Familial Brain Tumour Syndromes

Stephen Yip, M.D., Ph.D., FRCPC

Vancouver General Hospital
BC Cancer

2018

Objectives

1. Review basic genomic pathology of CNS tumours
2. List the common familial brain cancer syndromes
3. Describe their clinical presentations and underlying genetic features

Some Familial Brain Tumour Syndromes

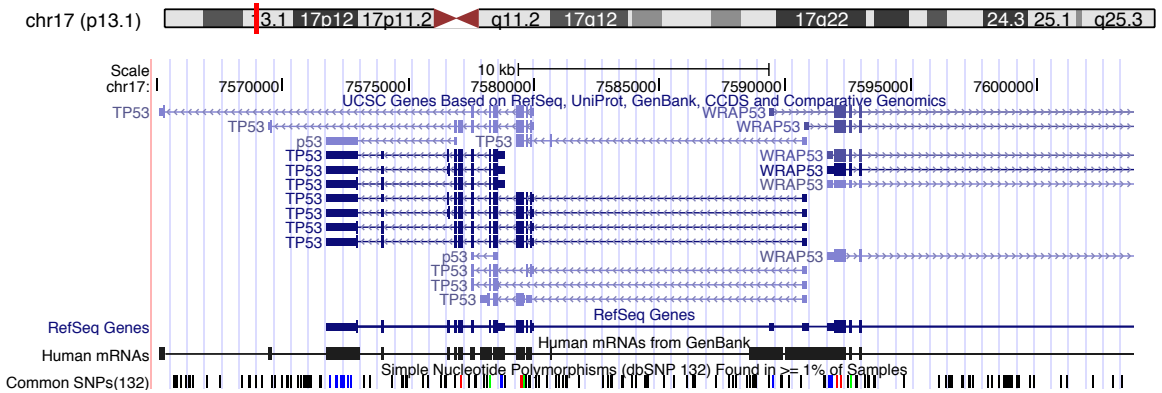
Tumour	Known genetic defects	Syndrome if germline ?
Neurofibroma	*NF1*	Neurofibromatosis 1
Multiple meningiomas, bilateral vestibular schwannomas	*NF2*	Neurofibromatosis 2
Hemangioblastoma	*VHL*	Von Hippel Lindau
Glioma (predisposition)	*P53, MSH2, MSH6*	Li-Fraumeni, Turcot
AT/RT, MRT, peripheral schwannoma	*SMARCB1*	Rhabdoid tumour predisposition, Familial schwannomatosis
Medulloblastoma (desmoplastic/nodular)	*PTCH*	Gorlin
Dysplastic gangliocytoma	*PTEN*	Lhermitte-Duclos
SEGA	*TSC1/2*	Tuberous Sclerosis
Glioma	*L2HGDH (IDH1/2)*	L-2-hydroxyglutaric aciduria
Pituitary adenoma (3 Ps)	*MEN1*	MEN (Werner Syndrome)
Psammomatous melanotic schwannoma	*PRKAR1A*	Carney Complex

Phakomatoses

- Neurocutaneous syndromes
- CNS disorders with concurrent skin and eye lesions
- Common ectodermal origin
  - Neurofibromatosis
  - Tuberous sclerosis
  - Ataxia telangiectasia
  - Sturge-Weber syndrome
  - Von Hippel-Lindau syndrome
  - Incontinentia pigmenti
  - Nevoid basal cell carcinoma syndrome (Gorlin)

