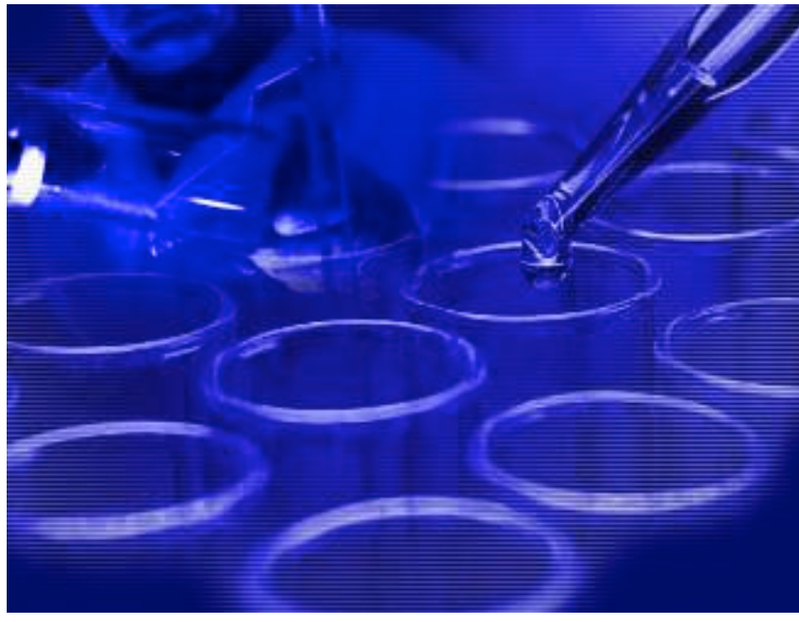
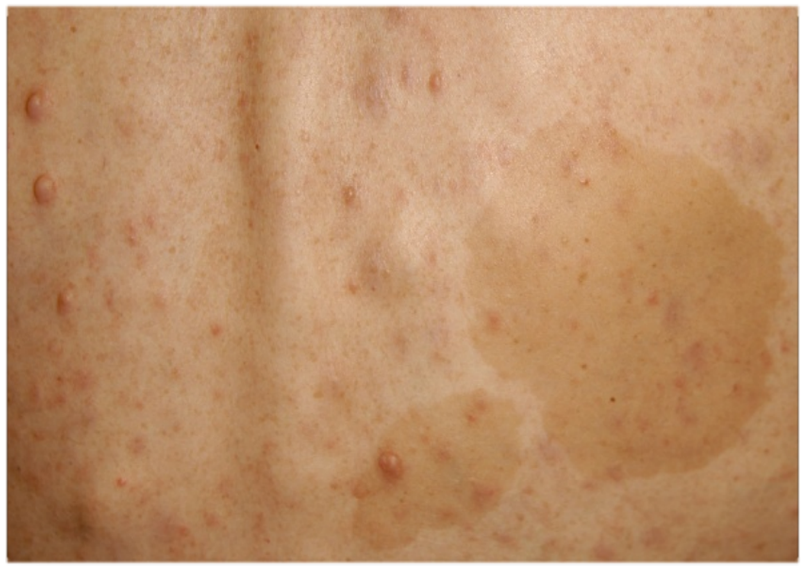
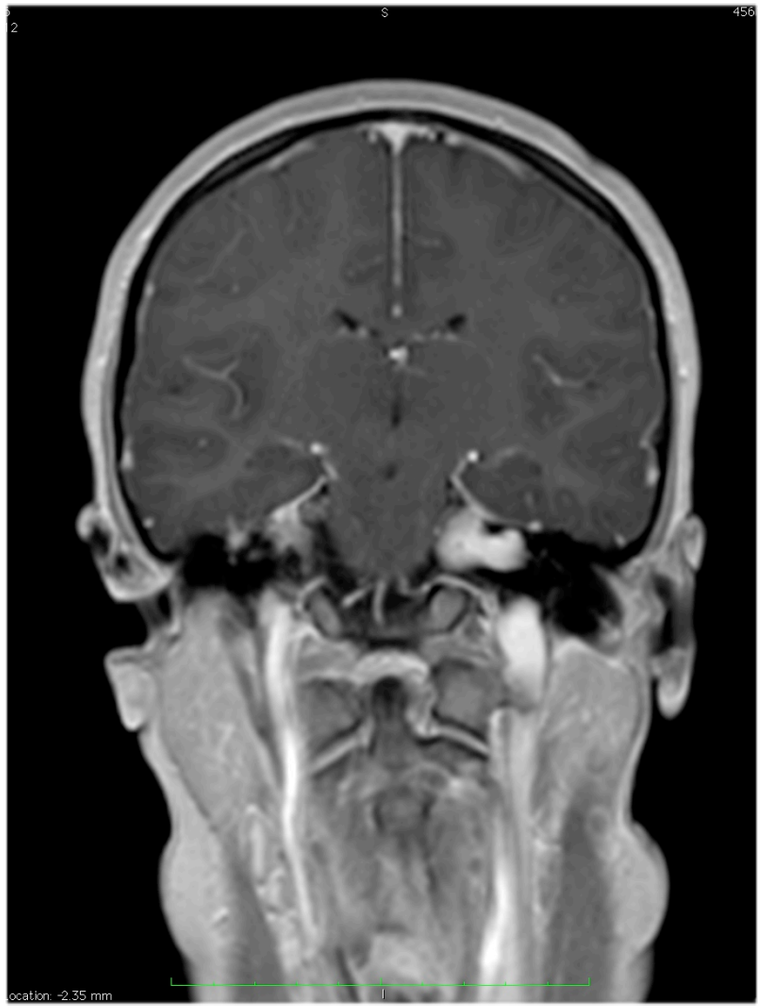
Advances in Diagnosis and Treatment of NF1

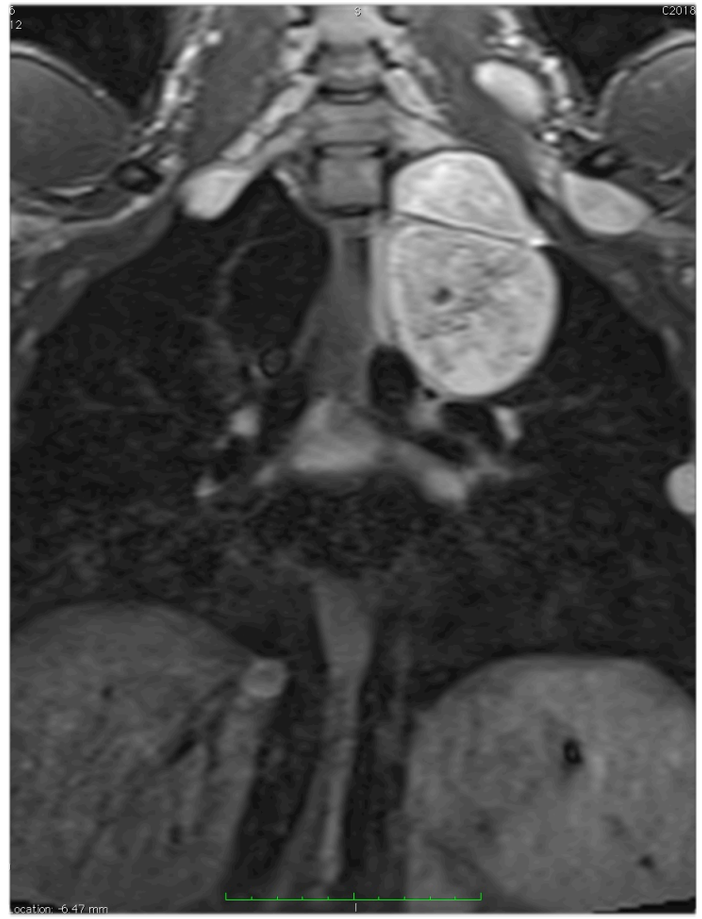


Bruce R. Korf, MD, PhD
Department of Genetics
University of Alabama at Birmingham

