a genetic disorder
- 50% of mutations are de novo which means these patients will not have a positive family history
NF1: The Basics

- NF1 is a multisystem disease with predominantly skin and neoplastic manifestations
- Mutation in the gene encoding neurofibromin, chrom 17
- Affects 1/3500 live newborns
- Equal gender predominance across ethnicities
- Associated malignancies:
  - malignant peripheral nerve sheath tumor (5-10%)
  - optic glioma
  - GI stromal tumor
  - leukemia
  - rhabdomyosarcoma
  - glioblastoma
  - glioblastoma
  - breast cancer
  - pheochromocytoma
  - duodenal carcinoid tumor
### NF1 Diagnostic Criteria

<table>
<thead>
<tr>
<th>NIH Consensus Criteria (need 2 or more)</th>
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<tbody>
<tr>
<td>6 or more CALM (&gt;5mm in children or &gt;15 mm in adults)</td>
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<tr>
<td>2 or more cutaneous neurofibromas OR 1 plexiform neurofibroma</td>
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<tr>
<td>Axillary or inguinal freckling</td>
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<tr>
<td>2 or more Lisch nodules (iris hamartomas)</td>
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<tr>
<td>Optic pathway glioma</td>
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<tr>
<td>Bony Dysplasia (sphenoid wing dysplasia, bowing of long bones +/- pseudarthrosis)</td>
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<tr>
<td>First degree relative with NF1</td>
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</table>

NF1 is diagnosed clinically. Commercial genetic testing investigates truncation of the NF1 gene and detects 50-70% of mutations.
Other Physical Exam Findings to Look for in NF1

- Axillary and groin freckling
  - Present in 85% of patients by 10 years of age
- Lisch Nodules: Hamartomas of the iris
  - Present in 25% of patients by 5 years, 50% by 10 years, 95% by 20
  - May require slit-lamp to diagnose, especially if few in number and patient is young
  - Do not affect vision
- Cutaneous Neurofibroma
  - Present in 20% of patients by 10 years of age, > 90% in adults
  - Lead to cosmetic problems, no malignant potential
  - Move with the skin

Lisch nodules
Other Neurofibromas

- Subcutaneous Neurofibroma (15% of patients)
  - Firm, rubbery, may be painful
  - Skin moves over them
- Plexiform Neurofibroma (25% of patients)
  - Soft plaque with overlying hyperpigmentation +/- hypertrichosis
  - Potential for malignant transformation (pain can be sign of malignancy)
  - Present at birth, but may be diagnosed later
  - Can involve all skin levels down to bone and viscera
  - May cause compression, distortion, or overgrowth of structures
- Spinal Neurofibroma - may have sensory and motor effects
Back to Case One

Claire
9 year old girl with multiple CALMs
Case One: History Continued

- PMH: no major illnesses or hospitalizations
- Medications: none
- Allergies: none
- Family history: adopted, unknown
- Social history: lives with parents and brother age 11. In 3rd grade
- ROS: occasional headaches, trouble with math in school
Skin Examination Continued

Axillary Freckling
Ask a thorough Review of Systems

- Optic gliomas – most common CNS tumor (15%), develops in children < 6 yo
  - Headaches, visual field defects, proptosis, strabismus, nausea, anorexia, hypothalamic dysfunction, precocious puberty
  - Only 1/3 develop symptoms – only treated if symptomatic
  - Imaging asymptomatic children is NOT recommended as they rarely progress
- Mental retardation is rare (4-8%)
- Learning disabilities are common (40-60%)
- Short Stature (33%)
- Macrocephaly (50%)
- Skeletal Problems
  - Scoliosis (10-26%)
  - Tibial dysplasia (2-3%) – manifests as bowing of lower legs → increase risk of fracture and pseudoarthrosis
- Hypertension (due to renal artery stenosis or pheochromocytoma)
Follow up and Referrals

- Claire has > 6 CALS
  - axillary freckling
  - learning disability
  - headaches
- You refer her to ophthalmology and genetics
- She undergoes genetic testing and is diagnosed with NF1
## Health Supervision for Children with NF1