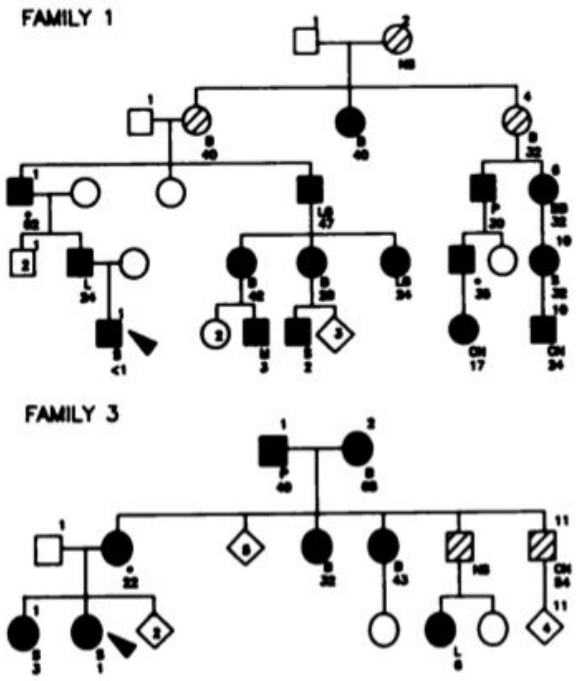
Cancer susceptibility syndromes

- Li- Fraumeni (TP53)
  - 17p13



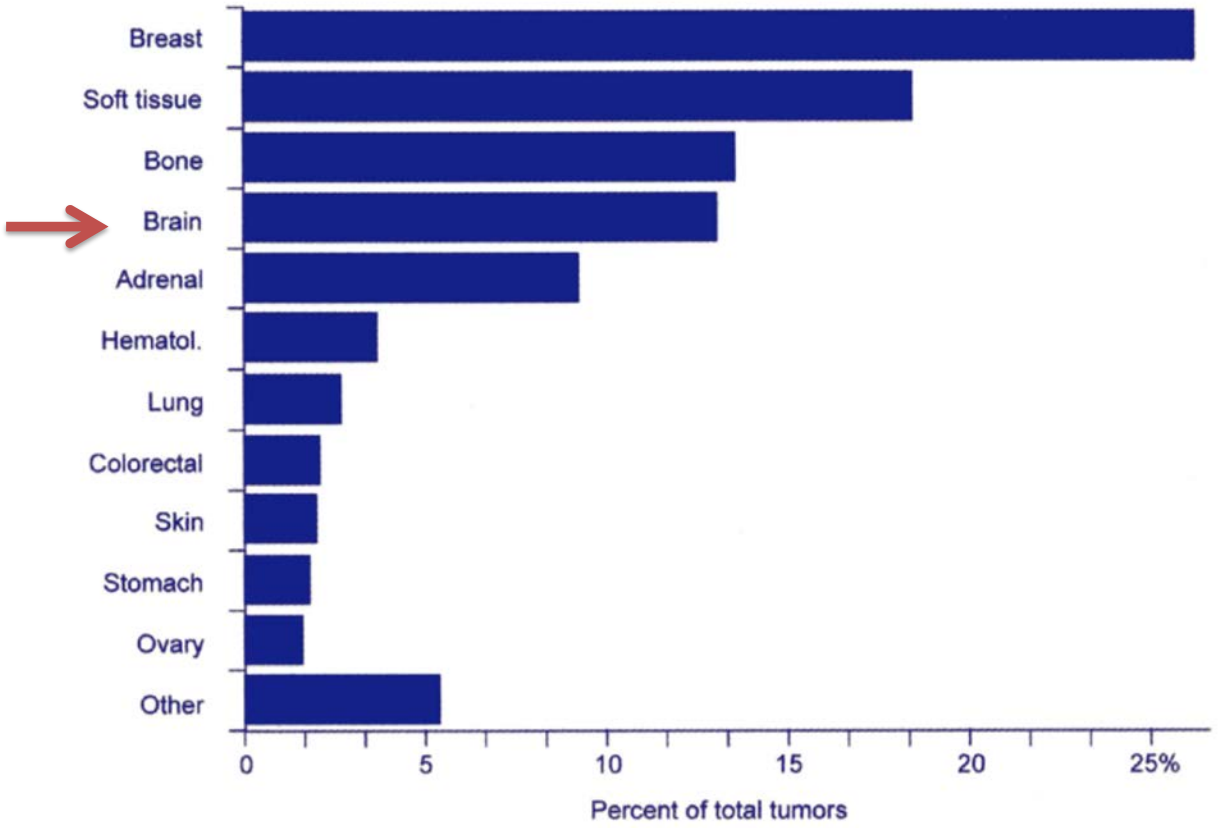
Li-Fraumeni Syndrome

- Autosomal dominant transmission pattern



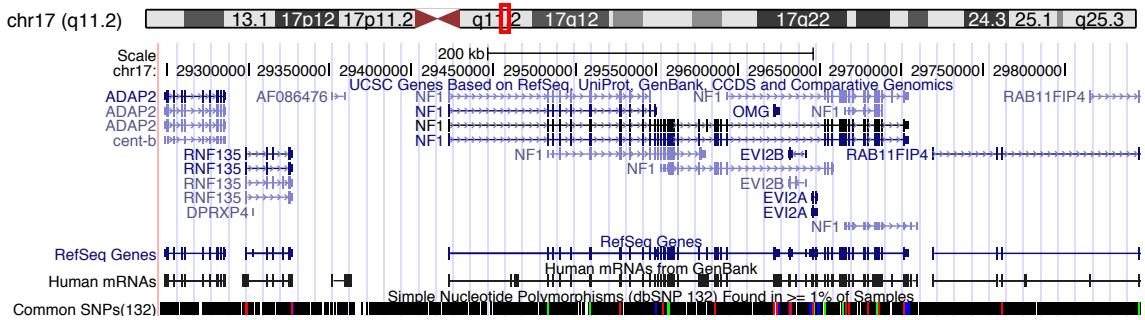
Li FP, Fraumeni JF, Jr., Mulvihill JJ, et al: A cancer family syndrome in twenty-four kindreds. Cancer Res 48:5358-62, 1988

Distribution of cancers in Li-Fraumeni Syndrome



Neurofibromatosis 1 (NF1)

- Neurofibromin - 17q11



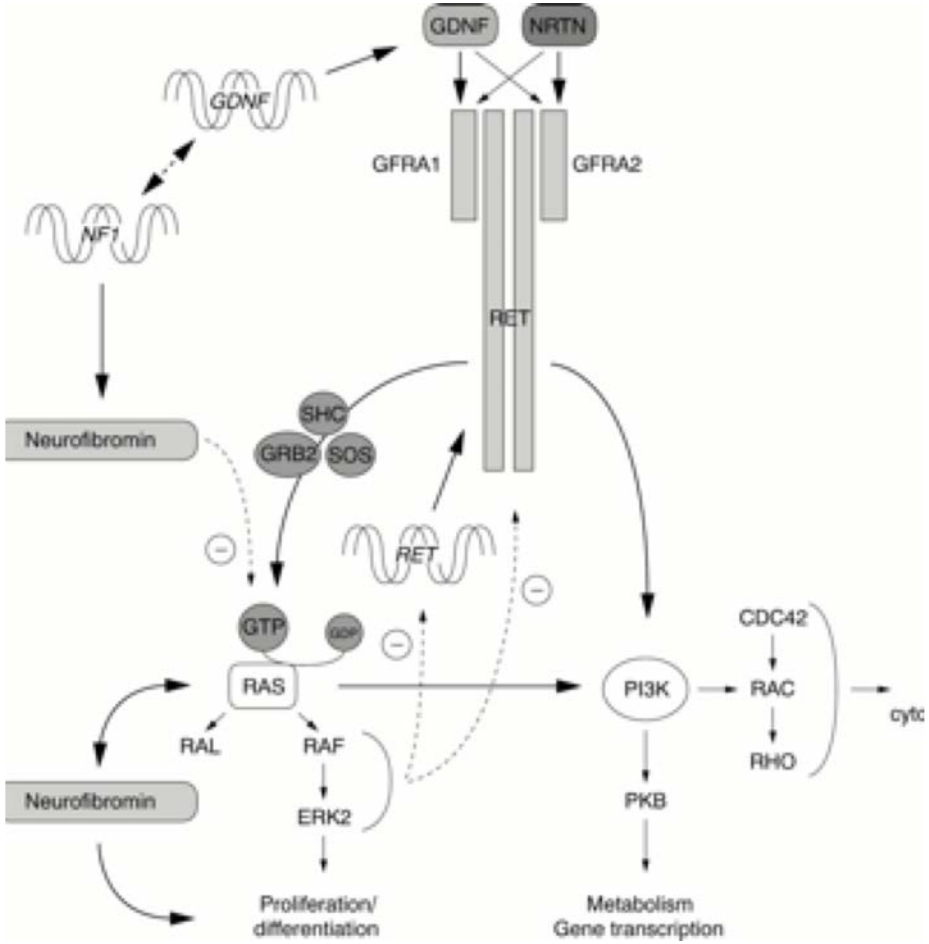
- Autosomal dominant
- De novo mutation, mosaicism
- 13kb
  - 3 alternatively spliced isoforms
  - No hot spot mutations, >300 identified (E10a-10c), pseudogenes

Neurofibromatosis 1 (NF1)

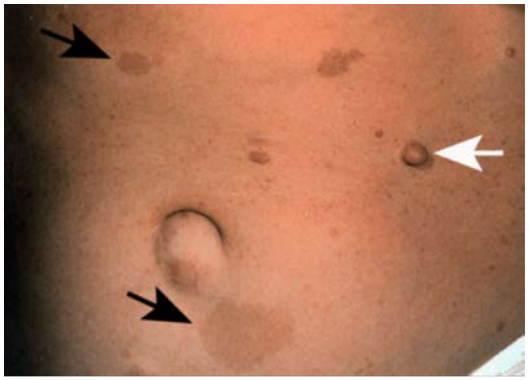
- Prevalence 1:3000
- Higher in Arab-Israeli subpopulations
- Dermal neurofibroma
  - Well- circumscribed, non- encapsulated
  - Schwann cells and fibroblasts, endothelial cells, lymphocytes, and mast cells
- Plexiform neurofibroma
  - Diffuse enlargement of major nerve trunks and branches “ropey”
  - 10% lifetime risk of malignant progression
- Gliomas
  - Pilocytic astrocytomas along the optic pathway
- Others
  - Macrocephaly, ADHD, epilepsy, hydrocephalus, aqueductal stenosis

