The Inside Out of Neurocutaneous Disorders

Robert Greenwood
Sometimes spots and knots have a purpose that tells you something about the organism that has them.
Oxymorons That Will Not Be Used In This Lecture

- Black Light
- Never generalize!!
- Exact estimate
# Neurocutaneous Disorders

## General Concepts

1. The skin can be a window that allows you to see the medical future of an infant.
2. The cutaneous signs can be subtle.
3. As in many other genetic diseases variable penetrance and expression are the rule.
4. Family history and examination of other family members is a very important tool in making a diagnosis.
5. Hair and teeth are skin appendages and are often affected when skin is affected.
6. **Look on the Web**
   - [http://tray.dermatology.uiowa.edu/DDX/macule.html](http://tray.dermatology.uiowa.edu/DDX/macule.html)
   - [http://dermatlas.med.jhmi.edu/derm/](http://dermatlas.med.jhmi.edu/derm/)
   - [http://dermatology.cdlib.org/](http://dermatology.cdlib.org/)
Neurocutaneous Disorders

1. Neurofibromatosis I & II
2. Tuberous Sclerosis
3. Von Hippel Lindau disease
4. Sturge Weber Syndrome
5. Klippel-Trenaunay-Weber Syndrome
6. Osler-Weber-Rendu Syndrome
7. Wyburn-Mason Syndrome
8. Linear Sebacious Nevus Syndrome
9. Neurocutaneous Melanosis
10. Waardenburg Syndrome Type 1 & 2
11. Fabry's Disease
Neurocutaneous Disorders

Incidence

- Neurofibromatosis type 1
  - 1/1,000-1/7,800
  - (30/100,000)

- Tuberous Sclerosis
  - 10.6/100,000

- Ataxia Telangiectasia
  - 1.7/100,000

- Xeroderma Pigmentosum
  - 1/100,000 - 1/250,000

- Neurofibromatosis type 2
  - 1/200,000
## Neurocutaneous Disorders

### Identified Chromosome Defects

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Chromosome</th>
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<tbody>
<tr>
<td>NF1</td>
<td>17q11.2</td>
</tr>
<tr>
<td>NF2</td>
<td>22q12.2</td>
</tr>
<tr>
<td>TS</td>
<td>16p13.3, 12q14, 9q34</td>
</tr>
<tr>
<td>Incontinentia Pigmenti</td>
<td>Xq28 - X-linked dominant</td>
</tr>
<tr>
<td>Hypomelanosis of Ito</td>
<td>? 9q33-qter, 15q11-q13, and Xp11</td>
</tr>
<tr>
<td>A-T</td>
<td>11q22.3</td>
</tr>
<tr>
<td>Von Hipple Lindau</td>
<td>11q13, 3p26-p25</td>
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<tr>
<td>Osler - Rendu -Weber Disease</td>
<td>9q34.1</td>
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</tbody>
</table>
Neurocutaneous Disorders

Inheritance

- Autosomal Dominant
- Autosomal Recessive
- X-linked Recessive
- Sporadic
Genetics Principles: NF1 and Other Neurocutaneous Disorders

- Penetrance
- Expression
  - Variable expressivity
- Pleiotropy
- Mosaicism
- Heterogeneity- locus and allelic
Neurocutaneous Diseases
Autosomal Dominant Inheritance

- Neurofibromatosis
- Tuberous Sclerosis
- Von Hippel-Lindau Disease
- Lentigines-Deafness-Cardiopathy Synd.
- Hypomelanosis of Ito
- Osler-Weber-Weber-Rendu Disease
Neurocutaneous Diseases
Autosomal Recessive Inheritance

- Ataxia-Telangiectasia
- Xeroderma Pigmentosum
- Cockayne’s Syndrome
- Rothmund-Thomson Syndrome
- Sjogren-Larsson Syndrome
- Neuroichthyosis
- Werner Syndrome and Progeria
Neurocutaneous Diseases
X-Linked Inheritance

- Incontinentia Pigmenti
Neurocutaneous Diseases
Sporadic Congenital and Angiomatoses

- Neurocutaneous Melanosis
- Linear Sebaceous Nevus
- Sturge-Weber Syndrome
- Klippel-Trenaunay Syndrome
- Wyburn-Mason Syndrome
Classification of Neurocutaneous Disorders and Cancer

Oncogene or tumor suppressor gene abnormalities.