The Neurofibromatoses







NF1 →

CHROMOSOME 17

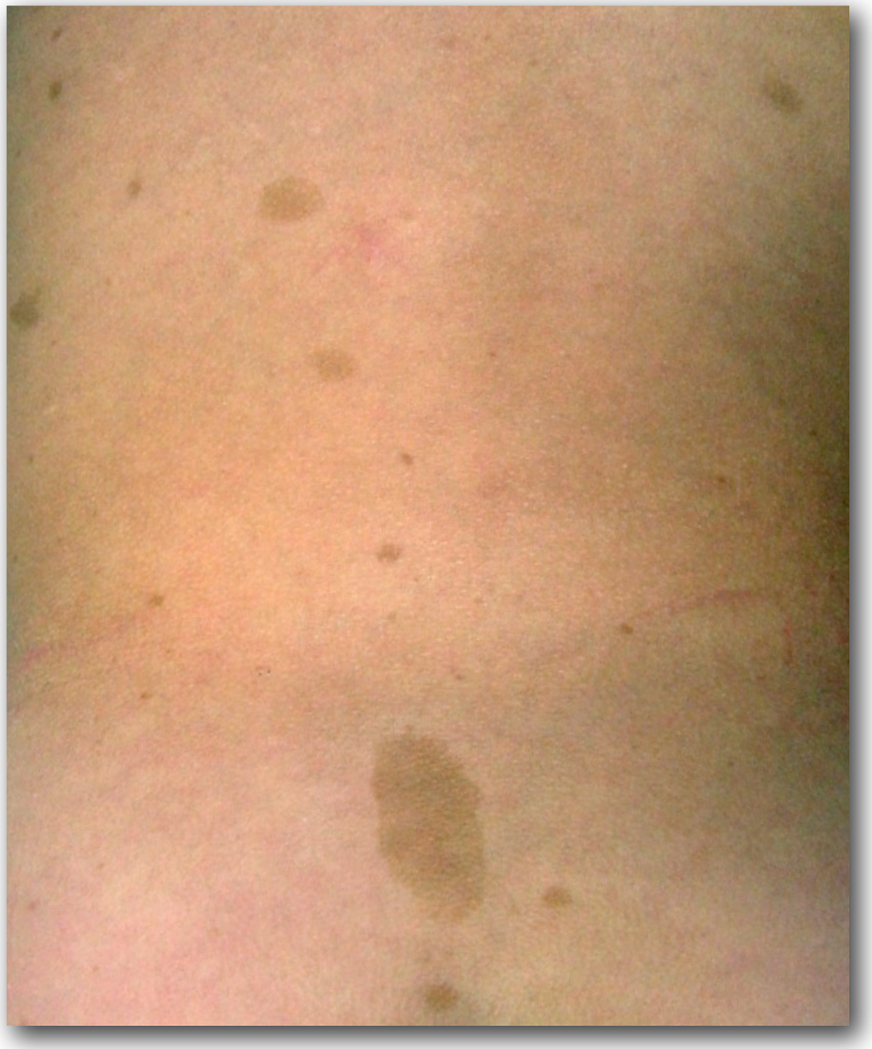
NF2 →

← SCHWANNOMATOSIS

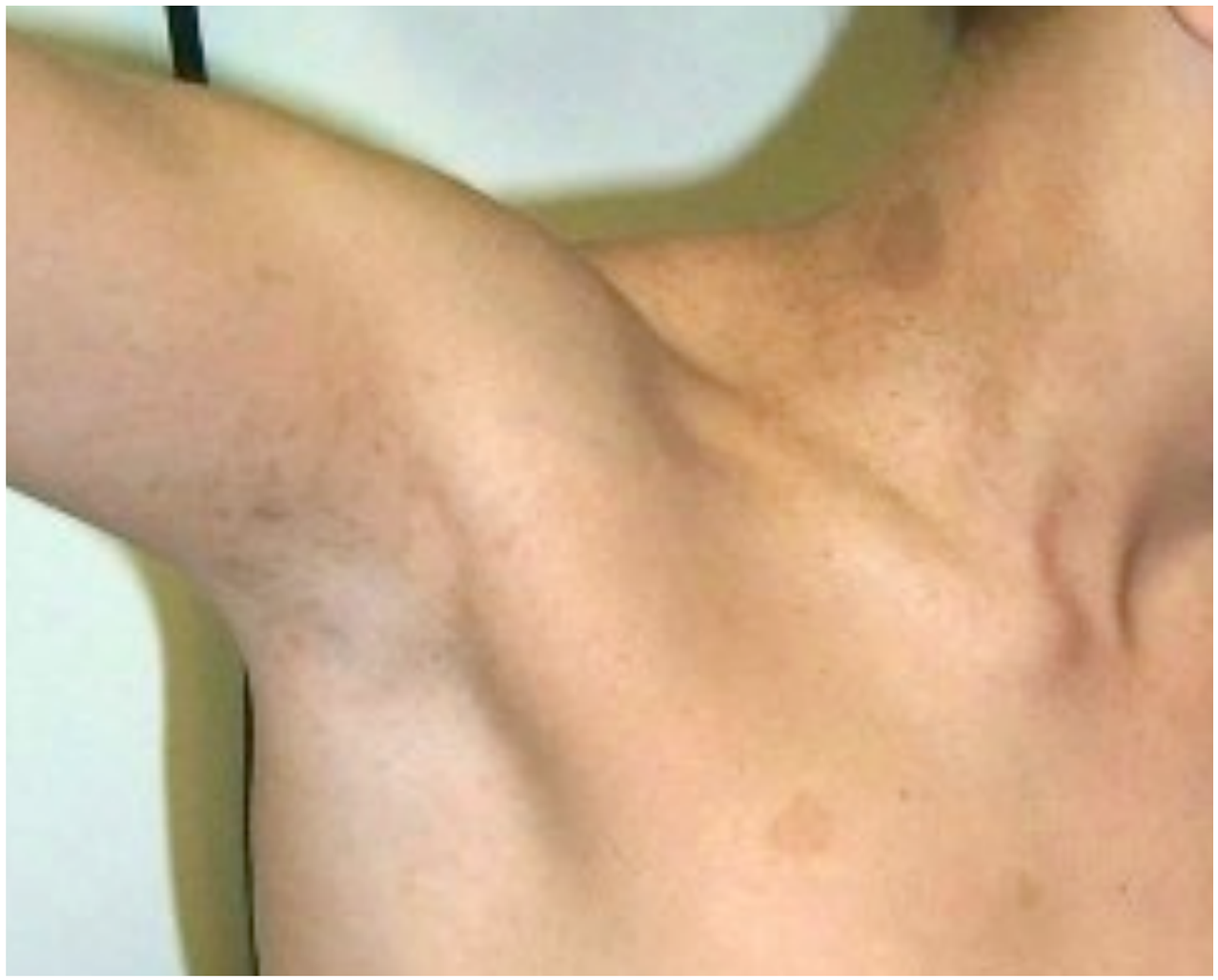
NF1 Diagnostic Criteria

- Cafe-au-lait macules (≥6, 5 mm prepuberty, 15 mm post-puberty)
- Skin fold freckles
- Neurofibromas (≥2 or one plexiform)
- Iris Lisch nodules (≥2)
- Optic glioma
- Skeletal dysplasia (tibial or orbital)
- Affected first-degree relative