Neurofibromin

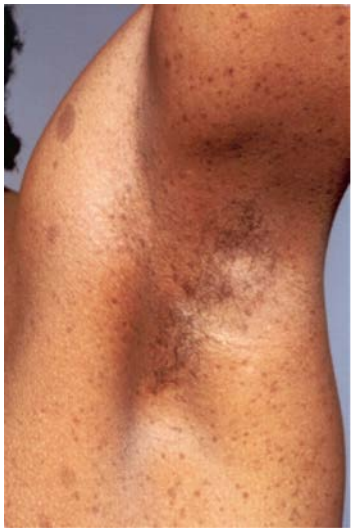
- 220- 250 kD
- RasGTPase – activating protein
- Loss of function leads to activation of RAS isoforms and downstream growth and survival pathway



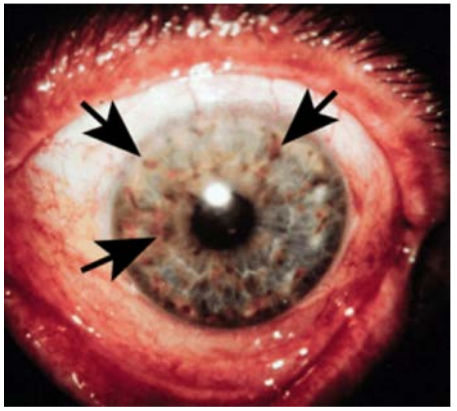
Neurofibromatosis 1 (NF1)



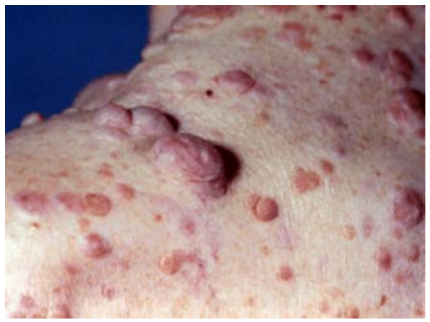
Café au lait spots
Sessile cutaneous neurofibroma



Axillary freckling



Lisch Nodule

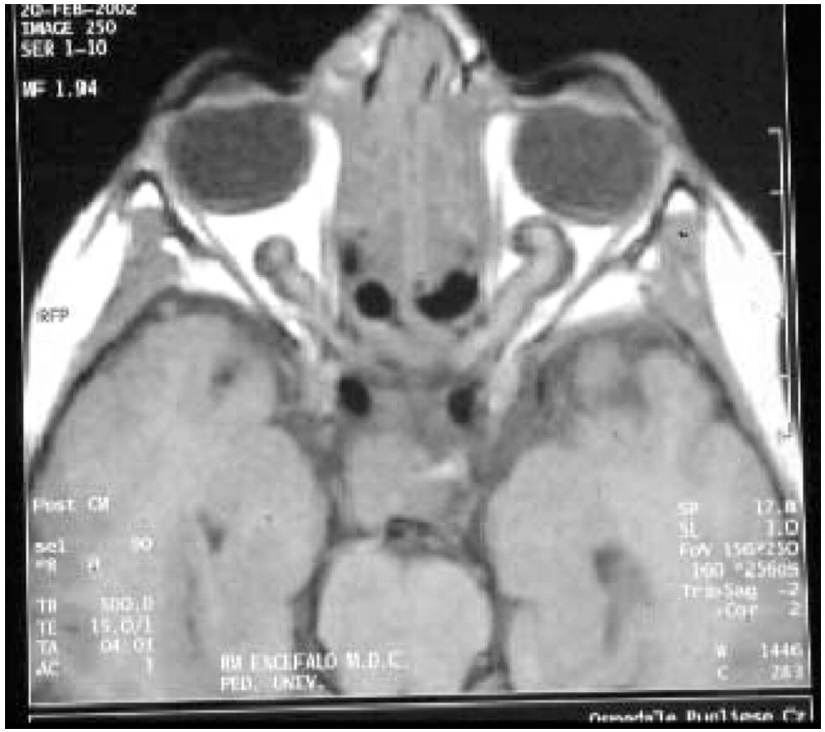


Cutaneous neurofibroma

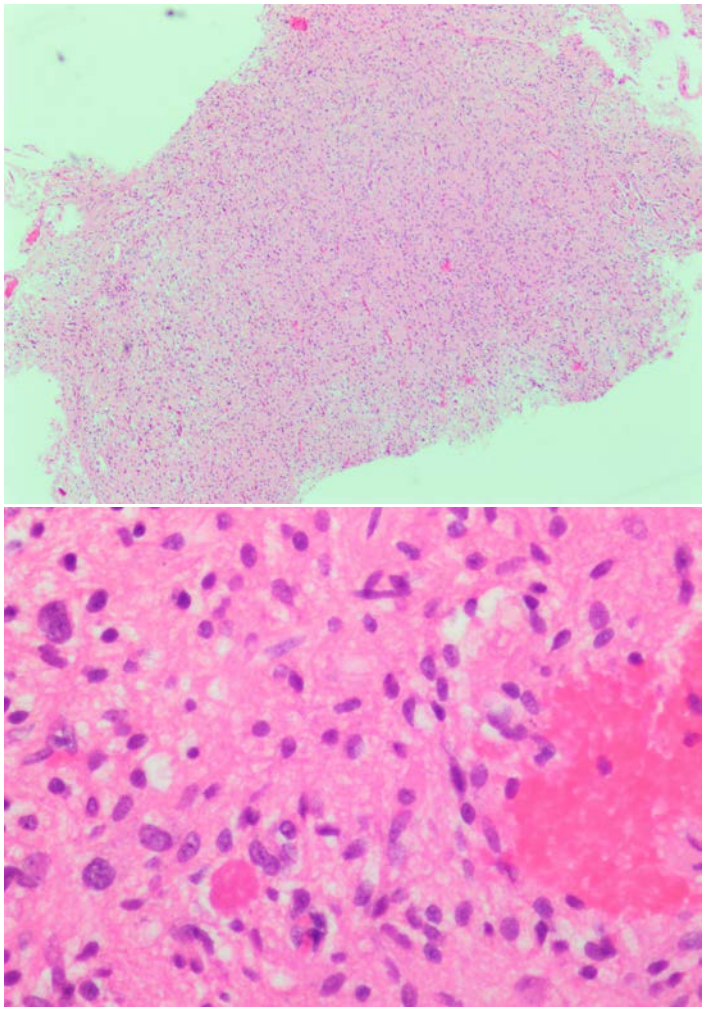
Levy AD, Patel N, Dow N, et al: From the archives of the AFIP: abdominal neoplasms in patients with neurofibromatosis type 1: radiologic-pathologic correlation. Radiographics 25:455-80, 2005