- Caretaker - does not control cell growth directly but instead controls the rate of mutation
- Gatekeeper - controls either the rate of cell birth or the rate of cell death
Familial Cancer Syndromes-Disorders of the Caretakers

- Nucleotide Excision Repair Syndromes: Xeroderma Pigmentosum, Cockayne Syndrome, and Trichothiodystrophy
- Ataxia-Telangiectasia
- Bloom Syndrome
- Fanconi Anemia
- Hereditary Nonpolyposis Colorectal Cancer (HNPCC)
- Werner Syndrome
- Peutz-Jeghers Syndrome
- Juvenile Polyposis Syndrome
Nucleotide Excision Repair (NER) Defects

- Xeroderma pigmentosum (XP)
- Cockayne syndrome (CS)
- Photosensitive form of trichothiodystrophy (TTD)
Nucleotide Excision Repair (NER) Defects

- All are recessive
- All have extreme sunlight sensitivity and 1000X frequency skin cancers
- Progressive degeneration of skin and eyes
- In some accelerated neurologic degeneration and neuronal death
- Key features CS and TTD
  - CS- short stature, severe neurological abnormalities with dysmyelination, cataracts, bird-like face
  - TTD- brittle hair and nails, ichthiosis, other symptoms similar to CS
Xeroderma Pigmentosus

- Skin abnormalities
  - Erythema and bullae (acute sensitivity in infancy)
  - Freckles
  - Xerosis (dryness) and scaling
  - Areas of hyperpigmentation alternating with hypopigmentation
  - Telangiectasia
  - Atrophy
  - Benign lesion: actinic keratoses, keratocanthomas, angiomas, fibromas
  - Malignant lesions: basal cell carcinoma, squamous cell carcinoma, melanoma

- Ophthalmologic abnormalities
  - Conjunctivitis with photophobia, lacrimation, edema
    - Cornea: keratitis, opacification, impaired vision
    - Neoplasms of conjunctiva, cornea, and lids
Xeroderma Pigmentosa Neurologic Manifestations

- Microcephaly
- Low intelligence
- Progressive mental deterioration
- Progressive sensorineural deafness
- Abnormal motor activity
- Hyporeflexia or areflexia
- Primary neuronal degeneration
Ataxia-Telangiectasia (A-T)

1. Progressive gait and truncal ataxia with onset from 1 to 3 years of age; progressively slurred speech;
2. Choreaathetosis, seizures,
3. Oculomotor apraxia,
4. Oculocutaneous telangiectasia, usually by 6 years of age;
Ataxia Telangiectasia

- Telangiectatic lesions of conjunctivae, malar eminences, ear lobes and upper neck
- Ataxia, choreoathetosis and nystagmus
- Immunologic deficiencies
- Cancer proneness- 38% lymphoreticular
Ataxia Telangiectasia
A-T

- Incidence - 1/40,000 births
- Carrier frequency 1%
- Female carriers RR of 5 for breast cancer
- Chromosome 11q22.3- *ATM* (ataxia-telangiectasia mutated), is a member of a family of phosphatidylinositol-3-kinase–related genes involved in cell cycle control, intracellular protein transport, and DNA damage response
Incontinentia Pigmenti

- X-linked, lethal in hemizygous males
- Vesicular rash in newborn period
- Neonatal seizures
- Polymorphic pigmented lesions develop in infancy
Incontinentia Pigmenti

- Erythematous bullous lesions at birth
- Second stage crusting of lesions (verrucous)
- Third stage whorls, zebra stripes, speckles or other patterns of pigmentation
- Microcephaly and micropolygyria
- Mental retardation
- Dental anomalies and ocular abnormalities
Incontinentia Pigmenti
Incontinentia Pigmenti
Incontinentia Pigmenti

**Dental anomalies—both primary and secondary dentition**

- Hypodontia (small teeth)
- Partial anodontia (lack of teeth)
- Delayed eruption
- Impacted dentition
- Malformed crowns (cone or peg-shaped)
Incontinentia Pigmenti

- **Ophthalmic**
  - Strabismus
  - Cataracts
  - Optic atrophy
  - Anophthalmia (absence of eye)
  - Microphthalmia
  - Retinal vasculopathy (Fig 1)
  - Changes such as retrolental fibroplasia
Central nervous system symptoms and findings