Pigmentary Signs

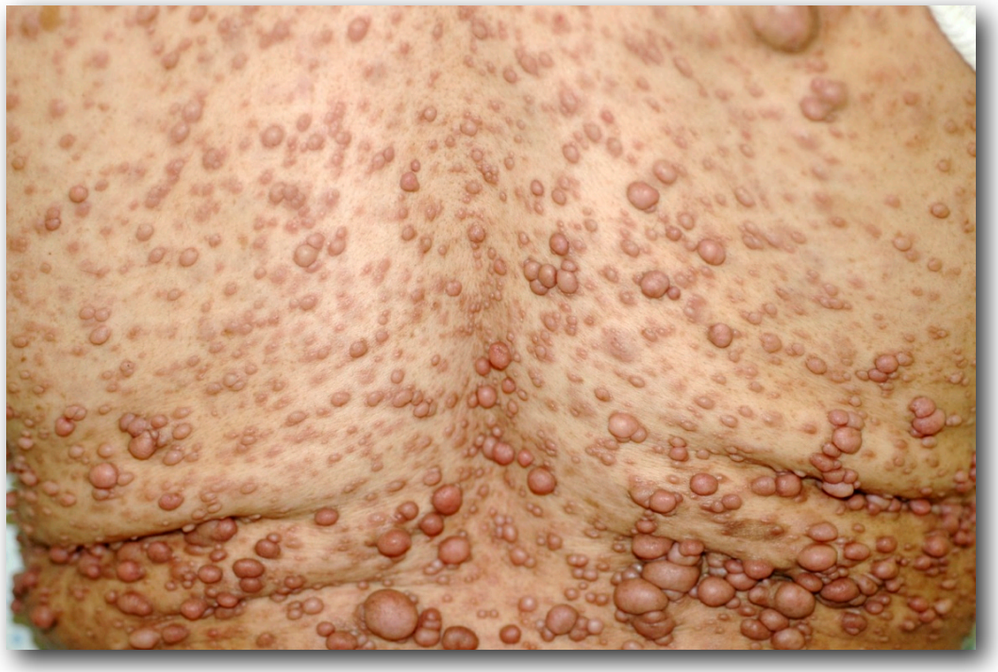


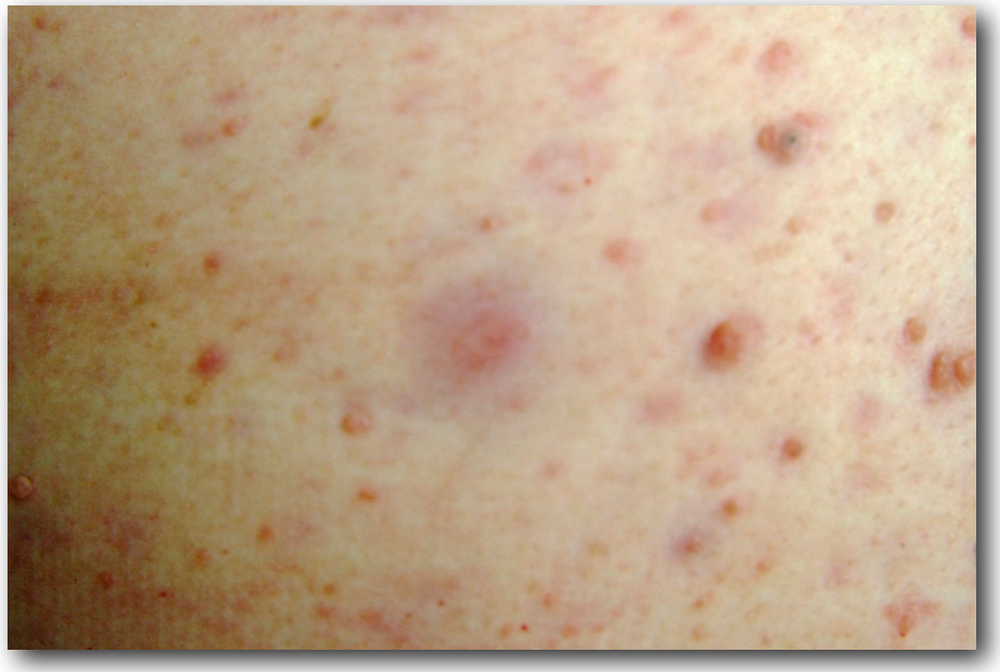
café-au-lait spots

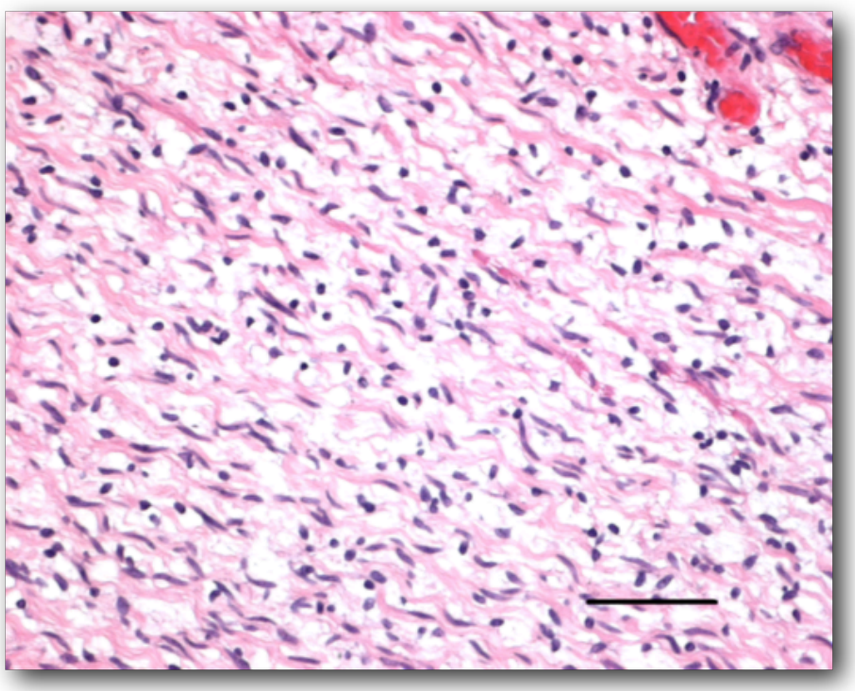


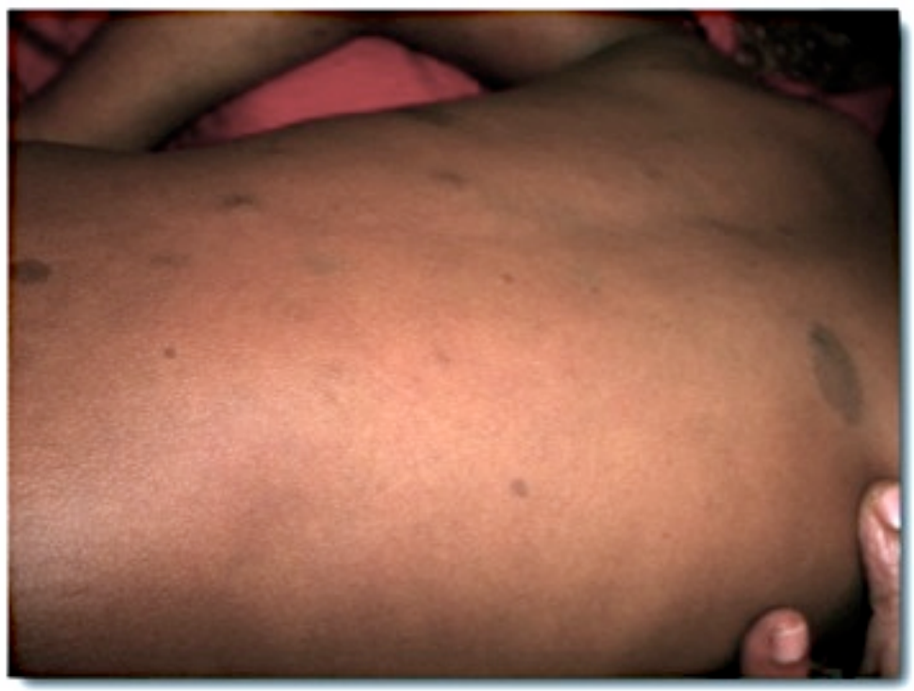
skin fold freckles

Neurofibromas

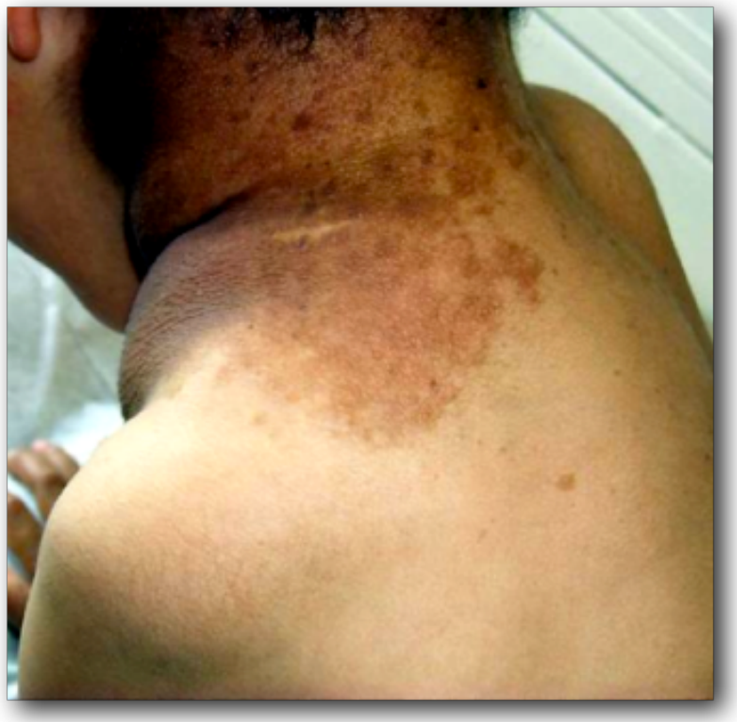


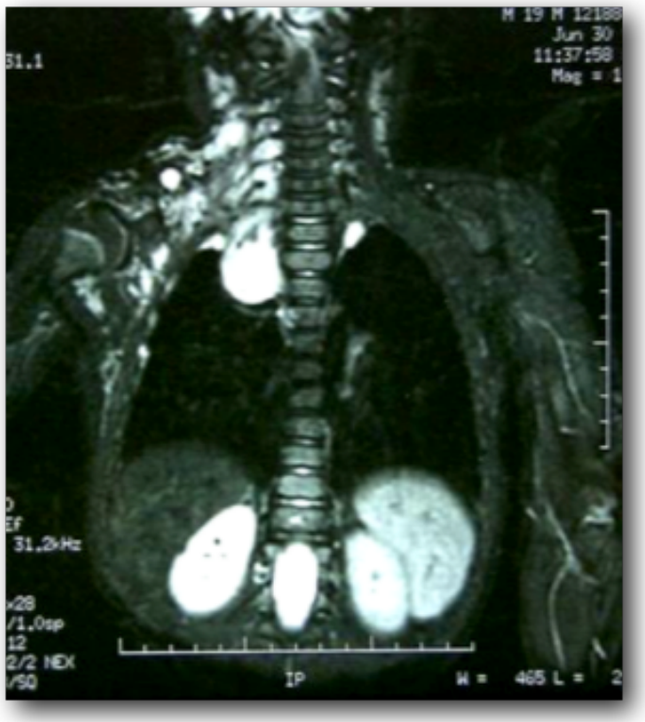


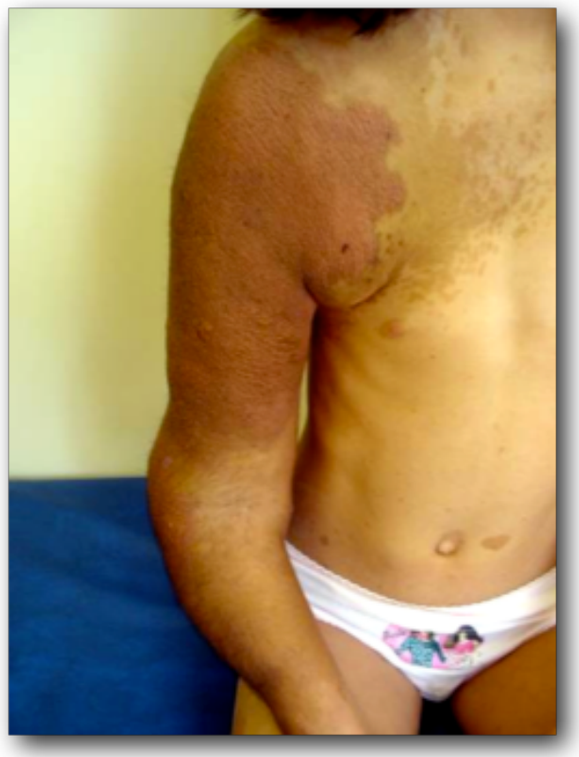


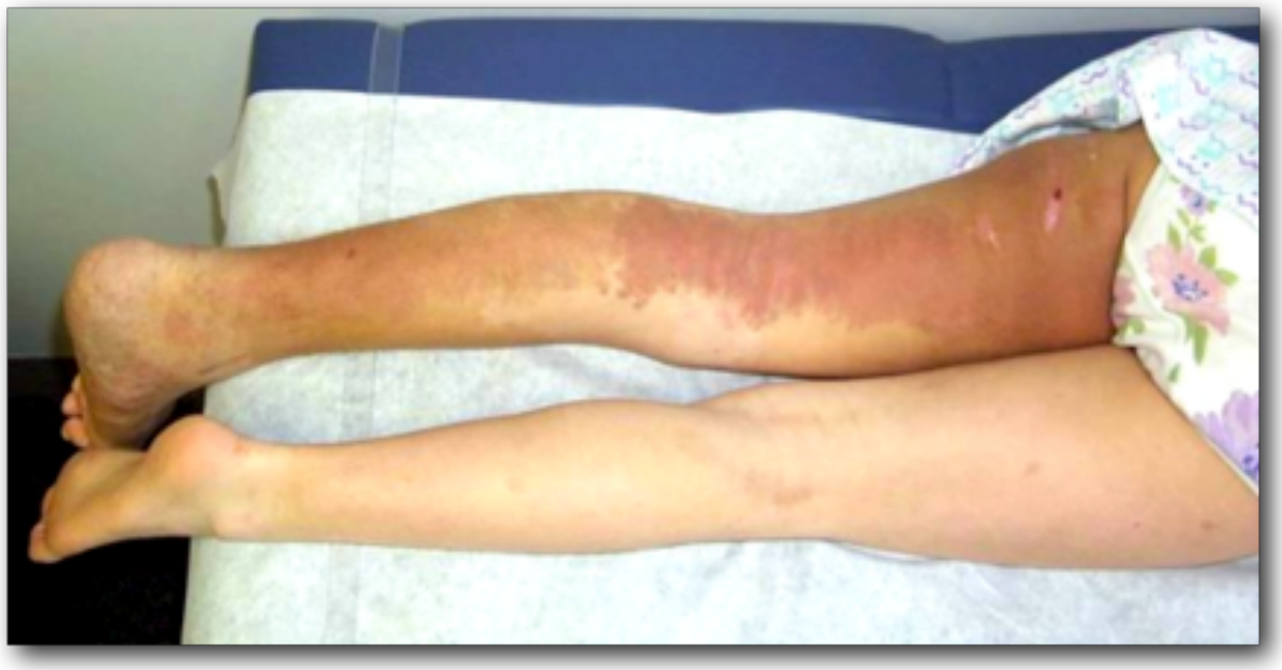


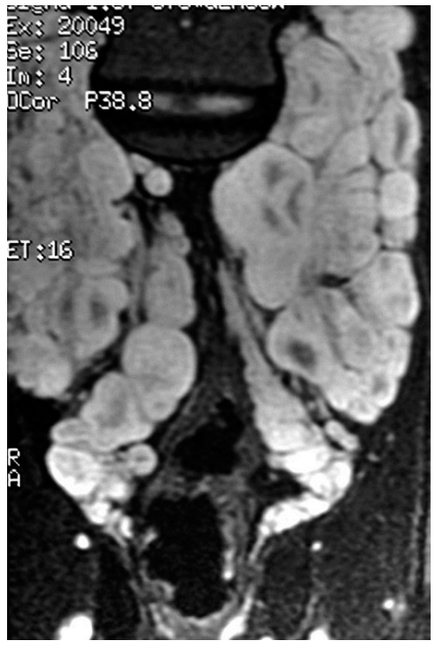
Plexiform Neurofibroma