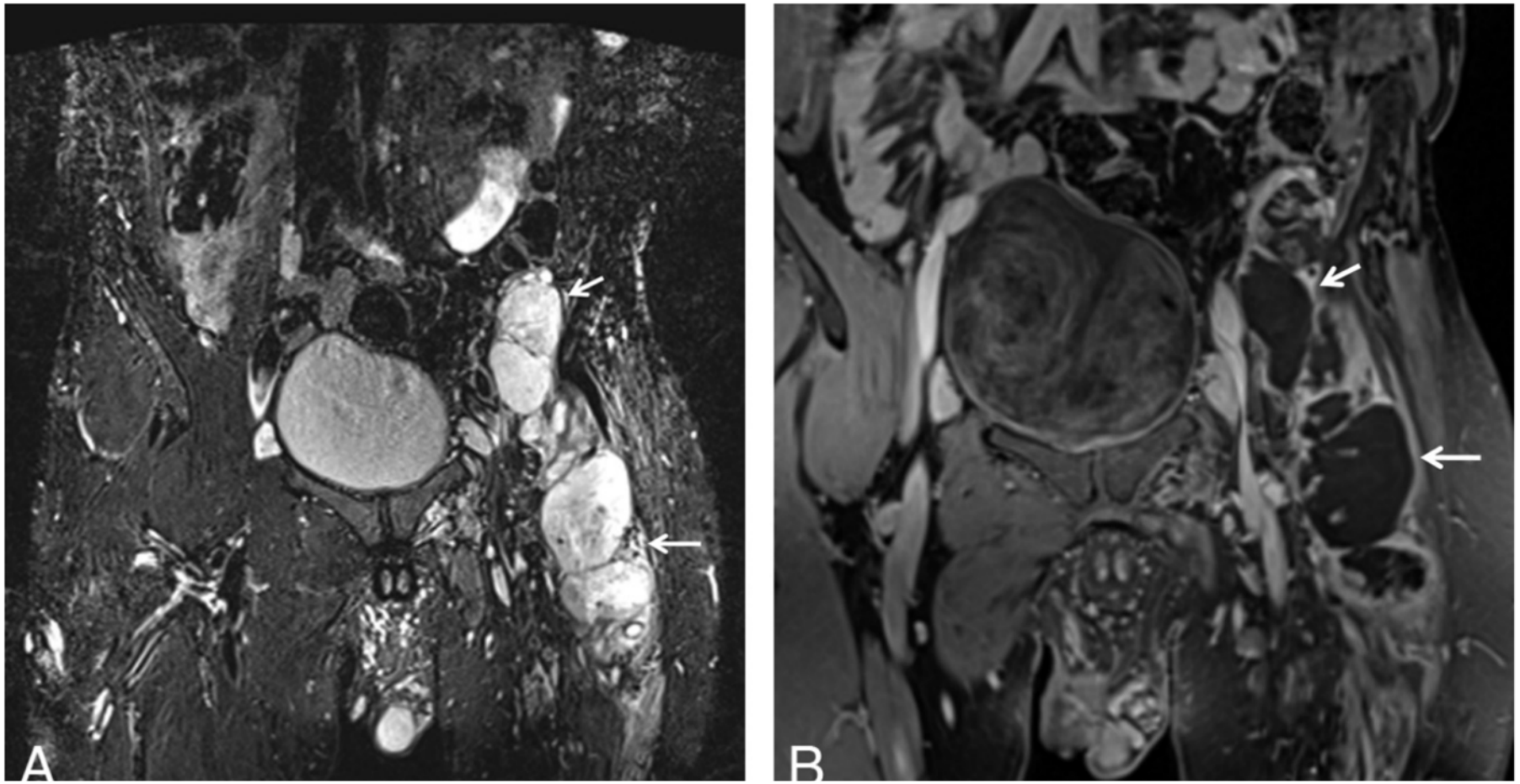
Jones J, Brenner C, Chinn R, et al: Radiological associations with dermatological disease. Br J Radiol 78:662-71, 2005

Optic pathway glioma – pilocytic astrocytoma



http://dx.doi.org/10.1136/bjo.2004.043802

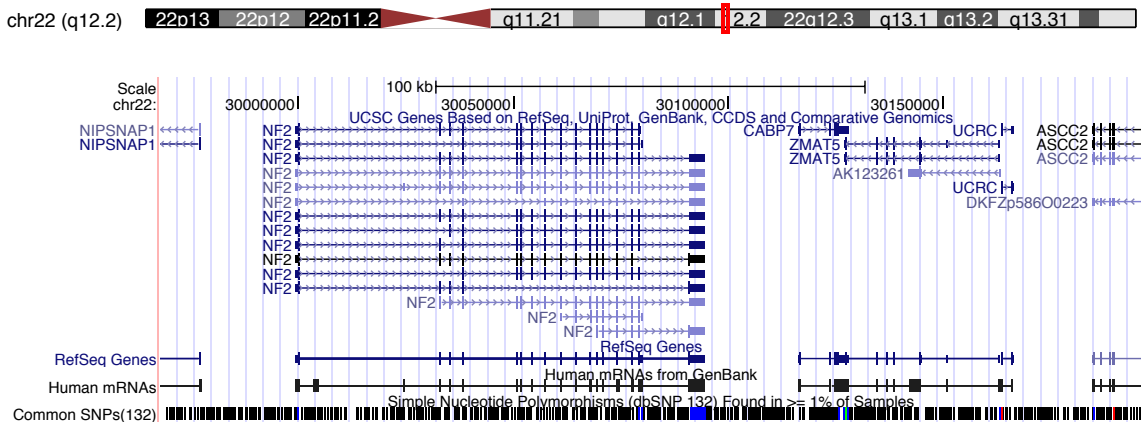




https://doi.org/10.3174/ajnr.A2257

Neurofibromatosis 2 (NF2)

- Merlin - 22q12

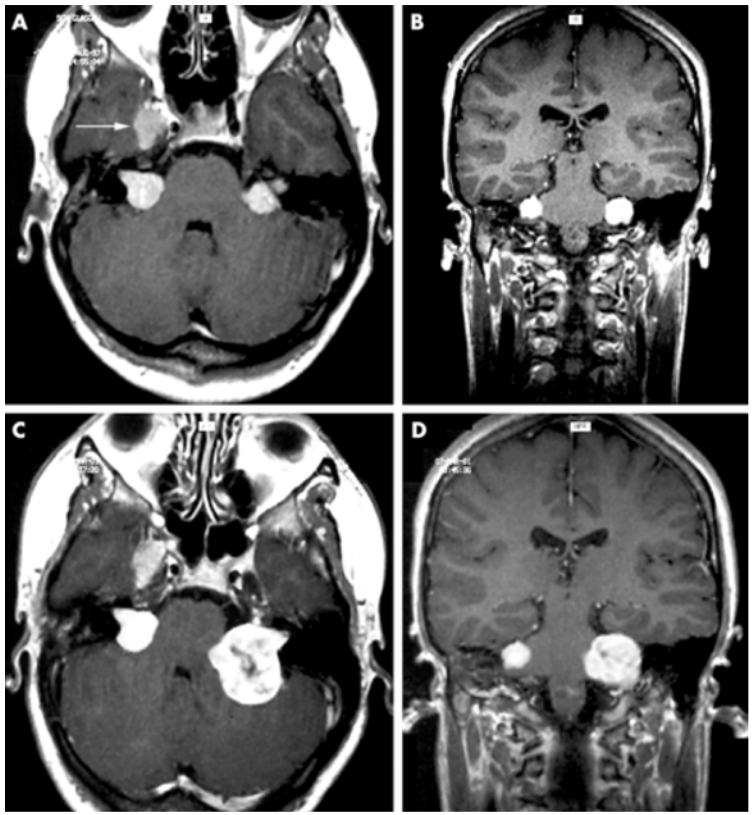


- Autosomal dominant
- 110 kb
  - 17 exons, 2 alternatively spliced isoforms

Neurofibromatosis 2 (NF2)