- Seizures
- Mental retardation
- Ataxia
- Spastic abnormalities
- Microcephaly
- Cerebral atrophy
- Hypoplasia of corpus callosum
- Hydrocephalus
- Porencephalic cysts
- Hemorrhagic necrosis
- Neuronal heterotopias
Incontinentia Pigmenti
Hypomelanosis of Ito

- Hypopigmentation in whorls
- Seizures
- Mental retardation
- Ophthalmologic anomalies
- Heterotopias
Hypomelanosis of Ito

- Small 0.5-1-cm hypopigmented or white macules coalesce to form reticulated patches along the lines of Blaschko.
  - The macules cover more than 2 dermatomes and are often on both sides of the body.
  - The patches are not symmetric.
  - A Wood lamp enhances the pattern, especially in white patients.

- Dysmorphism:
  - Cleft palate
  - Hemihypertrophy
  - Limb, hand, and/or foot abnormalities
  - Nail abnormalities
  - Hypotonia
  - Teeth abnormalities
  - Hair anomalies
  - Face and/or skull anomalies
Hypomelanosis of Ito
Familial Cancer Disorders - Disorders of Gatekeepers

- Von Hippel-Lindau Syndrome
- Neurofibromatosis type 1
- Neurofibromatosis type 2
- Tuberous sclerosis
NEUROFI BROMATOSIS TYPE 1
NF1 Molecular Biology

- NF1 gene localized on chromosome 17q11.2
- ~300 kb, contains 53 exons
  - intron 72b contains 3 previously identified genes
  - intron 37 contains the adenylate kinase 3 pseudogene
- Protein product is neurofibromin
  - 2818 amino acids
  - ? GTPase activator that regulates a tumor suppressor gene
NF1 Genetics

- Autosomal dominant
  - Complete penetrance
- Half of the NF1 cases are new mutations
- More than 200 different gene mutations
  - Most gene abnormality have been unique
- Extremely variable expression
**Neurofibromatosis Type 1**

- NF1, von Recklinghausen Disease
- Prevalence: 1/3000
- No racial or ethnic predilection
  - 1/7800 in the USSR
  - 1.04/1000 in Israel military recruits
Criteria for the diagnosis of NF1 requires two or more of the following:

- Six or more cafe'-au-lait macules (over 5 mm in prepubertal individuals and over 15 mm in postpubertal individuals)
- Two or more neurofibromas of any type or one plexiform neurofibroma.
- Freckling in the axillary or inguinal region
- Optic glioma
- Two or more Lisch nodules (iris hamartomas)
- A distinctive osseous lesion such as sphenoid dysplasia or thinning of long bone cortex with or without pseudarthrosis
- A first-degree relative with NF-1 by the above criteria
NF1

- café-au-lait spots
Pigmentation overlying plexiform neurofibroma
Neurofibromatosis Type 1

Axillary Freckling
Plexiform Neurofibroma of the Facial Nerve
### NF1 Time Line For Complications

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Incidence</th>
<th>CONGENITAL (0-2 yrs)</th>
<th>PRESCHOOL (2-4 yrs)</th>
<th>LATE CHILDHOOD &amp; ADOLESCENCE (6-16 yrs)</th>
<th>ADULTHOOD (16+yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Café au lait spots</td>
<td></td>
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</tr>
<tr>
<td>Plexiform Diffuse neurofibroma</td>
<td>25%</td>
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<tr>
<td>Superficial or nodular</td>
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<tr>
<td>Tibial dysplasia</td>
<td>3 %</td>
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<tr>
<td>Skinfold freckling</td>
<td></td>
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<tr>
<td>Optic glioma</td>
<td>15 – 20 %</td>
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<tr>
<td>Learning disabilities</td>
<td>30 – 65 %</td>
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<tr>
<td>Complications</td>
<td>CONGENITAL (0-2 yrs)</td>
<td>PRESCHOOL (2-4 yrs)</td>
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<tr>
<td>Hypertension</td>
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<td></td>
</tr>
<tr>
<td>Headaches</td>
<td>10 – 20 %</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dermal neurofibroma</td>
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<tr>
<td>Scoliosis</td>
<td>12 – 20 %</td>
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<tr>
<td>Malignant peripheral nerve sheath tumors</td>
<td>1 – 4 %</td>
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</tbody>
</table>
Macrocephaly and Somatic Growth in NF1

• **Absolute macrocephaly** (head circumference ≥ 98% ile) reported in 43-45% of patients with NF-1
  - Recent NF multicenter study-
    - 24% have macrocephaly (OFC ≥ 2 standard deviations above the population mean).