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Age</th>
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<tbody>
<tr>
<td>Growth</td>
<td>At every well child check (Neonatal, 2mo, 4mo, 6mo, 9mo, 12mo, 15mo, 18mo, 2-21 years annually)</td>
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<tr>
<td>Blood pressure</td>
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<tr>
<td>Skin exam</td>
<td></td>
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<tr>
<td>Bone examination (tibial dysplasia, scoliosis, hypertrophy)</td>
<td>*Sub-specialty audiology at 1 and 4 years and sub-specialty development and behavior at 4 years</td>
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<tr>
<td>Neurologic examination</td>
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<tr>
<td>Vision screening*</td>
<td></td>
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<tr>
<td>Hearing screening*</td>
<td></td>
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<tr>
<td>Genetic counseling</td>
<td>Prenatally and once in adolescence</td>
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<tr>
<td>Phenotype review</td>
<td>Prenatally, neonatal, or at time of diagnosis</td>
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<tr>
<td>Ophthalmologist eye exam</td>
<td>Annually starting at 12 months</td>
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<tr>
<td>Psychological/social adjustment</td>
<td>Every well visit starting at 12 months</td>
</tr>
<tr>
<td>School placement/performance</td>
<td>Annually starting at 3 years</td>
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<tr>
<td>Sexual and reproductive issues</td>
<td>Once in childhood (5-13 years), annually starting at 13 years</td>
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Case Two

Alex
Case Two: History

• HPI: Alex is a 14 year old male with at least 7 café au lait patches measuring >15mm, relative macrocephaly, axillary freckling and a learning disability

• No history of neurofibromas, bony changes, Lisch nodules or optic gliomas
Case Two: History Continued

- Genetic testing is negative for NF1 gene
- Further testing reveals: **SPRED1 gene mutation → Legius Syndrome**
Legius Syndrome

• ‘RAS-opathy’ due to SPRED1 gene mutation
• Patients have CAL spots, freckling, macrocephaly and in some, mild neurocognitive delays
• Single case of AML
• No other neoplastic findings commonly seen in NF-1
Case Three

Maria
Case Three: History

- HPI: Maria is a 3 year old girl who presents with 4 hypopigmented patches
What procedure would you use to further evaluate this patient?

A. Dermoscopy
B. Fungal Culture
C. **KOH** preparation
D. **Wood’s Lamp**
Case Three, Question 1

Answer: D

What procedure would you use to further evaluate this patient?

A. Dermoscopy
B. Fungal Culture
C. KOH preparation
D. Wood’s Lamp – to screen for other hypopigmented lesions including ash leaf spots or confetti hypopigmentation seen in tuberous sclerosis
Differential Diagnosis of Hypopigmented Macules or Patches

- Tuberous Sclerosis (TS)
- **Tinea Versicolor**
- **Vitiligo** (early)
- **Post inflammatory hypopigmentation**

Due to the number of hypopigmented lesions, this case is concerning for Tuberous Sclerosis and the patient is referred to genetics who confirms the diagnosis of TS with genetic testing.
Tuberous Sclerosis: The Basics

- Neurocutaneous disorder due to mutations in TSC1 or TSC2 genes encoding hamartin and tuberin proteins, respectively
- Leads to a lack of inhibition of mTOR → hamartomas
- Incidence is 1:6,000 to 1:100,000
- Found in all races, equal gender distribution
- Autosomal dominant transmission
- Principal early manifestations
  - Seizures
  - Mental retardation
  - > 3 Hypomelanotic macules (≥ 5mm or more) polygonal or oval shaped (Ash leaf spots) or small confetti-like hypopigmented macules
Other Skin Findings in TS

- Facial angiofibromas are pathognomonic but may not appear until 3rd and 4th year of life
- Shagreen patch: connective tissue nevus, skin colored, occurs on back and buttocks
- Dental enamel pits
- Ungual fibromas
- Intraoral fibromas
TS: Other Associated Symptoms

- CNS tumors (gliomas)
- Eye (retinal plaques)
- Heart (benign rhabdomyomas)
- Hamartomas of mixed cell type in kidney, liver, thyroid, testes, or GI
Tuberous Sclerosis Clinical Diagnostic Criteria
2012 Consensus Conference