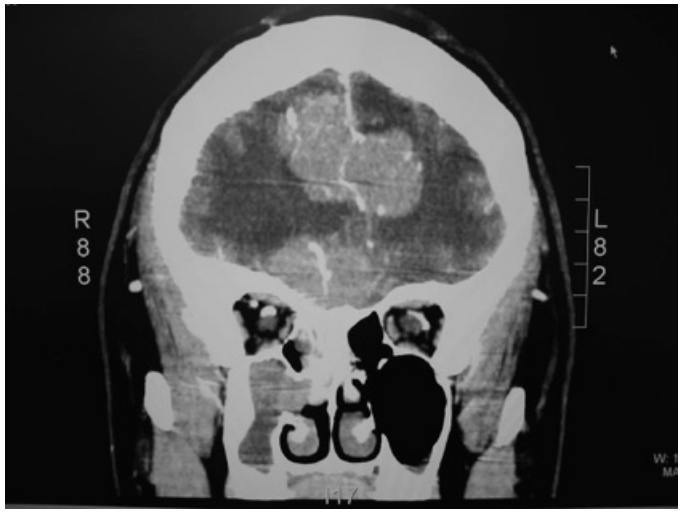
- Incidence 1:25000- 40000
- 50% are de novo germline mutations (founders)
- Schwannoma (WHO I)
  - Earlier onset, bilateral vestibular schwannomas
  - Also can affect other CNs including V, VII, XII
- Meningioma (WHO I)
  - Earlier onset, might behave more aggressively
- Glioma
  - 80% are spinal intramedullary/cauda equina tumours – can present as multiple masses
  - 10% intramedullary
  - 65-75% are ependymomas
- Others
  - Schwannosis, meningoangiomatosis

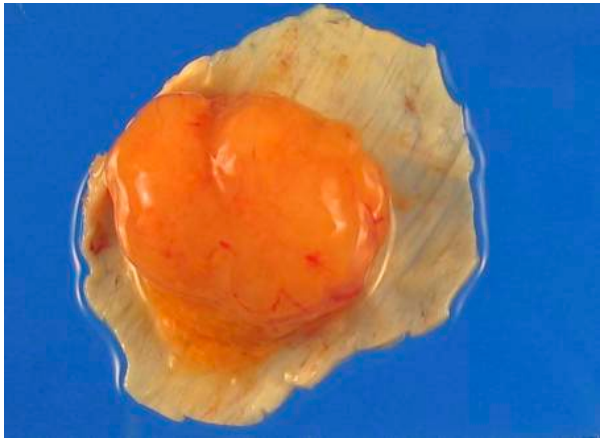
Neurofibromatosis 2 (NF2)

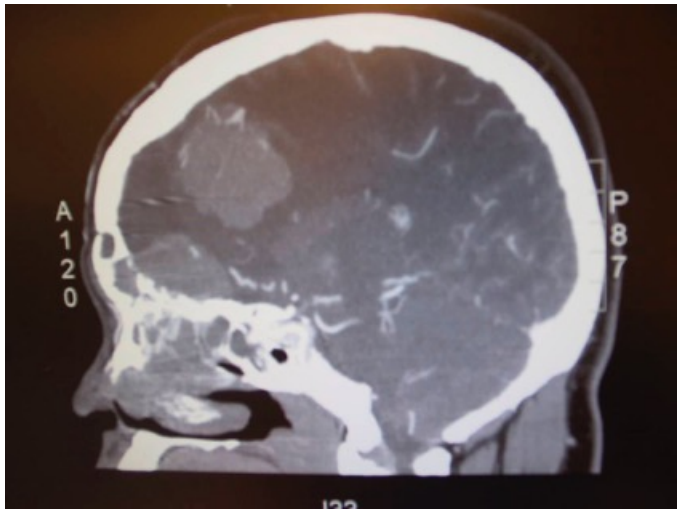


Overell J, Lindahl A: Neuro-otological syndromes for the neurologist. J Neurol Neurosurg Psychiatry 75 Suppl 4:iv53-59, 2004

Neurofibromatosis 2 (NF2)







Neurofibromatosis 2 (NF2)

ORIGINAL ARTICLE

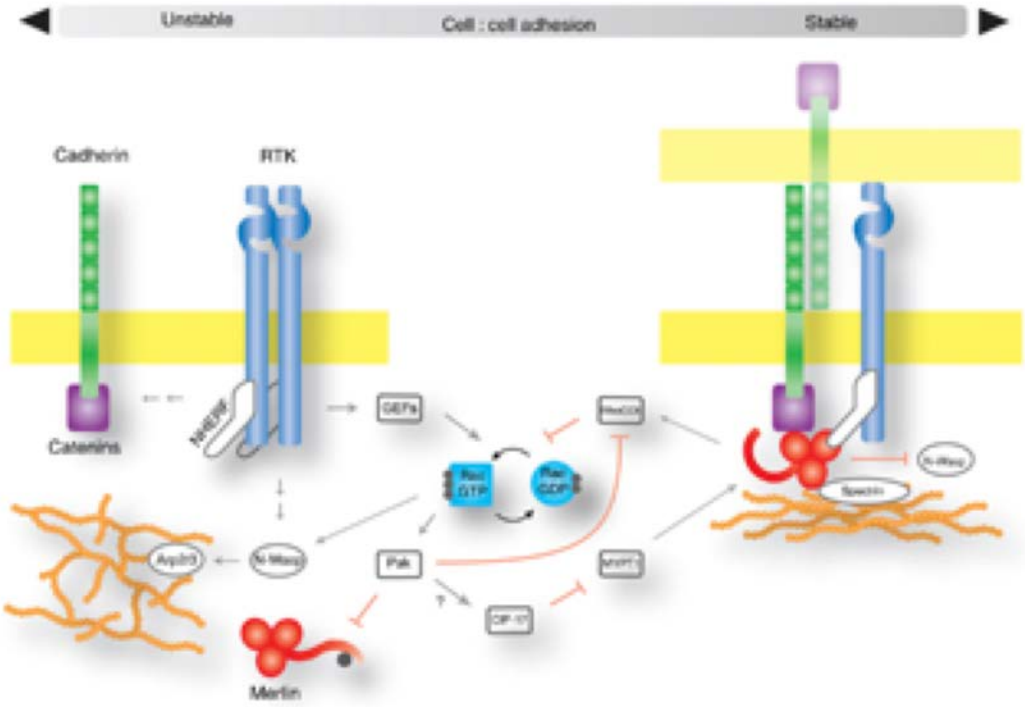
Hearing Improvement after Bevacizumab in Patients with Neurofibromatosis Type 2

Scott R. Plotkin, M.D., Ph.D., Anat O. Stemmer-Rachamimov, M.D., Fred G. Barker II, M.D., Chris Halpin, Ph.D., Timothy P. Padera, Ph.D., Alex Tyrrell, Ph.D., A. Gregory Sorensen, M.D., Rakesh K. Jain, Ph.D., and Emmanuelle di Tomaso, Ph.D.