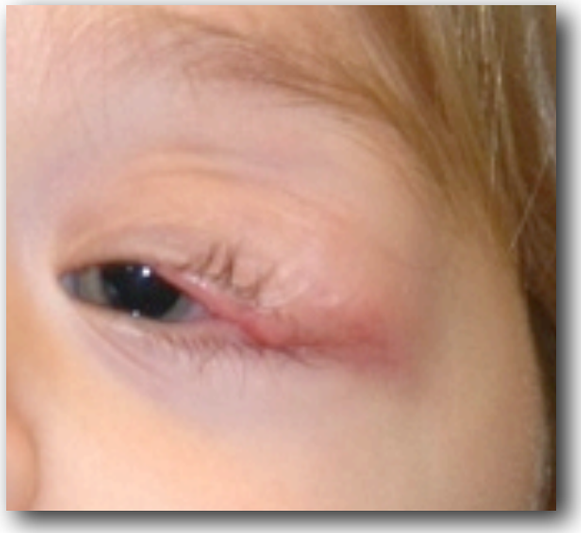


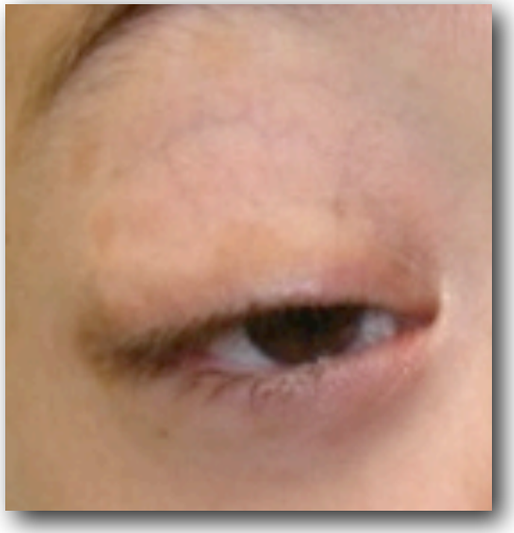


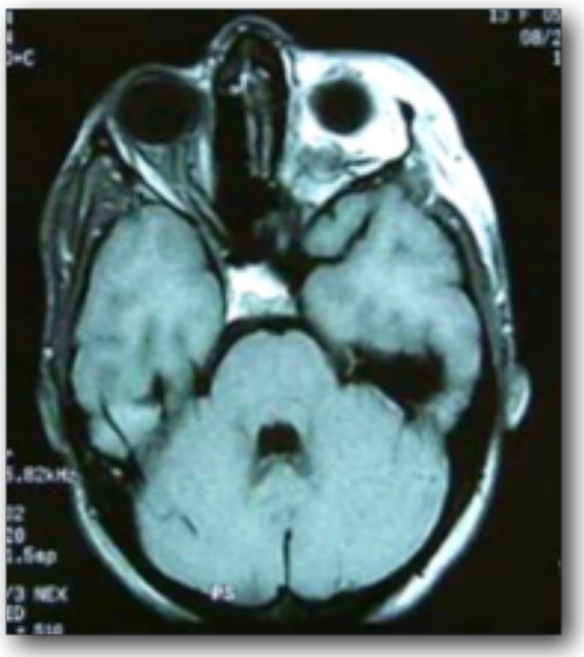


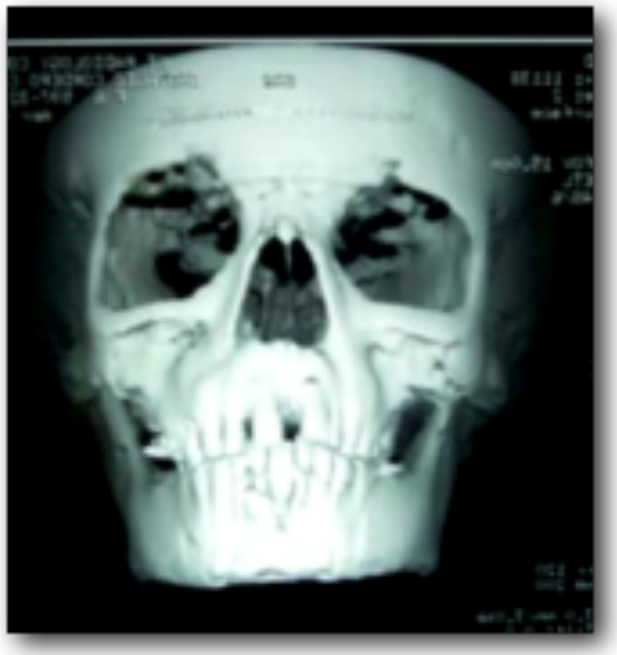


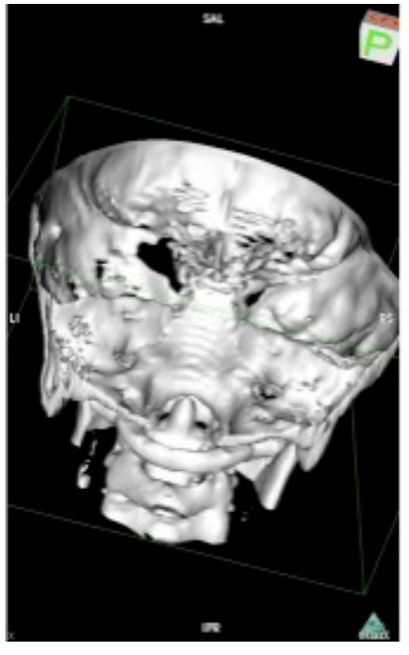
Orbital Plexiform Neurofibroma





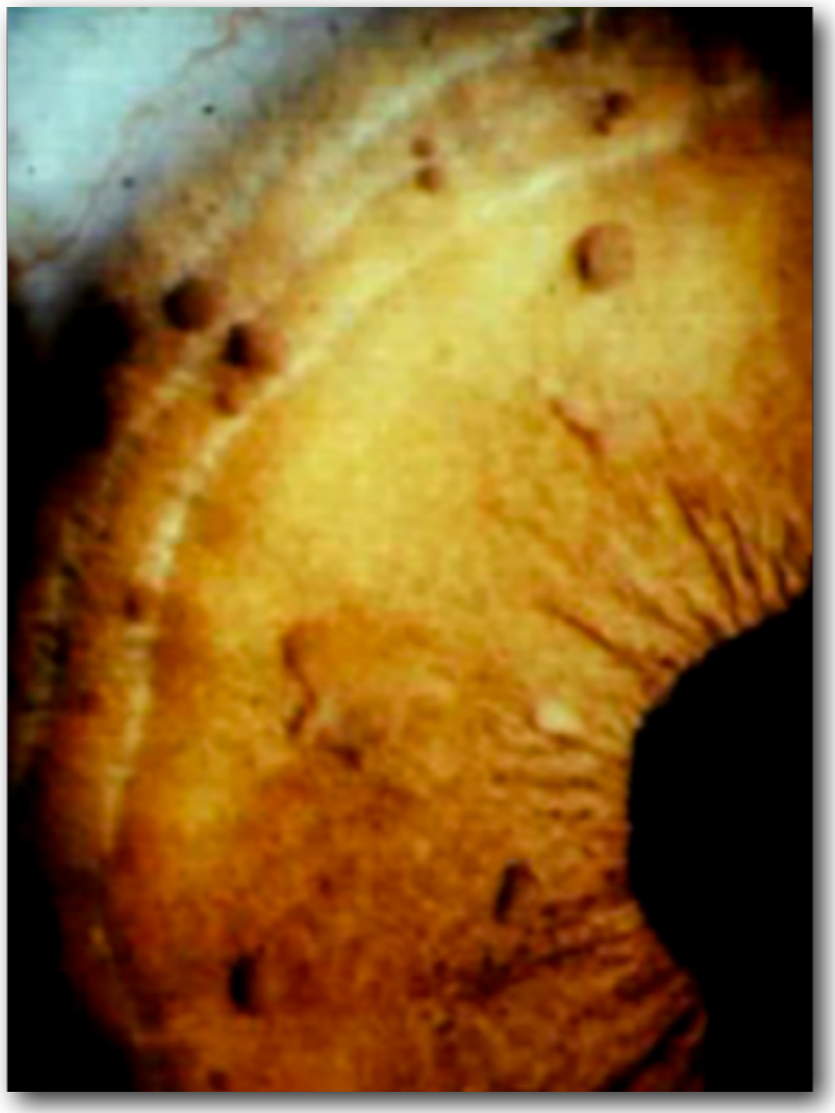




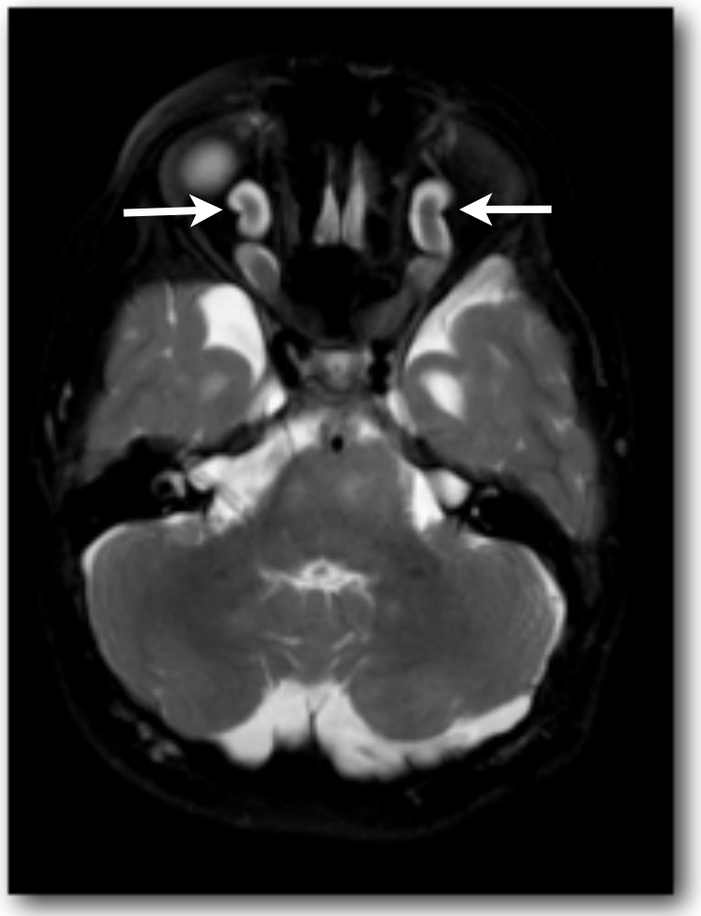


Lisch Nodules

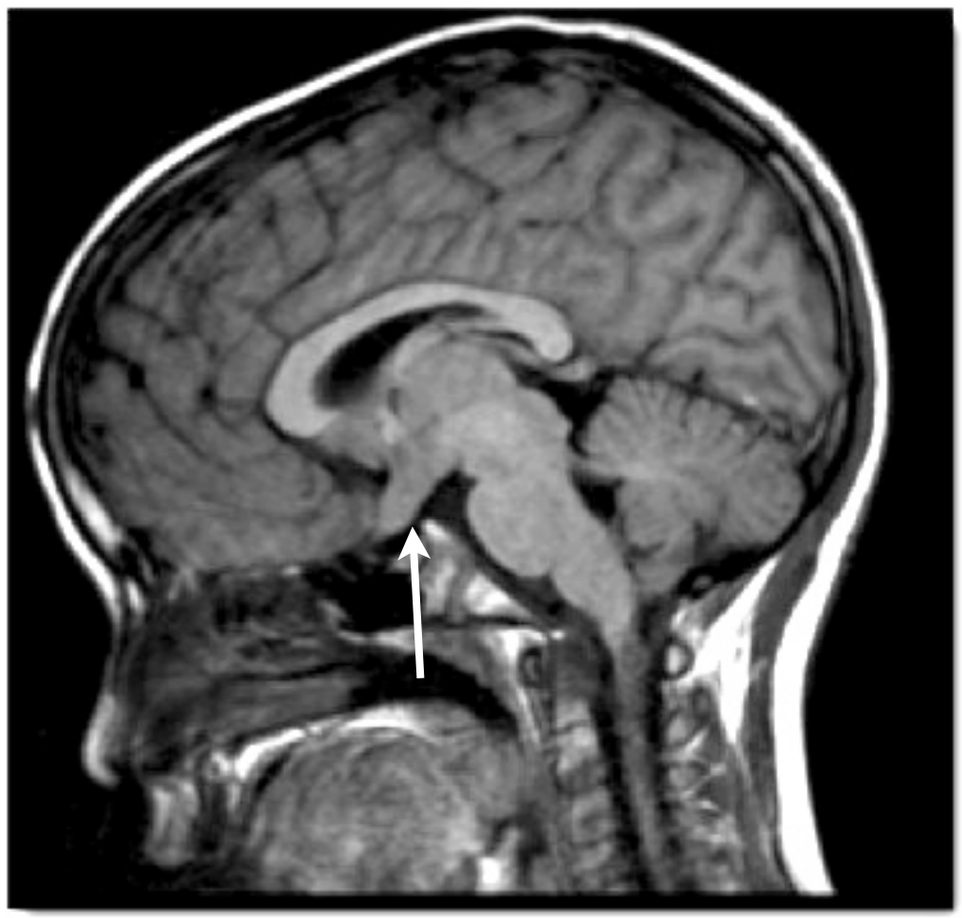
- appear after age 6 years
- melanocytic hamartomas
- no effect on vision
- require slit lamp