• 13% of patients have short stature (≥ 2 standard deviations below the population mean)
Optic glioma
Other MRI Abnormalities

- Areas of increased T2 signal intensity
  - 43 - 79% of NF1 in pediatric age group
  - Most- multiple, no mass effect.
  - Path- atypical glial infiltrate, microcalcification, and areas of dysmyelination and spongy changes in WM around lesion.

- Areas of increased T1 signal intensity
- Ventricular enlargement
Learning is often affected in NF1 children. Visuospatial function is most clearly affected.

The brains of NF1 children are larger and the pattern of growth of NF1 children may be different.

- The increased brain size in NF1 children is due to increased gray and white matter.
- Visual spatial function is one of the most consistent deficits and has correlated with right hemisphere gray matter volume.
Conclusions Contd.

- The brains of NF1 children also have lower NAA/creatine, and NAA/Cho ratios in the thalamus.
- T2 hyperintensities may be a marker for a more diffuse process.
  - They may be positively correlated with cognitive deficits.
Conclusions Contd.

- ADC in NF1 children is significantly different from other children but fractional anisotropy is only different in the hippocampus.

- The areas of the brain with greatest ADC differences are those where we find significantly greater brain volume, the parietal-occipital and frontal cortex. These same areas are thought to be important for attention and visual spatial function.
Neurofibromatosis Type 2

- Bilateral acoustic neuromas - diagnostic
- Other tumors - meningioma, ependymomas, spinal cord astrocytomas, dorsal nerve schwannomas
- Skin hyperpigmentation is variable
- Posterior subcapsular cataracts and Lisch nodules
Tuberous Sclerosis
Tuberous Sclerosis

- Incidence: 1 in 6000 - 9000
- Dominant inheritance but a high frequency of spontaneous mutation
  - 56% to 86% spontaneous mutation
- Variable expression within families
# Tuberous Sclerosis

<table>
<thead>
<tr>
<th>Gene</th>
<th>Location</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSC1</td>
<td>chromosome 9 q</td>
<td>hamartin</td>
</tr>
<tr>
<td>TSC2</td>
<td>chromosome 16 p</td>
<td>tuberin</td>
</tr>
</tbody>
</table>
Tuberous Sclerosis Revised Diagnostic Criteria

- **Definite TSC**
  - Two major feature or
  - One major plus 2 minor

- **Probable TSC**
  - One major and one minor

- **Possible TSC**
  - One major
  - 2 or more minor
Tuberous Sclerosis

- Primary Features
  - Facial angiofibromas
  - Multiple ungual fibromas
  - Cortical tubers
  - Subependymal nodules or giant cell astrocytoma
  - Retinal hamartomas
  - 3 or more hypomelanotic macules
  - Shagreen patch
  - Renal angiomyolipoma
  - Cardiac rhabdomyoma
  - Pulmonary lymphangiomatosis
Tuberous Sclerosis

Secondary features
- Affected first degree relative
- Dental enamel pits
- Bone cysts
- Forehead plaque
- Renal cysts- renal angiomyolipoma
- Renal cysts- histologic
- Hamartomatous rectal polyps
- Gingival fibromas
Tuberous Sclerosis
Cutaneous Manifestations

- Hypomelanotic macules - 90%
- Shagreen patch - 20 - 30%
- Ungual fibroma - 15 to 20%
- Facial angioma (adenoma sebaceum) - 75%
- Forehead plaque
- “Confetti” hypopigmented skin lesions
- Gingival fibromas
- Poliosis
Tuberous Scleriosis
Hypopigmented Macule
Tuberous Sclerosis
Hypopigmented Macule - Wood's Lamp
Tuberous Sclerosis
Early Adenoma Sebaceum
Tuberous Sclerosis
Late Adenoma Sebaceum
Tuberous Sclerosis
Ungual Fibroma
Tuberous Sclerosis
Shagreen Patch
Tuberous Sclerosis
Shagreen Patch
Tuberous Sclerosis
Other Manifestations

- **Cardiovascular**
  - cardiac rhabdomyomata - 30 to 50%
  - cardiac arrhythmia
  - cardiac thromboembolism