ABSTRACT

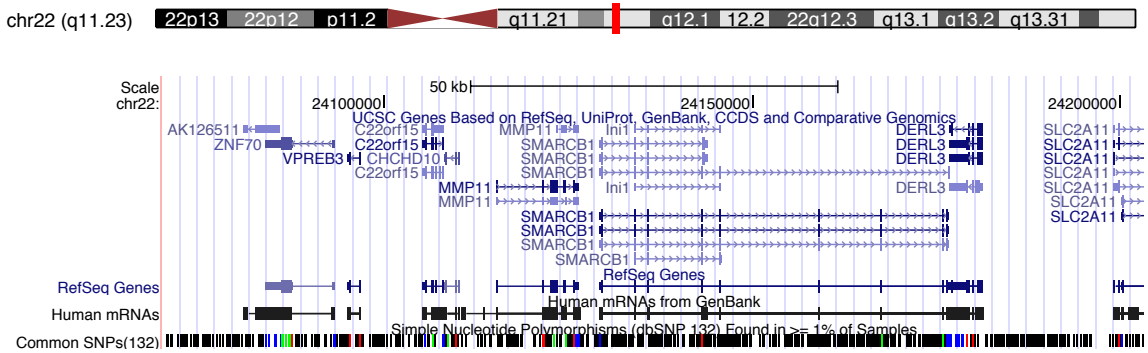
Neurofibromatosis 2 (NF2)

- Germ line mutations
  - Affecting splice junctions, nonsense mutations
  - Found throughout gene but concentrating in E1-8
  - Position 169 (E2) C->T at CpG
- Merlin
  - Regulates signal transductions from membrane associated proteins via interaction with actin cytoskeleton



Familial Schwannomatosis

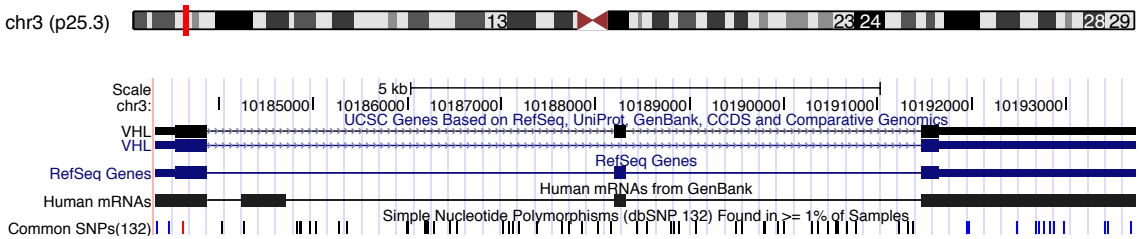
- SMARCB1 – 22q11



- Neurilemomatosis, multiple schwannomas
- Not affecting vestibular nerves or have other manifestations of NF2
- Autosomal dominant, sporadic

Von Hippel Lindau Syndrome (VHL)