Optic Glioma

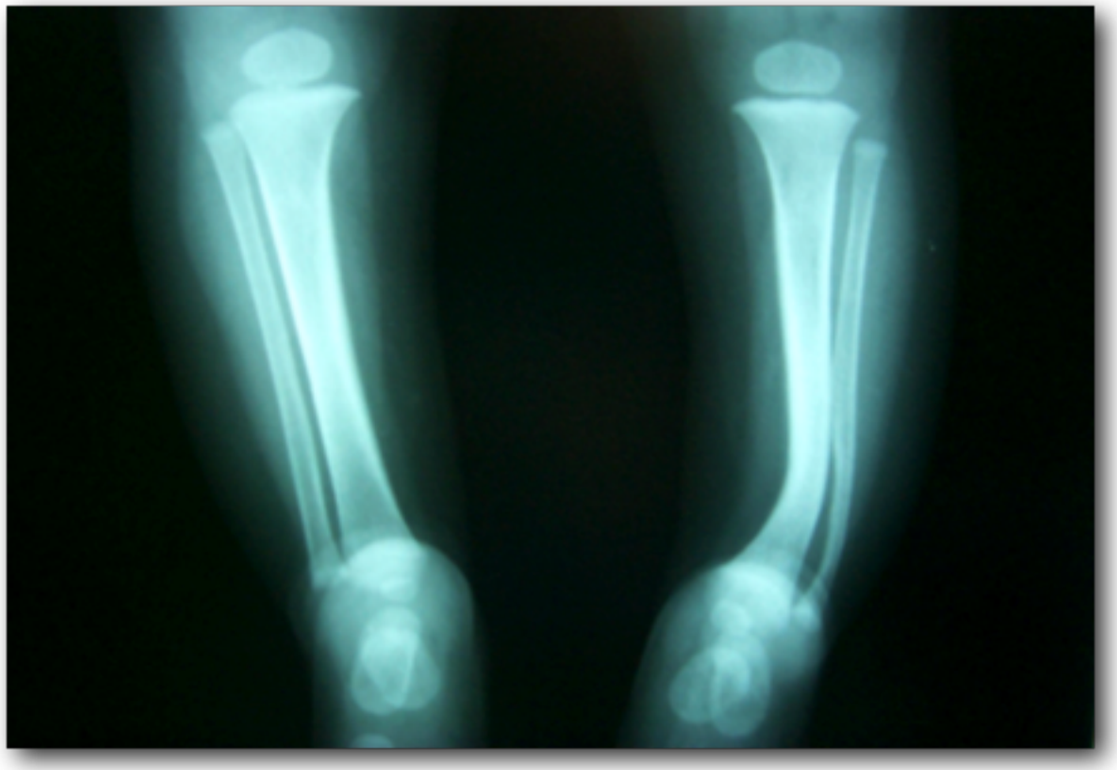


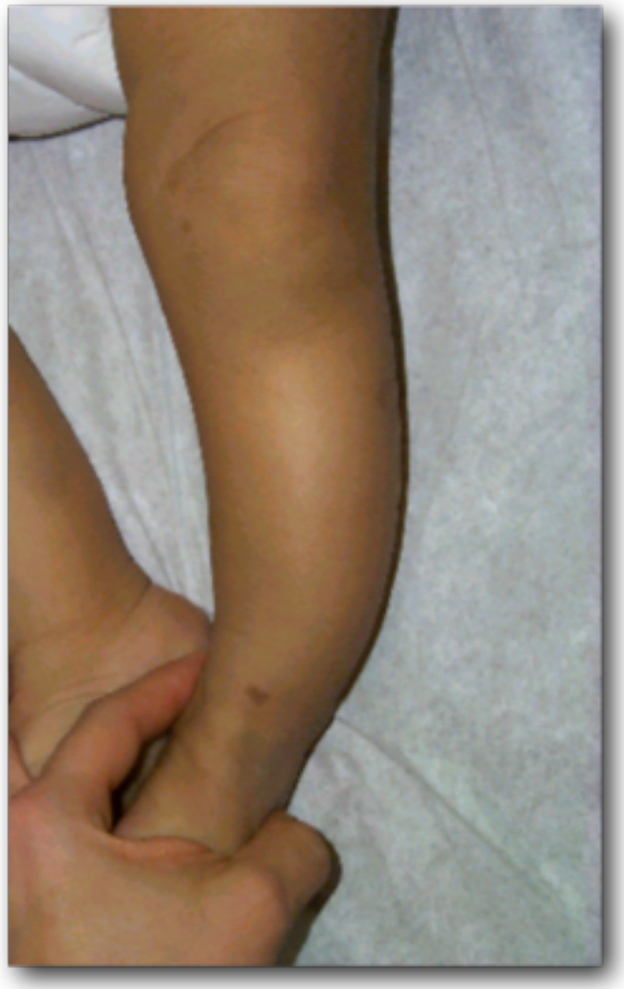
orbital



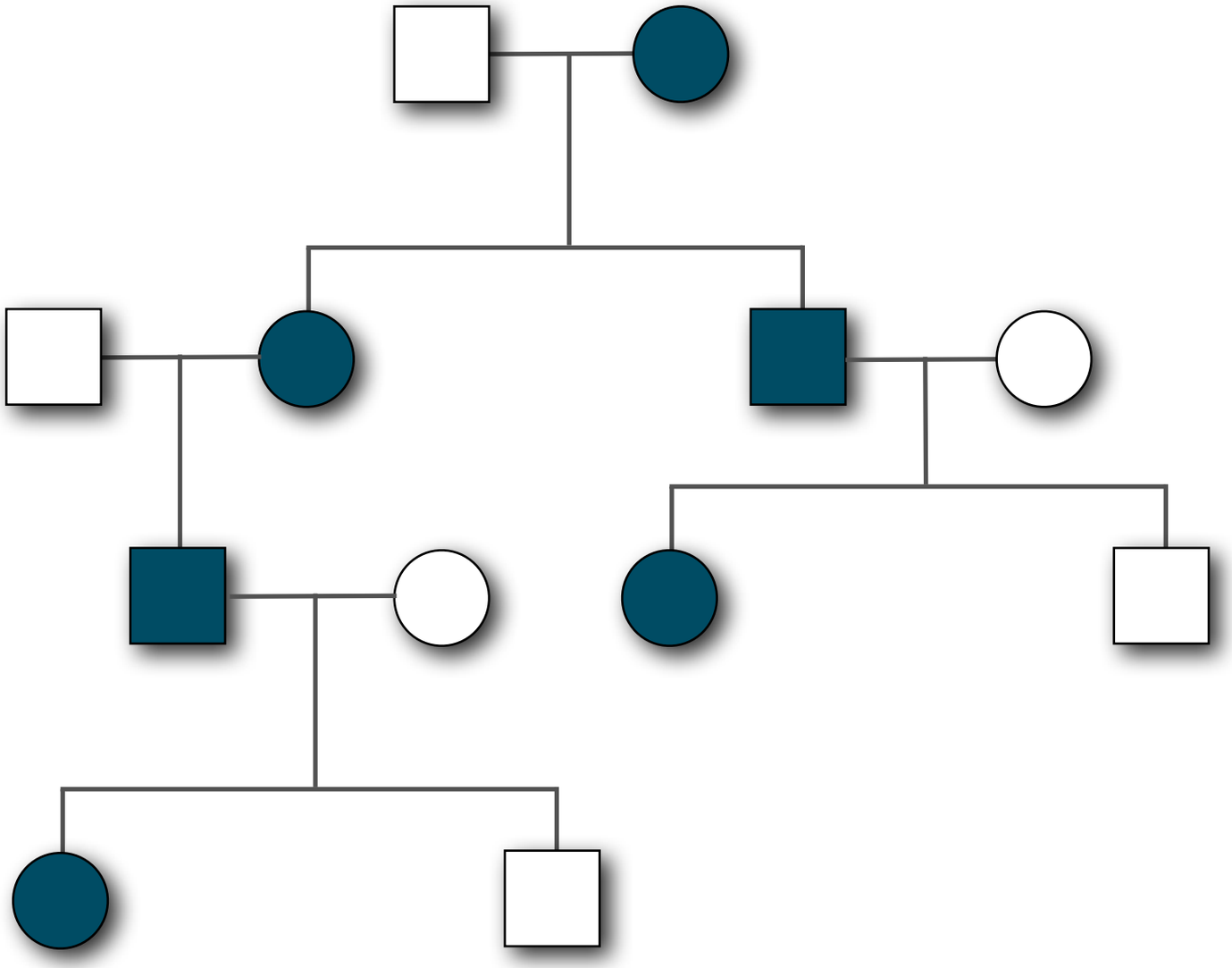
chiasm

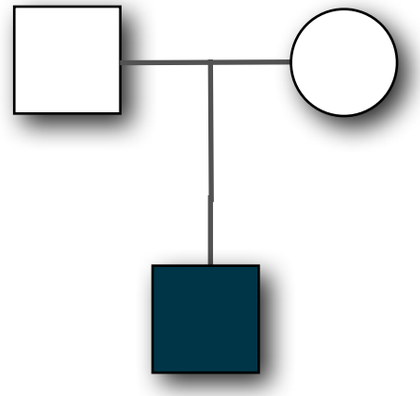
Skeletal Dysplasia





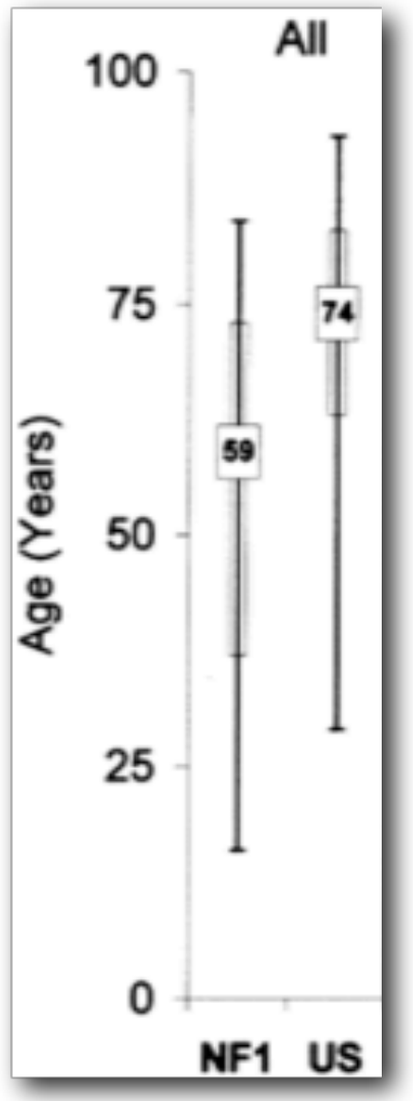
Genetic Transmission





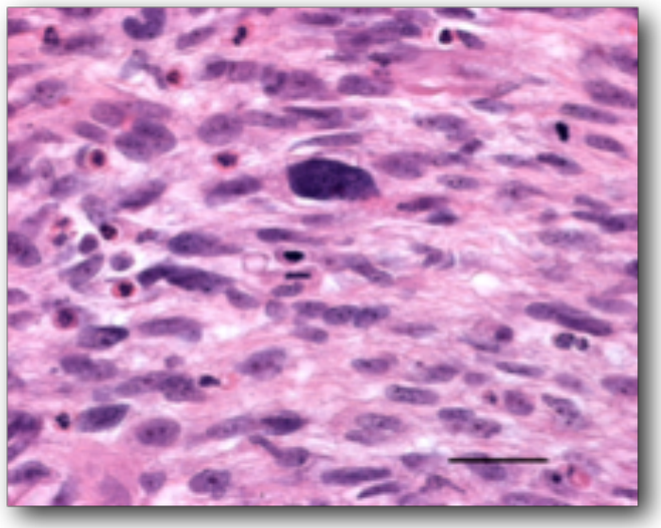
Life Expectancy

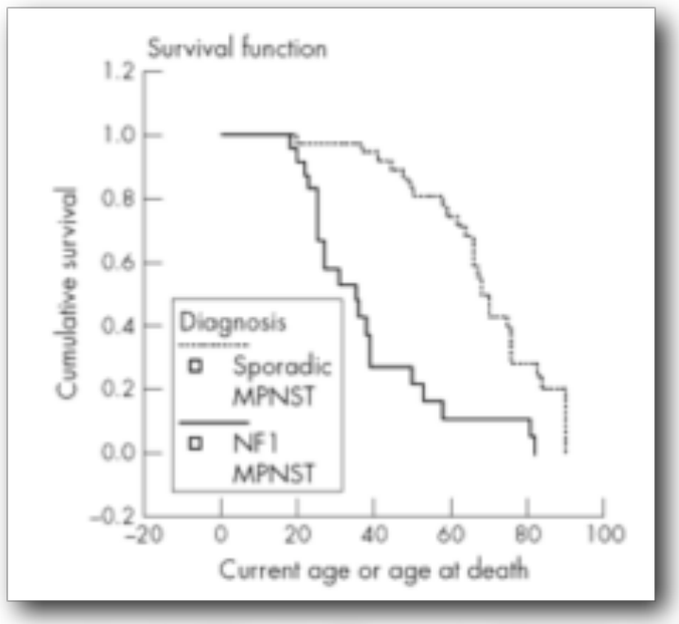
- Malignancy
  - MPNST
- Vascular dysplasia
  - renal artery stenosis
  - moya moya
  - dissection



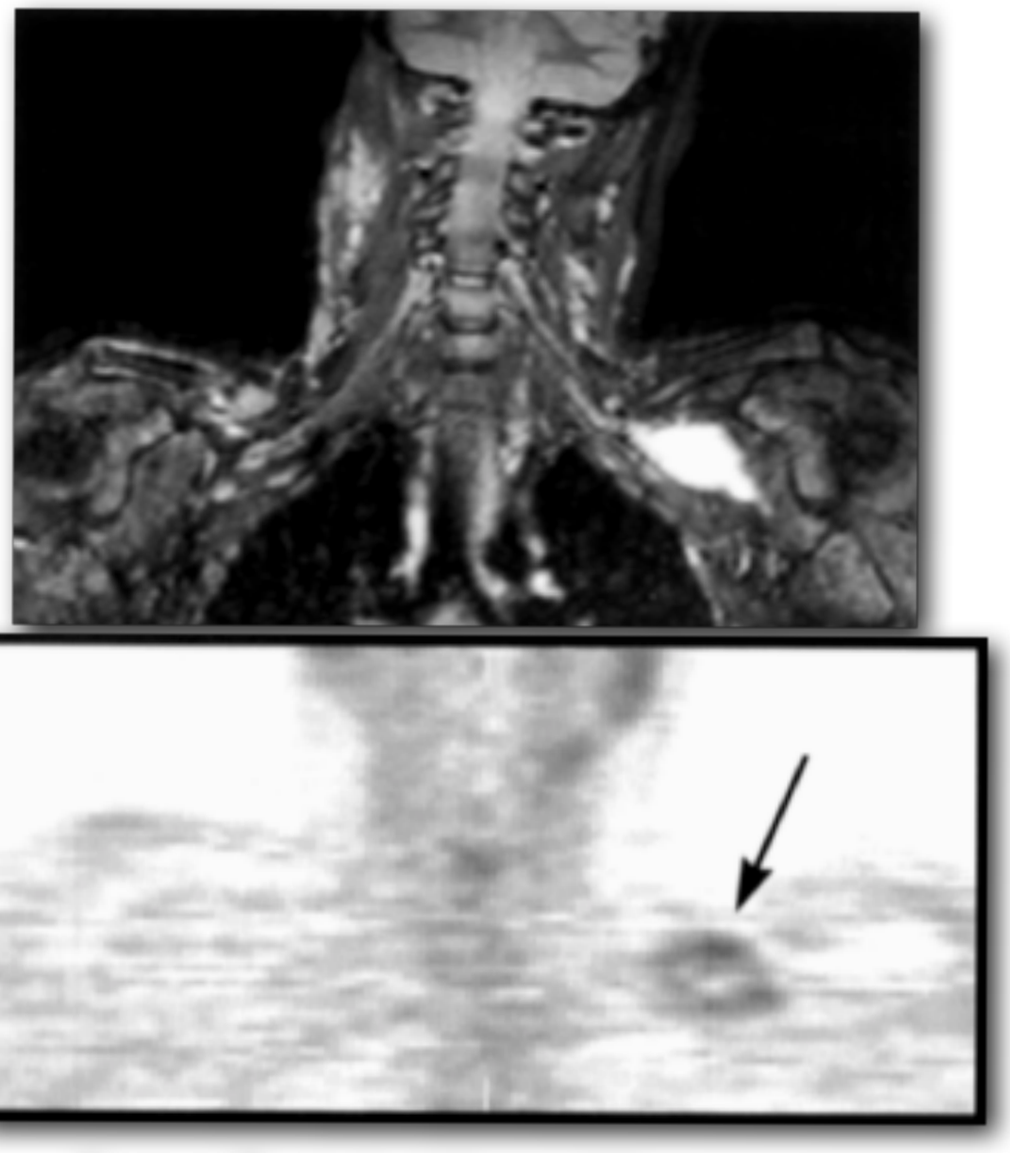
Rasmussen et al. *Am. J. Hum. Genet.,* 68:1110-1118, 2001