Major Features
- Hypomelanotic macules (≥3) (> 5mm diameter)
- Angiofibromas (≥3) or fibrous cephalic plaque
- Ungual fibromas (≥2)
- Shagreen patch
- Multiple retinal hamartomas
- Cortical dysplasia
- Subependymal nodules
- Subependymal giant cell astrocytoma
- Cardiac rhabdomyoma
- Lymphangioleiomyomatosis (LAM)*
- Angiomyolipomas (≥2)*

Minor Features
- “Confetti” skin lesions
- Dental enamel pits (≥3)
- Intraoral fibromas (≥2)
- Retinal achromic patch
- Multiple renal cysts
- Nonrenal hamartomas

Definitive Diagnosis
- Two major features OR
- One major with ≥ 2 minor

Possible Diagnosis
- One major feature OR
- ≥ 2 minor

*Combination of major criteria LAM and angiomyolipoma without other features does not meet criteria for a definitive diagnosis

Recommendations of the 2012 International Tuberous Sclerosis Complex Consensus Conference
Case 3: History Continued

Maria returns to clinic at age 13 years and is concerned about the angiofibromas on her face.

Physical Exam:
0.1-0.5 cm
dome shaped,
smooth, red,
purple or skin
colored papules
Angiofibromas: Management

Observation only

Laser ablation (PDL, CO2 or other)

New off label topical therapy: rapamycin

- Rapamycin is an immunosuppressant that blocks the mTOR pathway. It can be used to successfully prevent and treat angiofibromas of the face in TS

Pre-treatment

Partial improvement after 3 months of topical rapamycin
# TS Surveillance Recommendations

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Recommendation (2012 International Tuberous Sclerosis Consensus Conference)</th>
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</thead>
<tbody>
<tr>
<td>Genetics</td>
<td>Genetic testing and family counseling</td>
</tr>
</tbody>
</table>
| Neurology | • MRI of brain at diagnosis and every 1-2 years in asymptomatic patients < 25 years (more frequently if subependymal giant cell astrocytoma present)  
  • Screen for neuropsychiatric disorders annually with formal evaluation in infancy, childhood, adolescence, and early adulthood  
  • Obtain baseline EEG and repeat in patients with known or suspected seizure activity |
| Renal     | • MRI of abdomen at diagnosis every 1-3 years throughout lifetime  
  • GFR and blood pressure annually |
| Lung      | • Screen for LAM symptoms annually (exertional dyspnea)  
  • High resolution chest CT and PFTs at diagnosis  
  • High resolution chest CT every 5-10 years in asymptomatic patients at risk of LAM  
  • If lung cysts on baseline CT, PFT yearly and CT every 2-3 years |
| Skin/Teeth| Skin and dental inspection and exam annually                                |
| Heart     | • Echocardiogram every 1-3 years in asymptomatic pediatric patients until regression of cardiac rhabdomyoma is documented  
  • ECG every 3-5 years in asymptomatic patients of all ages |
| Eye       | Annual ophthalmologic evaluation if previous lesions or symptoms at baseline evaluation |
Case Four

Thomas
Case Four: History

Thomas is a 3 week old male who was found to have this pink/purple vascular patch on his face since birth. It gets darker when he cries, but has not grown or become raised since birth.
Case Four: Physical Exam

- Physical Exam: Pink/purple vascular patch in a unilateral V1 distribution involving the eyelids

- Diagnosis: Port Wine Stain/Capillary Malformation
Case Four, Question 1

Involvement of the eyelid in this case makes referral to ophthalmology important to screen regularly for what condition?

A. Cataracts
B. Conjunctivitis
C. Glaucoma
D. Uveitis
Case Four, Question 1

Answer C

Involvement of the eyelid makes referral to ophthalmology important to screen regularly for what?