- VHL - 3p25

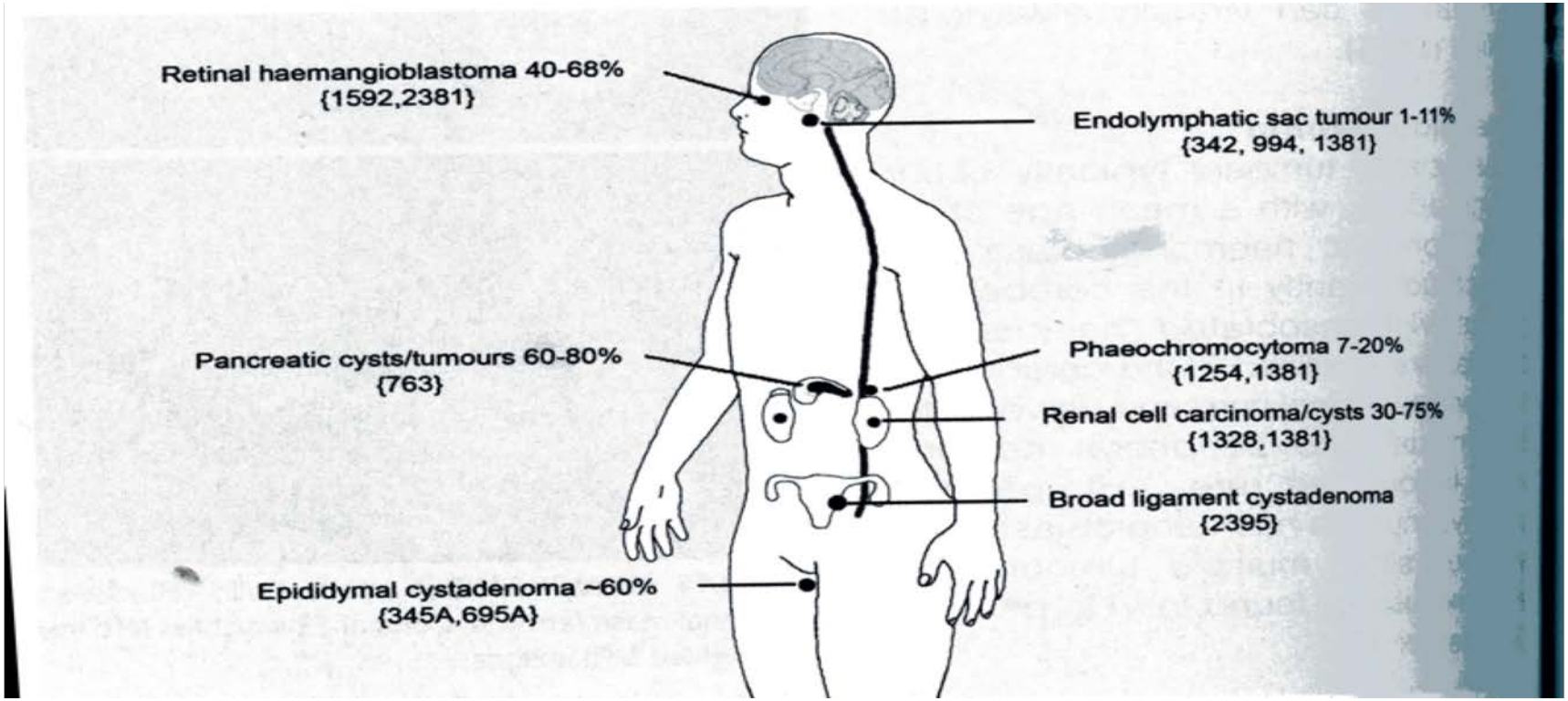


- Autosomal dominant
- 639 nucleotides

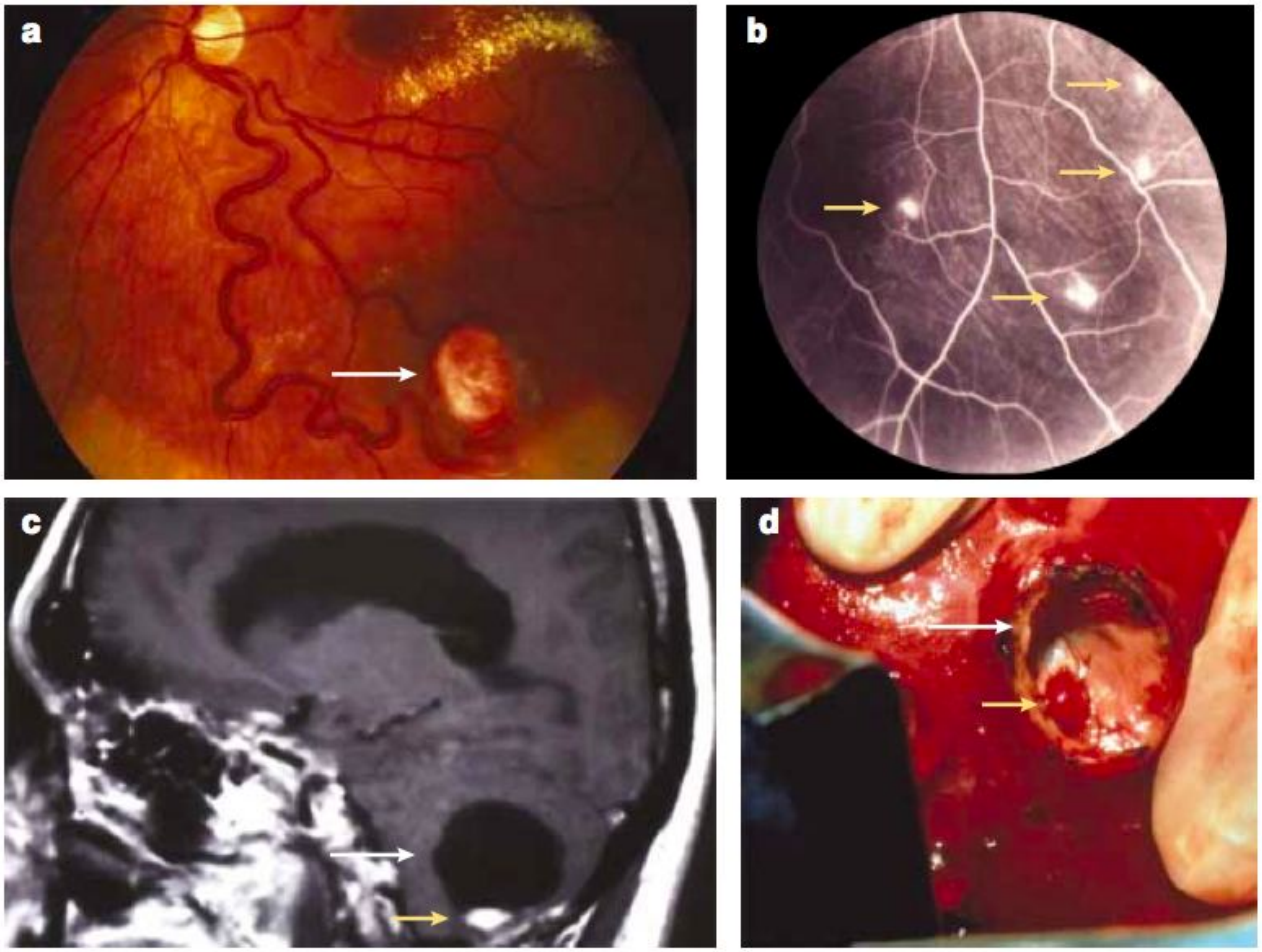
Von Hippel-Lindau Disease (VHL)

- Incidence 1:36000- 45500
- Hemangioblastoma
  - CBx, BS, SC, nerve roots
  - ***Multiple and recurrent***
  - Vascular & stromal cells
- Extra CNS manifestations
  - Retinal angiomas
  - Clear cell RCC, Pheochromocytoma
  - ELST, pancreatic lesions (cysts, serous cystadenomas, neuroendocrine tumours)

Von Hippel-Lindau Disease (VHL)

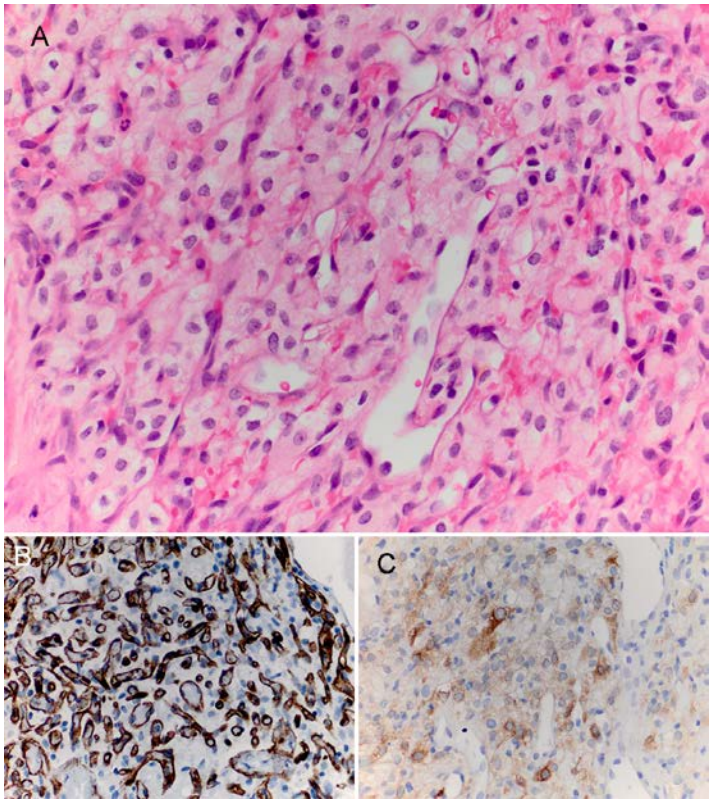


Von Hippel-Lindau Disease (VHL)