MPNST



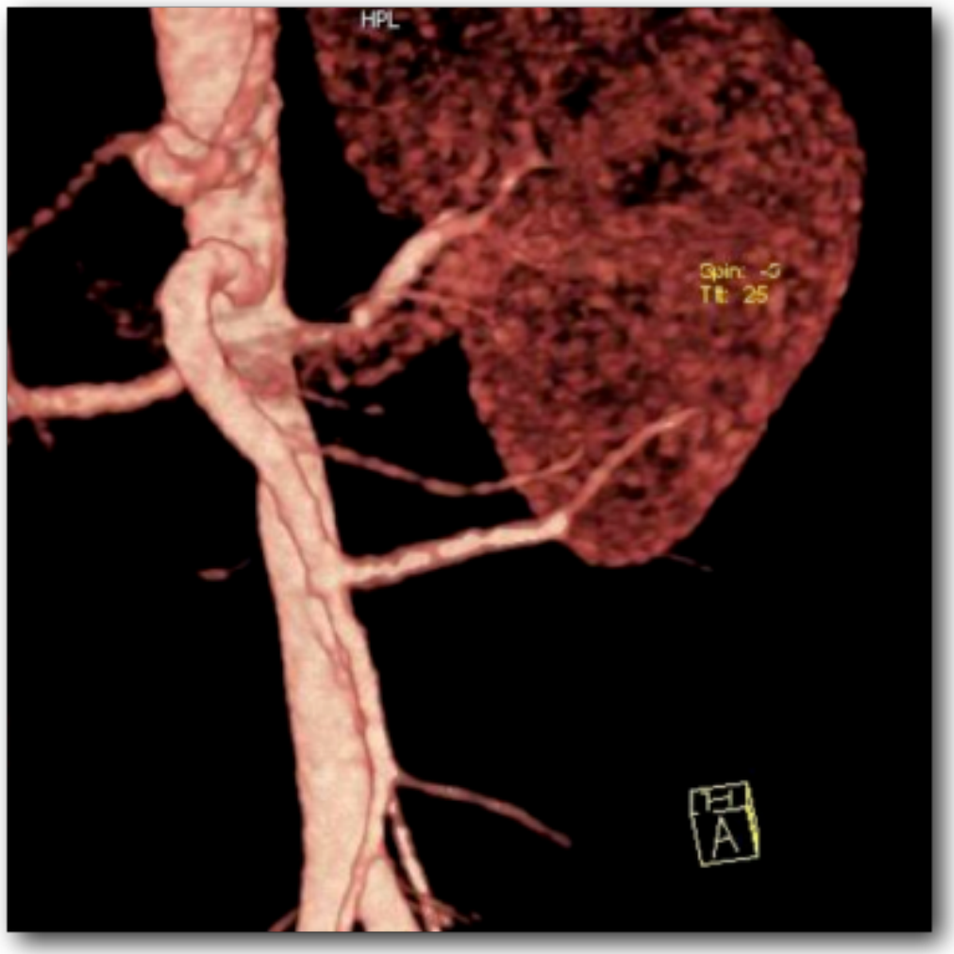


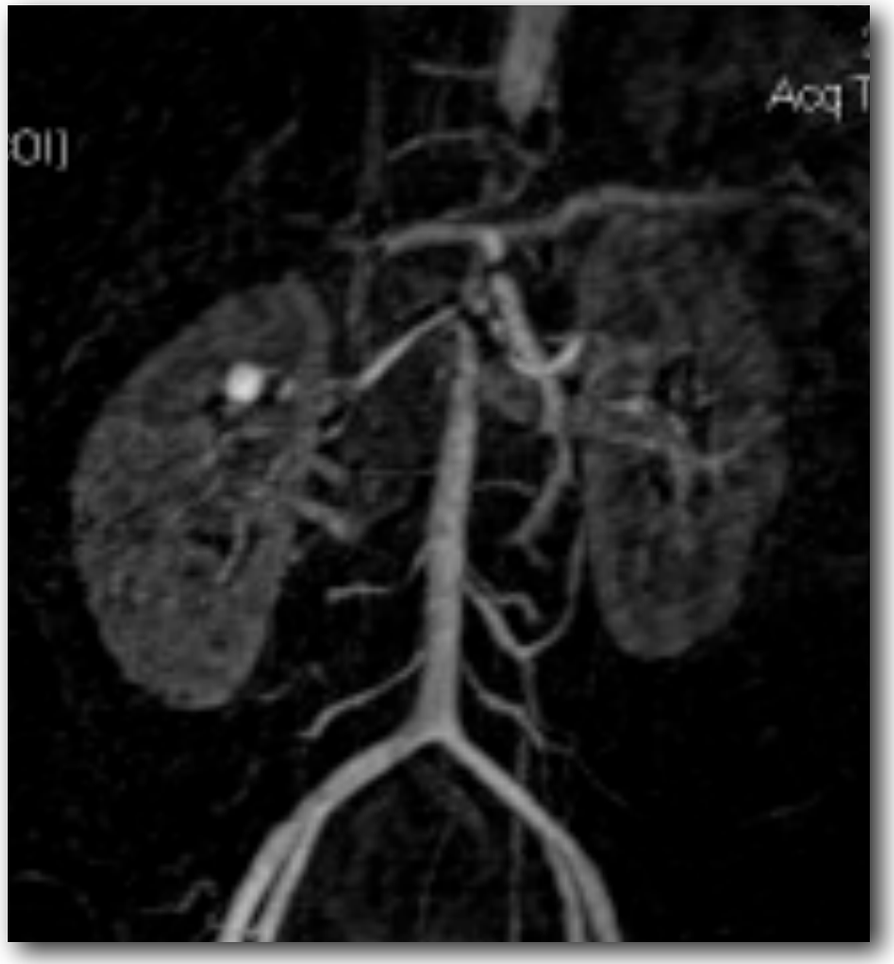
Evans et al., J. Med. Genet. 2002; 39:311.



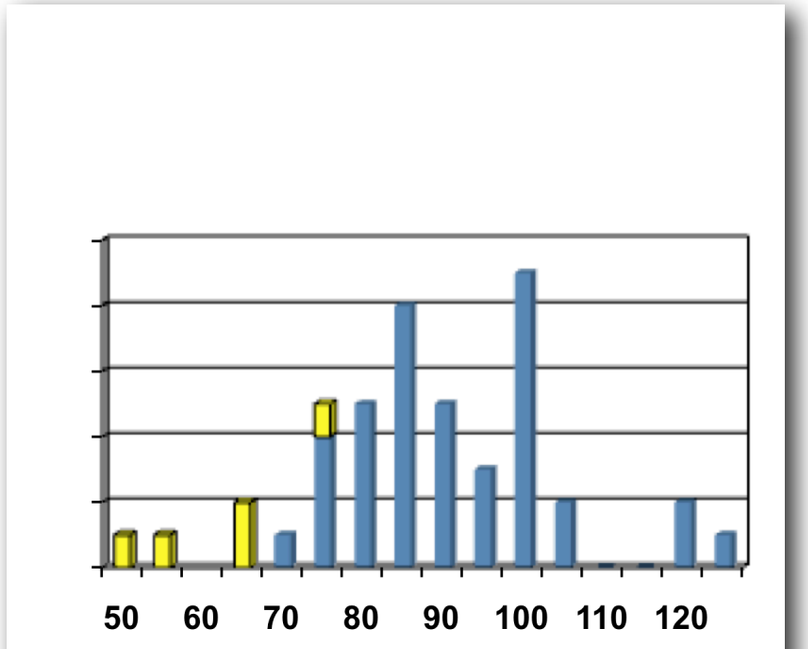
Ferner R et al. *J Neurol Neurosurg Psychiatry* 2000;**68:**353-357)

Vascular Dysplasia

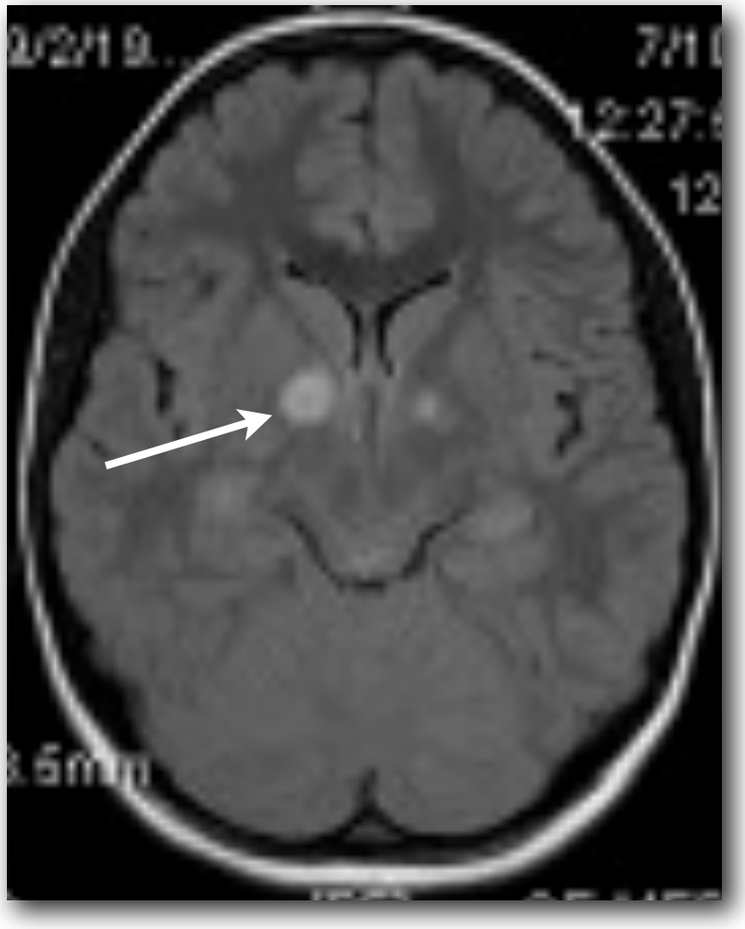




Neurocognitive Dysfunction



North et al., Neurology 44:878, 1994.



Natural History

- plexiform neurofibroma
- tibial dysplasia

- optic glioma
- Lisch nodules
- learning disability
- hypertension
- short stature
- macrocephaly

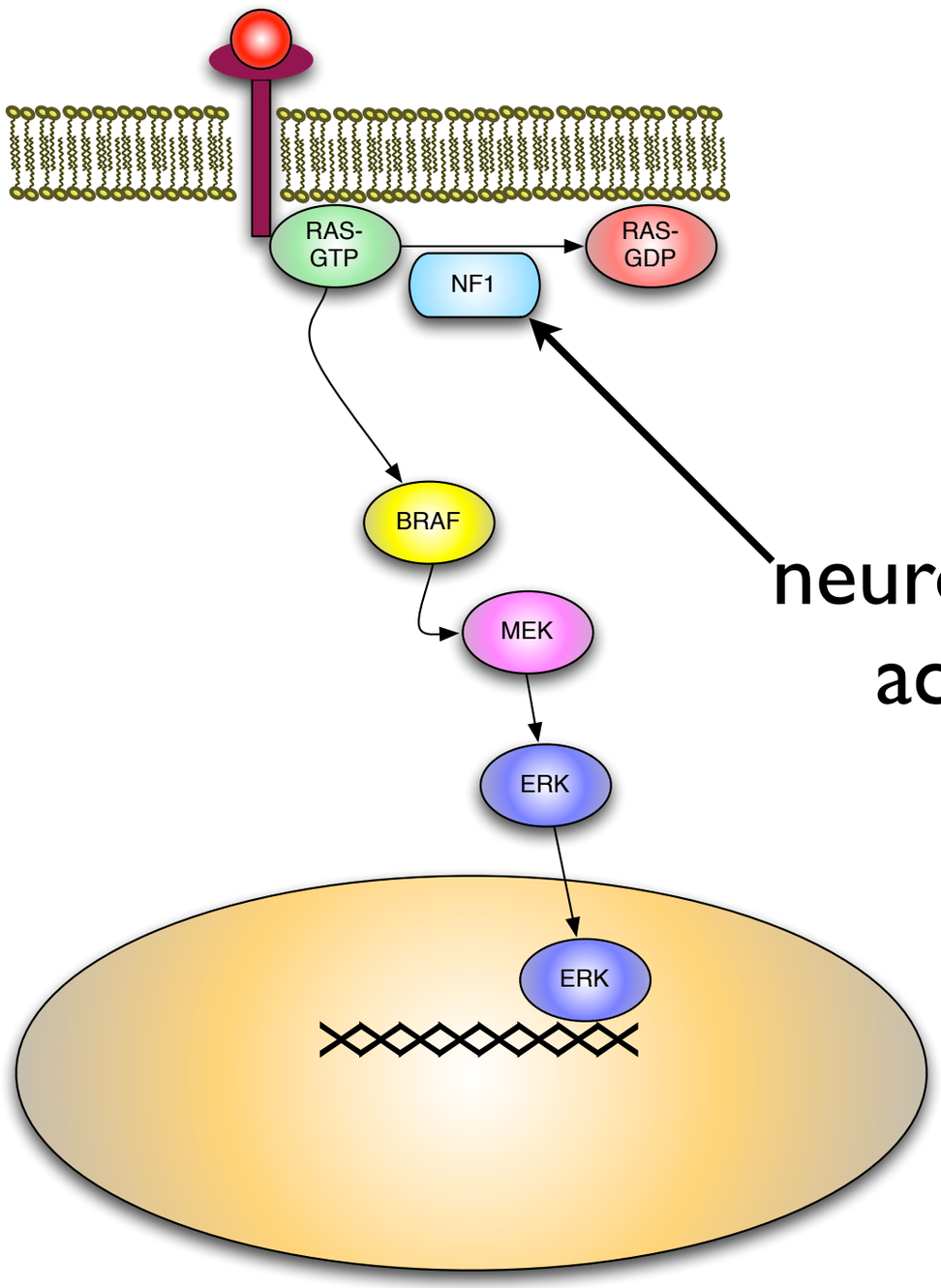
- neurofibromas
- MPNST
- scoliosis

- neurofibromas
- MPNST
- genetic risk

Follow-up

Physical Exam	Referrals	Testing
• Change in neurofibromas • Growth • Blood pressure • Neurological exam	• Ophthalmology • Development	• As indicated