- **Renal**
  - renal angiomyolipomas
  - renal cysts

- **Pulmonary**
  - 1%, females > males
  - pulmonary lymphangiomyomatosis
  - symptoms include pneumothorax, dyspnea, cough, hemoptysis, and pulmonary failure.
Tuberous Sclerosis Neurologic Manifestations

- Seizures- often infantile spasms
- Mental retardation and autistic-like behavior- 60%
- Focal neurologic deficits
- Brain tumors
  - 6-14% of TSC patients
  - giant cell astrocytoma
Tuberous Sclerosis Gene Function

- Tumor suppressor genes
- Hamartomas of tuberous sclerosis patients show loss of heterozygosity
- Sequence homologies at the protein level reveal a region of similarity between tuberin and the GTPase activating protein GAP3
TS and Adjacent Genes

- A contiguous deletion that affects both TSC2 and PKD1 genes results in early onset polycystic kidney disease.
- Some patients with contiguous deletions are milder because of somatic mosaicism.
Sturge Weber
Sturge-Weber Syndrome

- Unilateral or bilateral facial angioma in the distribution of the first branch of the trigeminal nerve
- Ipsilateral intracranial vascular anomalie of the capillaries and venules of the leptomeninges
- Glaucoma
Sturge-Weber Syndrome MRI
Sturge Weber Neurological Complications

- Hemiparesis
- Seizures
- Developmental Delay
- Headaches
Wyburn Mason Syndrome

- An uncommon disorder characterized by a vascular malformation of the midbrain associated with a unilateral retinal AVM, facial nevi, and mental changes
Wyburn Mason Syndrome

- Arteriovenous malformations of the retina and central nervous system
- Rare
- No sex predilection
- Variable neurological abnormalities
Wyburn-Mason Syndrome

Retina showing dilated vasculature in a child with reduced vision, seizures and facial vascular lesions.
von Hippel Lindau Disease

- Diagnostic Criteria
  - One or more hemangioblastomas either at the same or different sites
  - Other visceral lesions
  - Familial tumors

- Urinary metanephrine level, and VMA are elevated.
Klippel-Trenuanway-Weber Syndrome

- An uncommon neurocutaneous disorder characterized by extensive skin hemangiomas appearing in a dermatomal pattern, and associated with hemangiomas of the spinal cord.
- The lesions are unilateral and are often associated with osseous or muscular hypertrophy of the involved area. This may be a spinal variant of Sturge-Weber. Pattern of inheritance unknown.
Osler-Weber - Rendu Syndrome

- An uncommon disorder characterized by angiomas of the skin, mucous membranes, and nervous system.
- Autosomal dominant disorder
- Development of multiple small red or purple angiomas. These enlarge and may be the source of recurrent epistaxis or GI or GU hemorrhages.
- Scattered angiomas may develop in the brain or spinal cord, producing hemorrhage or localized cerebral spinal dysfunction.
Linear Sebacious Nevus
Linear Nevus Sebaceous Syndrome

- Linear patches of yellow papules
- Mental retardation
- Seizures
- Hemiparesis
- Ocular abnormalities- microphthalmia, anophthalmia, choristomas, and colobomata of lids, iris, choroids and optic nerve.
Linear Nevus Sebaceus Syndrome

- Brain Abnormalities
  - Hemiatrophy
  - Lipomas
Congenital Nevus

- Congenital nevi are melanocytic nevi present at birth.
  - They are probably best recognized as the large bathing suit nevi that may cover large portions of the body.
- Giant congenital nevi
  - Infant - usually larger than 6 cm on the trunk, 9 cm on the scalp.
  - Adult - greater than 20 cm in its largest diameter in an adult.
- The management of these larger lesions is controversial.
Neurocutaneous melanosis and encephalocraniocutaneous lipomatosis

Neurocutaneous melanosis and encephalocraniocutaneous lipomatosis

Funduscopic View- Right eye fundoscopic view demonstrating multiple large chorioretinal lacunae.
NEUROCUTANEOUS MELANOSIS

- **Signs**
  - Hydrocephalus
  - Macrocephaly
  - Increasing head circumference
  - Bulging fontanelle
  - Seizures
  - Developmental delay

- **Symptoms**
  - Headache
  - Vomiting
  - Failure to thrive
  - Weakness
  - Gait abnormalities
  - Bladder or bowel dysfunction
Neurocutaneous Melanosis

- Diagnosis
  - presence of neurologic symptoms
  - increased number of melanocytes within the central nervous system associated with large cutaneous nevi or multiple smaller nevi.