A. Cataract
B. Conjunctivitis
C. Glaucoma – can occur at any age in patients with port wine stains involving the eyelid
D. Uveitis
Port-wine Stain (PWS)

- Cutaneous capillary malformation (CM)
- Do not regress, unlike infantile hemangiomas, which are vascular tumors that proliferate and then involute
- May become darker in color or thickened over time
- Incidence is 3/1000 newborns
- May be associated with soft tissue or bony overgrowth
- Sturge Weber syndrome is associated with CM/PWS in the V1 distribution of the face
Sturge-Weber Syndrome (SWS)

- Sporadic genetic syndrome
- 1/20-50,000 live births, no sex predominance
- Caused by a mutation in the GNAQ gene
  - also present in non-syndromic port-wine stains
  - same mutation causes a different effect depending on the embryonic stage (in SWS mutation is earlier)
- Port-wine stain most often in V1 distribution
- Associated with vessel abnormalities of leptomeninges and the eye clinically presenting as seizures and glaucoma, respectively
Port-wine Stain Treatment

- Port-wine stains may be safely and effectively treated with laser to minimize darkening, thickening and avoid the psychological distress they may cause
  - There is no cure for the neurologic manifestations of SWS
- Considerations in pediatric patients include the risk of general anesthesia or sedation which may be required in young patients
- Side effects include pain, bruising, pigmentation changes or blistering (rarely scaring)
## Genodermatoses Summary

<table>
<thead>
<tr>
<th>Feature</th>
<th>NF1</th>
<th>TS</th>
<th>SWS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gene</strong></td>
<td>Neurofibromin</td>
<td>TSC1 (hamartin) or TSC2 (tuberin)</td>
<td>GNAQ</td>
</tr>
<tr>
<td><strong>Skin Findings</strong></td>
<td>CALS, skin fold freckling, plexiform neurofibroma, cutaneous neurofibromas</td>
<td>Hypopigmented spots, angiofibromas, ungual fibromas, fibrous cephalic plaque</td>
<td>Capillary Malformation/Port Wine stain of the face, usually V1 distribution</td>
</tr>
<tr>
<td><strong>Tumors</strong></td>
<td>Optic glioma, malignant peripheral nerve sheath, rhabdomyosarcoma, glioblastoma, pheochromocytoma</td>
<td>Retinal hamartomas, cortical tubers, subependymal nodules, subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangioleiomyomatosis (LAM), nonrenal hamartomas</td>
<td>Not associated with tumors/malignancies</td>
</tr>
<tr>
<td><strong>Other Systems Affected</strong></td>
<td>Renal artery stenosis, skeletal dysplasias, learning disabilities</td>
<td>Cortical dysplasia in brain</td>
<td>Leptomeningeal angiomatosis, seizures, glaucoma, learning disabilities</td>
</tr>
</tbody>
</table>
Take Home Points: Neurofibromatosis

- Café au lait spots are common in healthy individuals, but more than 6 lesions should prompt evaluation for NF1
- Frequency of café au lait spots varies with ethnicity and is higher in people with darker skin pigmentation
- NF1 is an autosomal dominant disease; however 50% of mutations are de novo with no family history
- Other symptoms associated with NF1 are axillary or inguinal freckling, neurofibromas, lisch nodules, optic gliomas, skeletal abnormalities, and various other tumors
- Children with NF1 need yearly ophthalmology exams starting at 1 year
- Legius syndrome is another Ras-opathy with similar dermatologic findings without the increased risk of neoplasms
Tuberous Sclerosis and Sturge-Weber Syndrome

**TS**
- Hypopigmented macules may be accentuated by examination with a Wood’s lamp
- Tuberous sclerosis is a disorder with early manifestations including hypomelanotic macules, mental retardation, and seizures
- Facial angiofibromas are pathognomonic for TS
- Topical rapamycin is an effective treatment for facial angiofibromas

**SWS**
- Port wine stain in a V1 distribution should prompt evaluation for Sturge-Weber syndrome (SWS)
- Port wine stains with involvement of the eyelid should prompt evaluation for glaucoma
- SWS is associated with capillary abnormalities of leptomeninges and the eye
- Port wine stains may be treated with laser
Acknowledgements

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- Peer reviewers: Erin Mathes, MD and Sheilagh Maguiness, MD
- Revisions: Patrick McMahon, MD
- Last revised: 3/1/15


To take the quiz, click on the following link:

https://www.aad.org/quiz/genetic-skin-disorders-learners