NF1 Gene



neurofibromin: GTPase activating protein

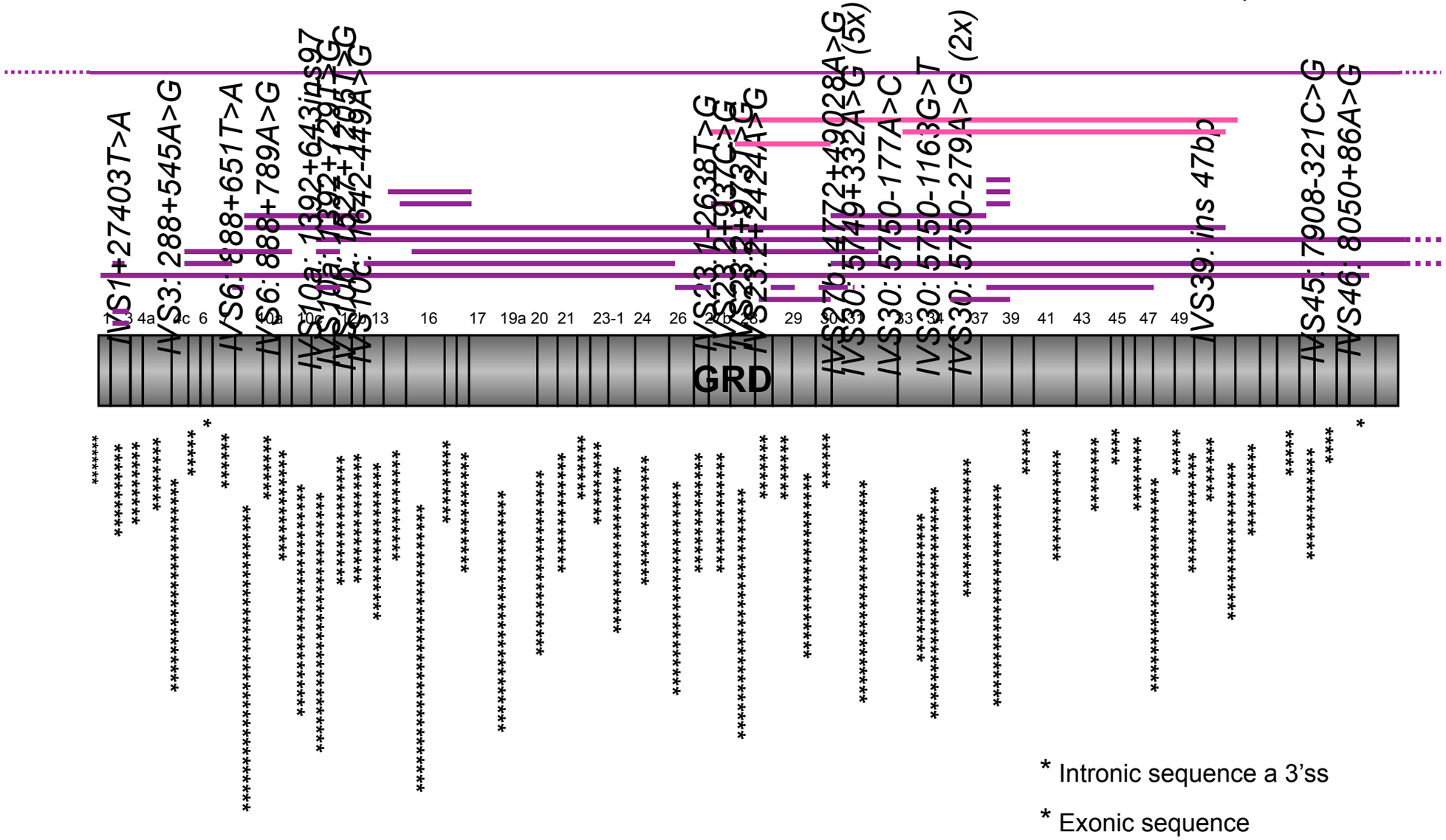
NF1 Mutations

Translocation: n=1

Total gene deletions: n=72

~5% total gene del; ~2-3% 1-multi exon del; ~2% deep intronic splice mutation; ~28% splice mutation (exon/ -borders ±30nt); ~48% nonsense/frameshift (~50:50); ~13% missense

(NF1: 1-1500)
April 2007



courtesy of Dr. Ludwine Messiaen

* Intronic sequence a 3'ss

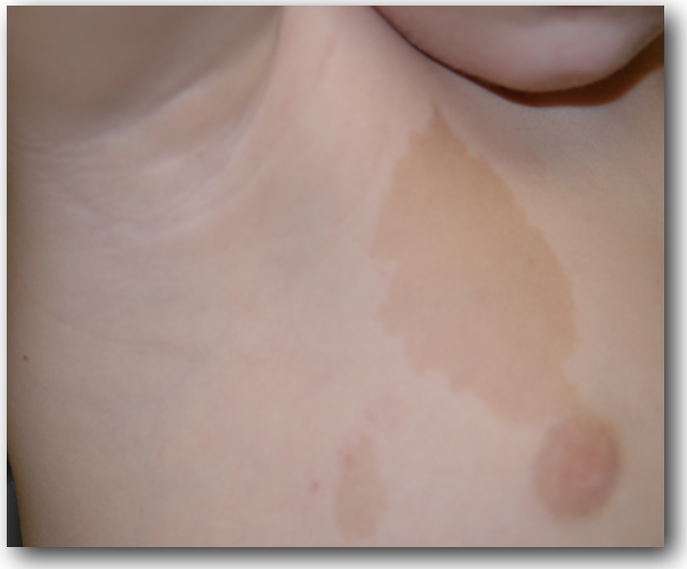
* Exonic sequence

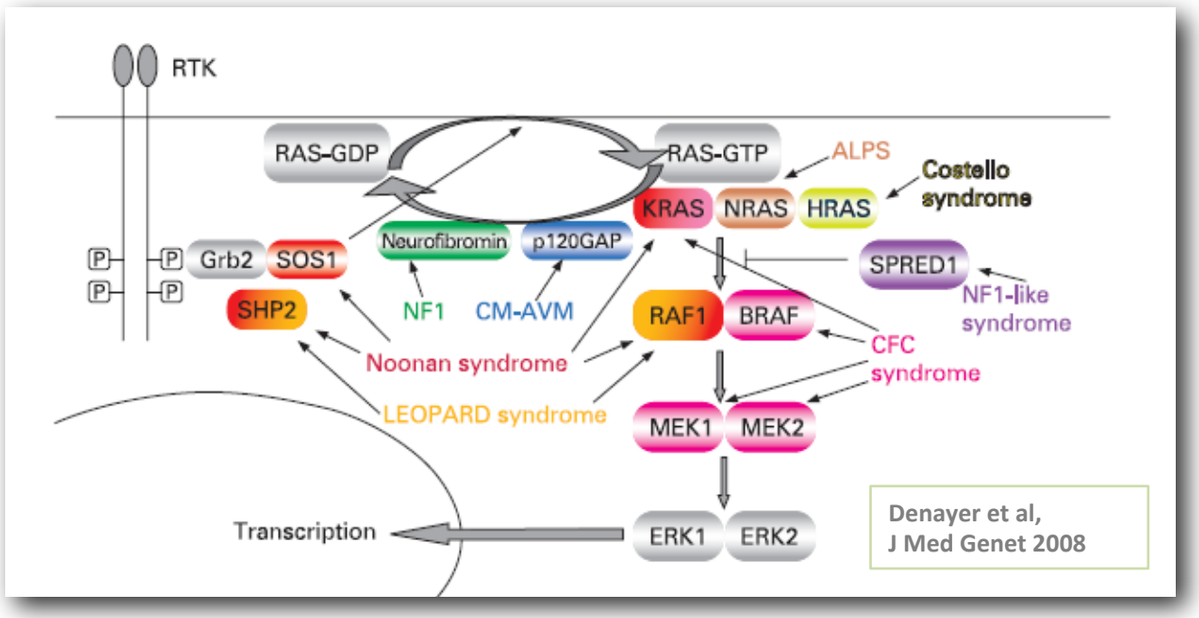
* Intronic sequence a 5'ss

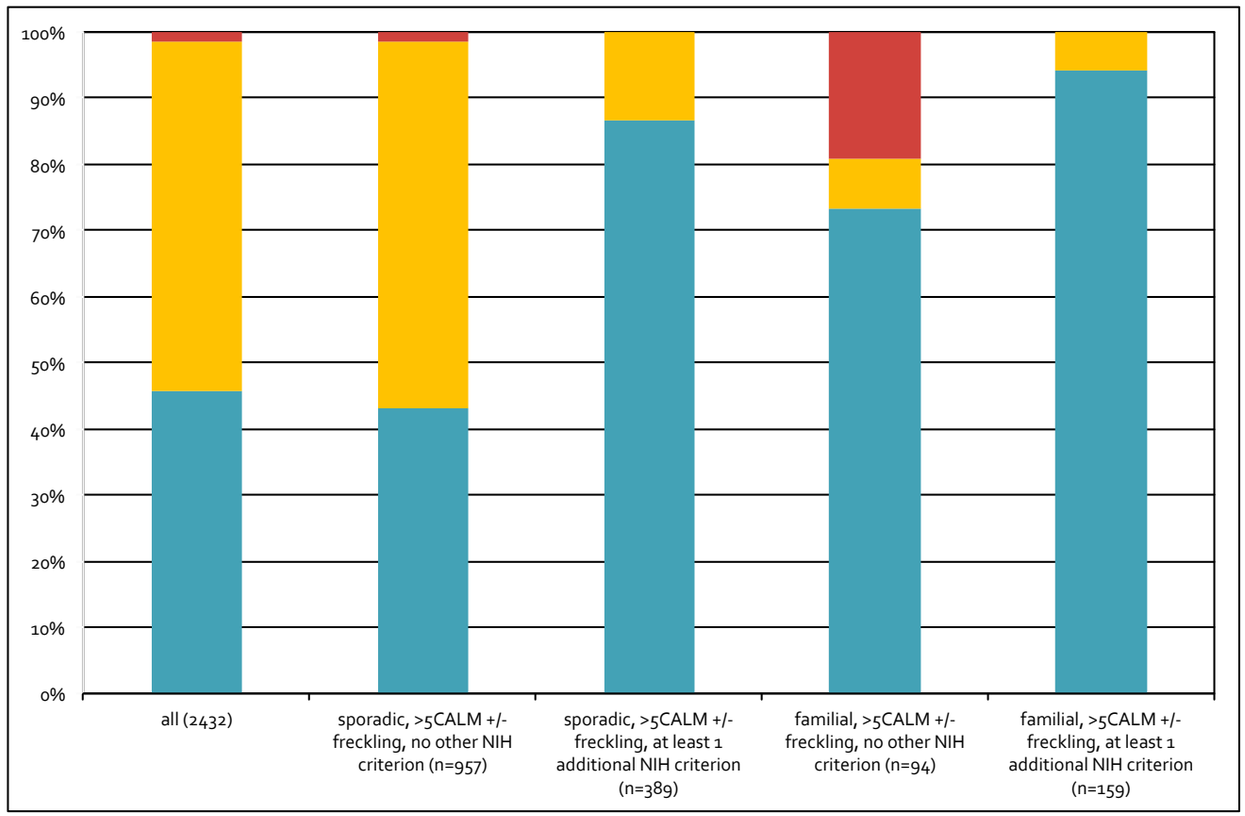
Indications for Genetic Testing

- Child with multiple cafe-au-lait spots
- Relative of affected individual
- Unusual presentation
- Prenatal diagnosis