- CNS melanocytes are usually found in the anterior temporal lobes, cerebellum, thalami, and base of the frontal lobe
Large Congenital Melanocytic Nevus Malignancy Risk

- Lifetime risk for melanoma estimated between 4.5-10%
- 5 year cumulative risk of 2.3% and relative risk of 101
- If melanoma develops, >50% develop <5 years and 70% by age 10
- Greater risk occurring on the axial site (head, neck, and/or trunk)
- No reports of melanomas arising in nevi restricted to an extremity or within congenital satellite nevi

J Am Acad Dermatol 1997;36:409-416
Arch Dermatol 1996;132:170-175
Pediatrics 2000;106:736-741
ASSOCIATED FINDINGS WITH GIANT CONGENITAL MELANOCYTIC NEVI

- **LOCAL CHANGES**
  - Loss of subcutaneous fat
  - Limb hypoplasia

- **MALIGNANCIES**
  - Rhabdomyosarcoma
  - Liposarcoma
  - Neuroblastoma
  - Primitive neuroectodermal tumors
  - Mixed malignant neoplasms

- **MALFORMATIONS**
  - Vascular
    - Supernumerary digits
    - Ear deformities
    - Preauricular appendages
    - Cryptorchidism
    - Club feet
Treatment of Giant Congenital Melanocytic Nevi

- **Dermabasion**
  - 12 patients treated between the first and fourteenth week of life.
    - 10- appreciable and stable reduction of the hyperpigmentation.
    - 6- reconstruction using grafts and flaps was required.
    - 1- developed minimal deviation melanoma

- **Curettage**
  - 16 patients treated during first 2 weeks of life
    - All had good cosmetic outcome
    - No melanoma


Arch Dermatol 2002 Jul;138(7):943-7
Waardenburg Syndrome
Type 1 & 2

- **Major criteria**
  - Congenital sensorineural hearing loss
  - Pigmentary disturbances of iris
  - Complete heterochromia iridum, two eyes of different color
  - Partial or segmental heterochromia; segments of blue or brown pigmentation in one or both eyes
  - Hypoplastic blue eyes, characteristic brilliant blue in both eyes
  - Hair hypopigmentation, white forelock
  - Dystopia canthorum, $W > 1.95$ averaged over affected family members (this was modified from the original proposal of $W > 2.07$ in the light of experience)
  - Affected first degree relative
Waardenburg Syndrome Type 1 & 2

- **Minor criteria**
  - Congenital leukoderma, several areas of hypopigmented skin
  - Synophyrys or medial eyebrow flare
  - Broad and high nasal root
  - Hypoplasia of alae nasi
  - Premature greying of hair, scalp hair predominantly white before age 30
Please Remember

- No matter how hard you try, you can't baptize cats.
- Never lick a steak knife.
Klippel-Tre´naunay Syndrome
Lymphatic Involvement

- **Definite:**
  - Lymphangioma circumscriptum
  - Macrocystic disease seen on MRI
  - Malformation of lymphatics on lymphoscintigraphy

- **Probable:**
  - Pseudoverrucous lymphedema changes or lymphedema
  - Recurrent cellulitis
  - Vascular ectasias (blebs)
  - Verrucous changes over stain

- **Possible:**
  - One episode of cellulitis
  - Non-pitting edema
  - No LM:
  - Lacking any of the features above
Fabry's Disease

- Caused by a deficit in alpha-galactosidase leading to an accumulation of ceramide trihexoside in the endothelium and media of blood vessels. Although the skin lesions are diagnostic, the vascular involvement tends to be more diffuse.

- An X-linked recessive disorder found mostly in males. Females tend to be asymptomatic heterozygotes who can be diagnosed by assaying alpha-galactosidase activity.
Fabry's Disease

- Neurologic involvement consists of a painful polyneuropathy caused by ceramide trihexoside deposition both perineurally and intraneurally. Cerebral thromboembolic lesions may be seen early in teens.
Fabry's Disease

- Angiokeratoma corporis diffusum a genetic disorder of the nervous system, and skin.
- Multiple small, flat, or slightly raised telangiectases on the abdomen and lower extremities.