Legius Syndrome

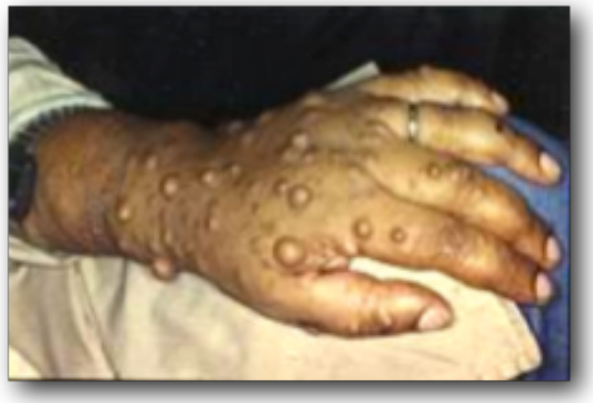


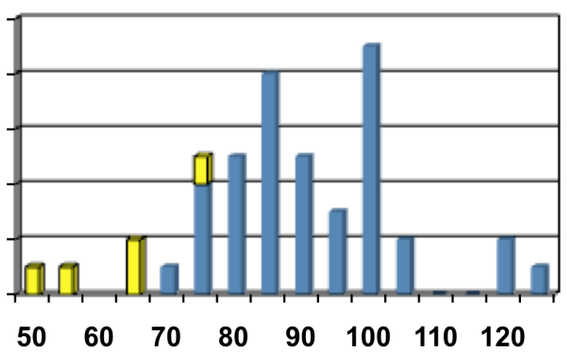




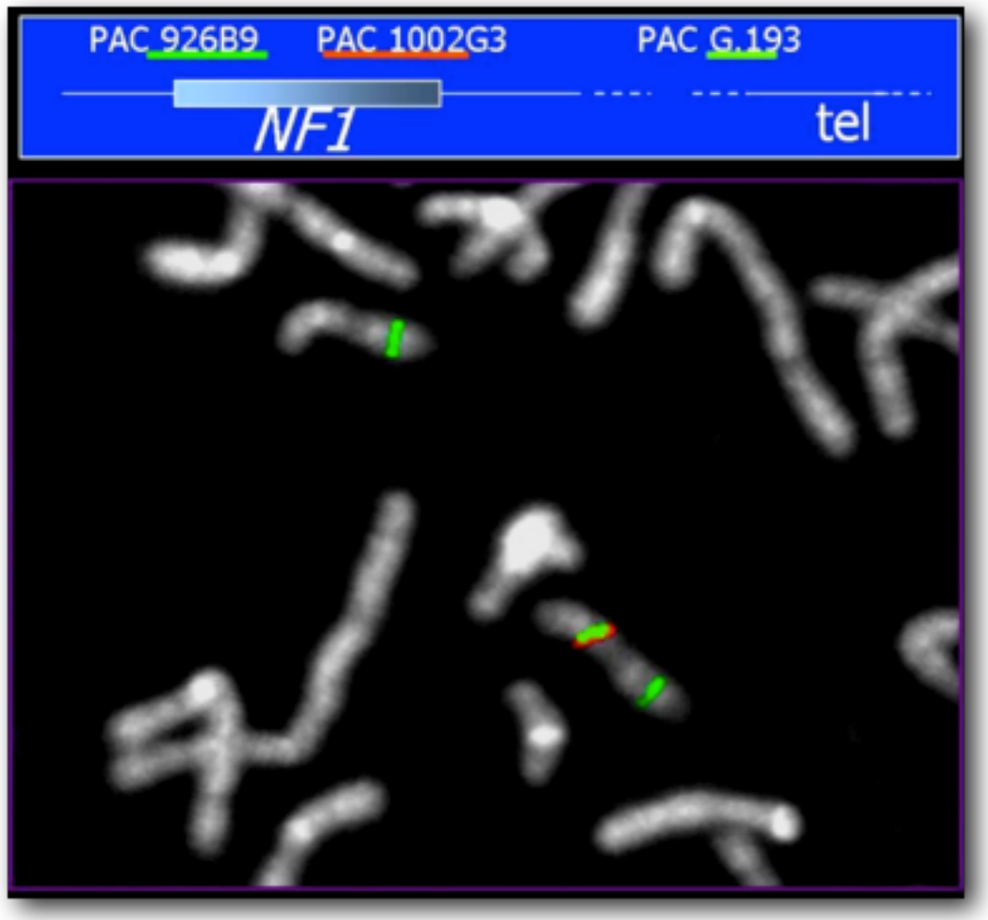
Messiaen et al, JAMA 302: 2111; 2009

NF1 Deletions

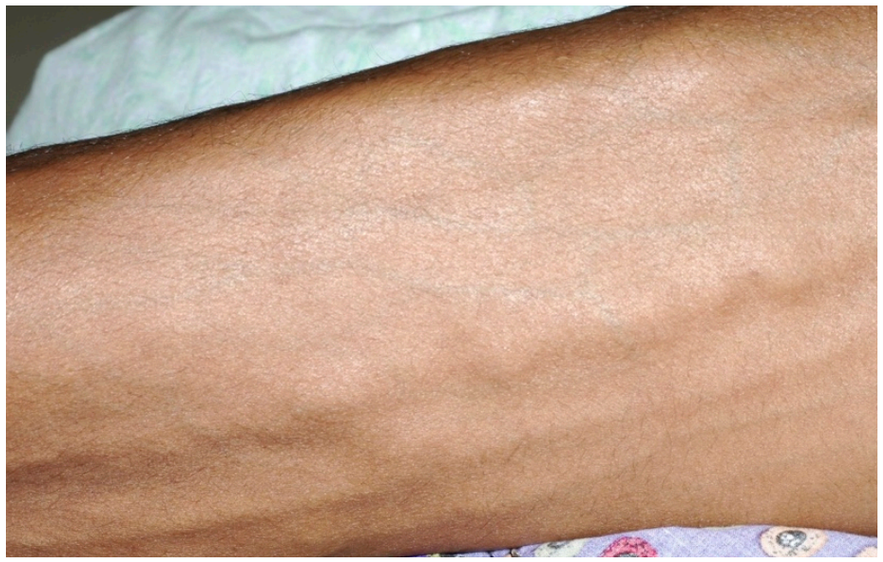


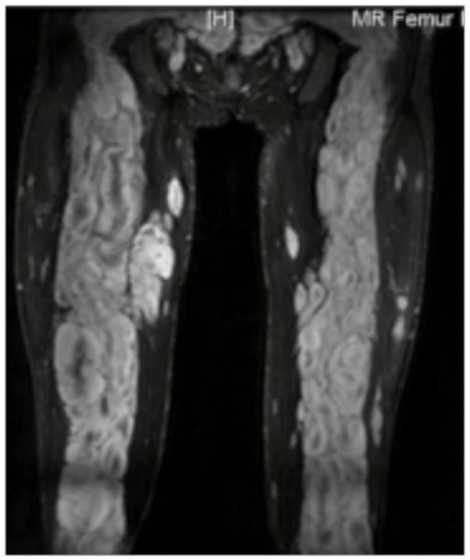


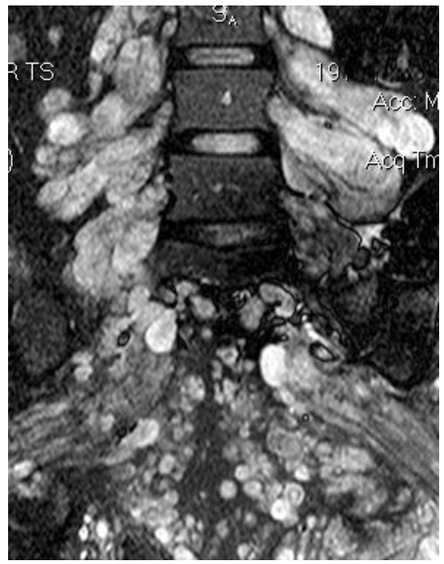
North et al., Neurology 44:878, 1994.



“Spinal NF”

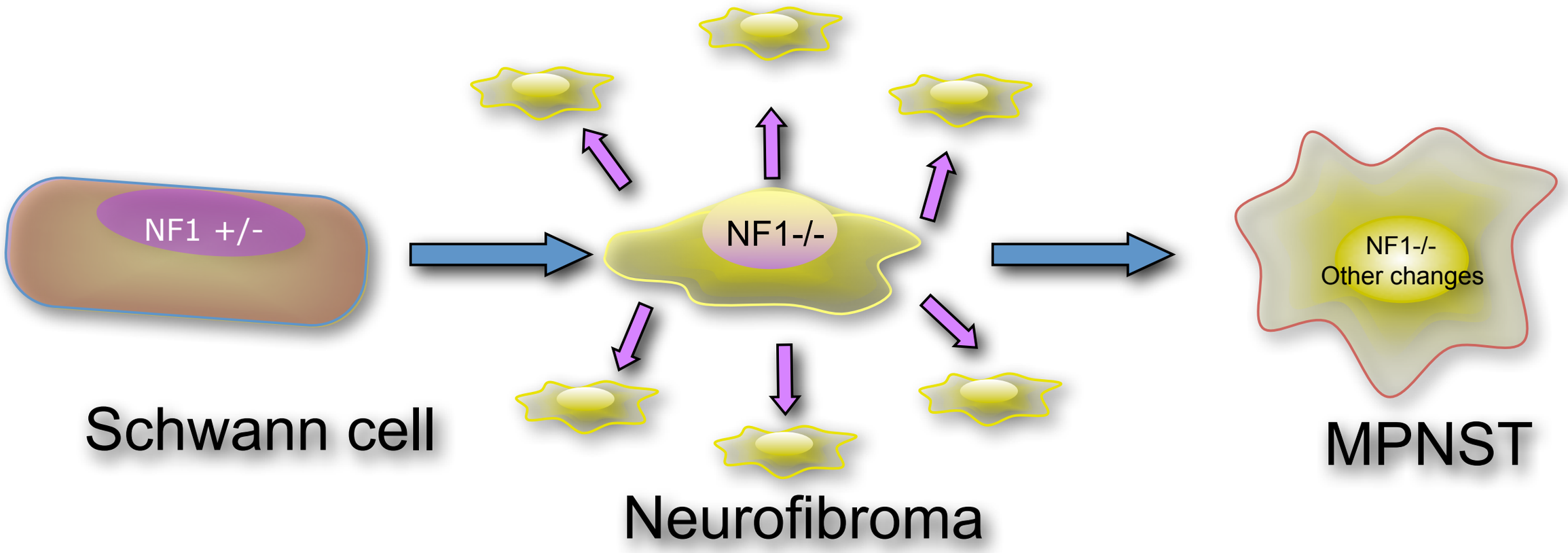




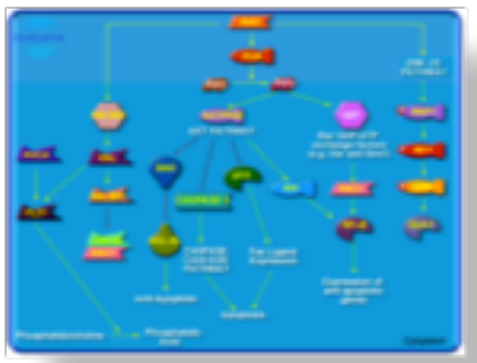


predominantly missense and splicing mutations

Pathogenesis of Neurofibromas



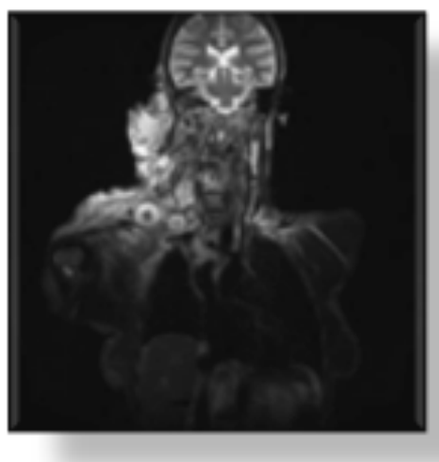
Drug Discovery

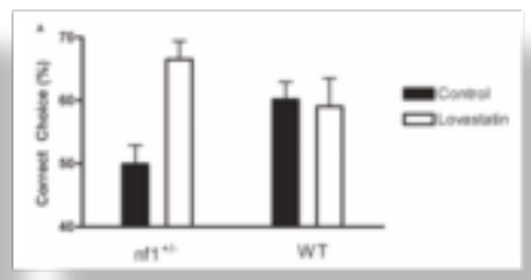


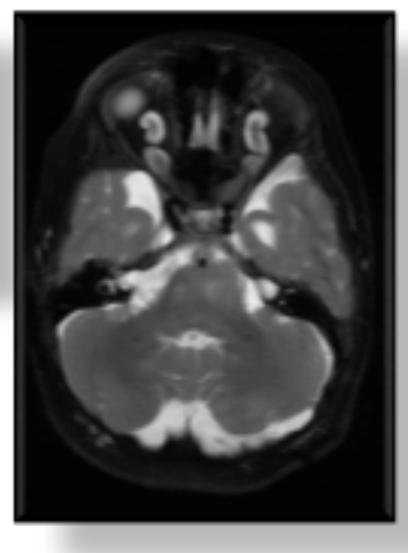
NF Consortium

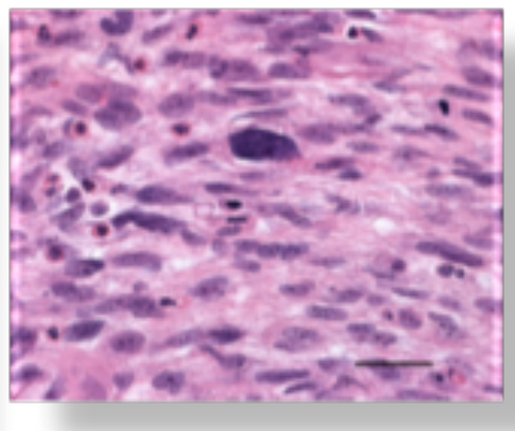
Clinical Trials

Plexiform Neurofibroma	Learning Disability	Low-grade Glioma	Malignant Peripheral Nerve Sheath Tumor
STOPN	STARS	RAD001	MPNST









Patient Education

Acknowledgements

- Radiology
  - Tina Young Poussaint
  - Diego Jaramillo
  - Eva Dombi
  - Stuart Royal
- Dermatology
  - Amy Theos
  - Kevin Boyd
- Genetics
  - Ludwine Messiaen
- Pathology
  - Steve Carroll
- NF Consortium
  - Karen Cole-Plourde
  - Alan Cantor
- Support
  - US Army CDMRP
  - NINDS