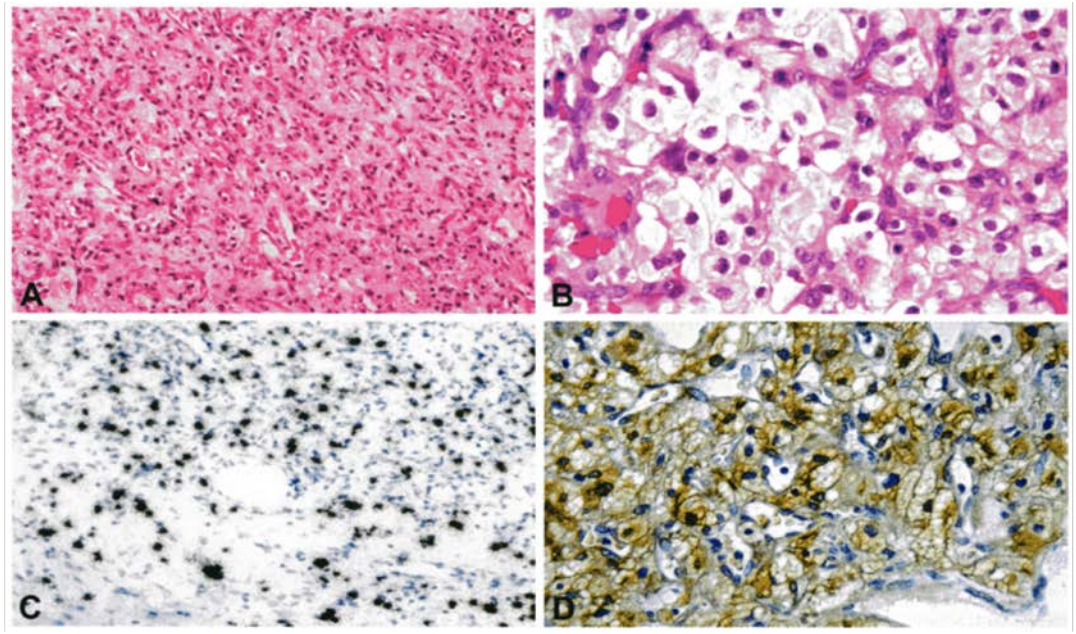
Kaelin WG, Jr.: Molecular basis of the VHL hereditary cancer syndrome. Nat Rev Cancer 2:673-82, 2002

Hemangioblastoma



PMID26086055

Clear cell RCC



Von Hippel-Lindau Disease (VHL)

Table 1 | **Characteristics of different types of VHL disease**

Type of VHL disease	*VHL* mutation type	Molecular defect	Clinical manifestation
Type 1	Loss of *VHL* or a mutation that affects protein folding	Upregulation of HIF-α and HIF target genes	Haemangioblastomas Diminshed risk of phaeochromocytoma Renal-cell carcinoma
Type 2A	*VHL* missense mutation	Upregulation of HIF-α and HIF target genes	Haemangioblastomas Phaeochromocytoma Low risk of renal-cell carcinoma
Type 2B	*VHL* missense mutation	Upregulation of HIF-α and HIF target genes	Haemangioblastomas Phaeochromocytoma High risk of renal-cell carcinoma
Type 2C	*VHL* missense mutation	pVHL retains ability to degrade HIF-α; decreased binding to fibronectin — fibronectin-matrix-assembly defect	Pheochromocytoma only

HIF, hypoxia-inducible factor; VHL, von Hippel–Lindau.

Kaelin WG, Jr.: Molecular basis of the VHL hereditary cancer syndrome. Nat Rev Cancer 2:673-82, 2002

Von Hippel-Lindau Disease (VHL)

- Promotes degradation of HIF1 complex that is normally assembled in hypoxic conditions
- Constitutive expression of VEGF
- No hot spots (throughout all 3 exons) but genotype:phenotype correlation
- CNS hemangioblastoma & RCC major cause of mortality
- Average life expectancy 40-50 yr
- Genetic testing for young patient w CNS hemangioblastoma

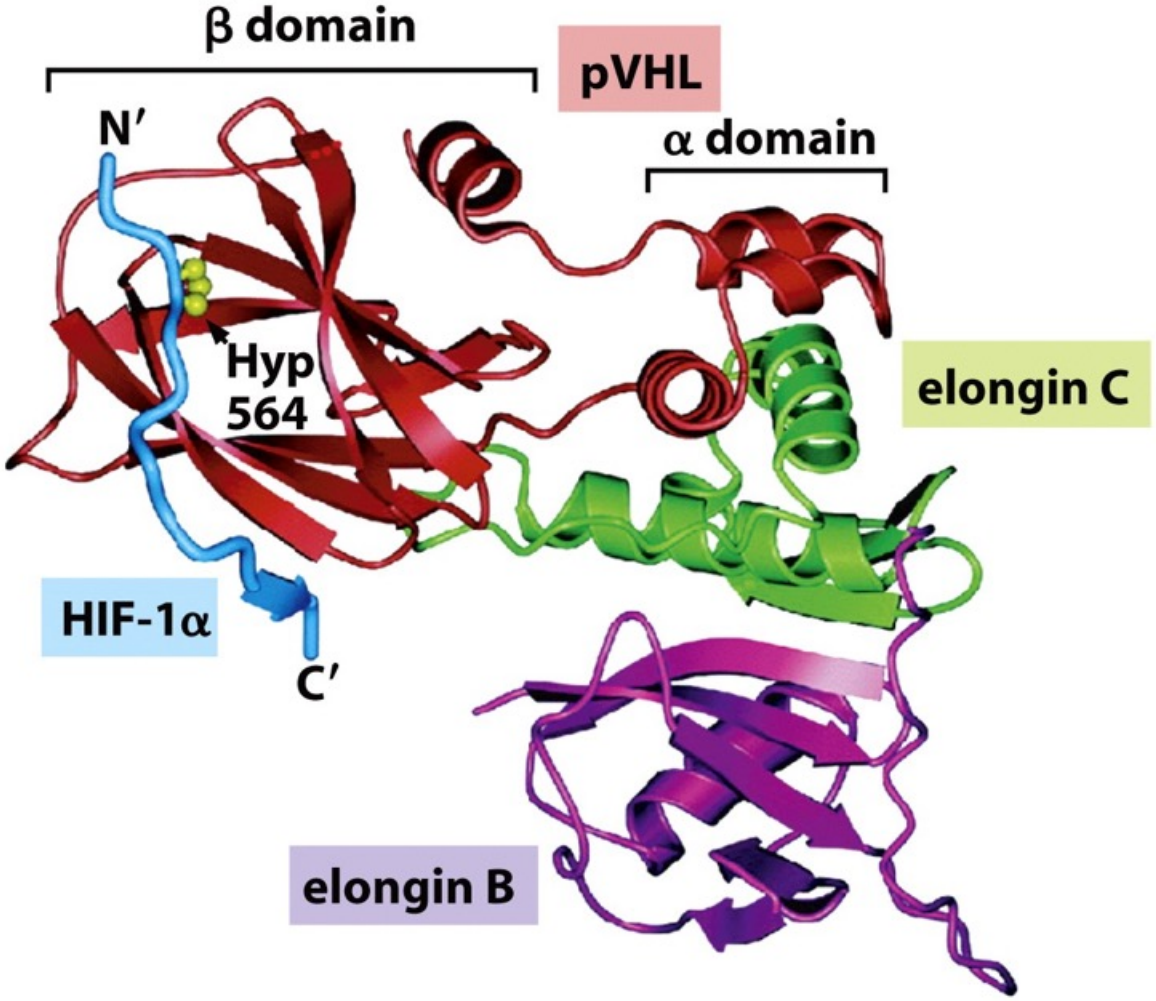


Figure 7.29b *The Biology of Cancer* (© Garland Science 2007)

Von Hippel-Lindau Disease (VHL)

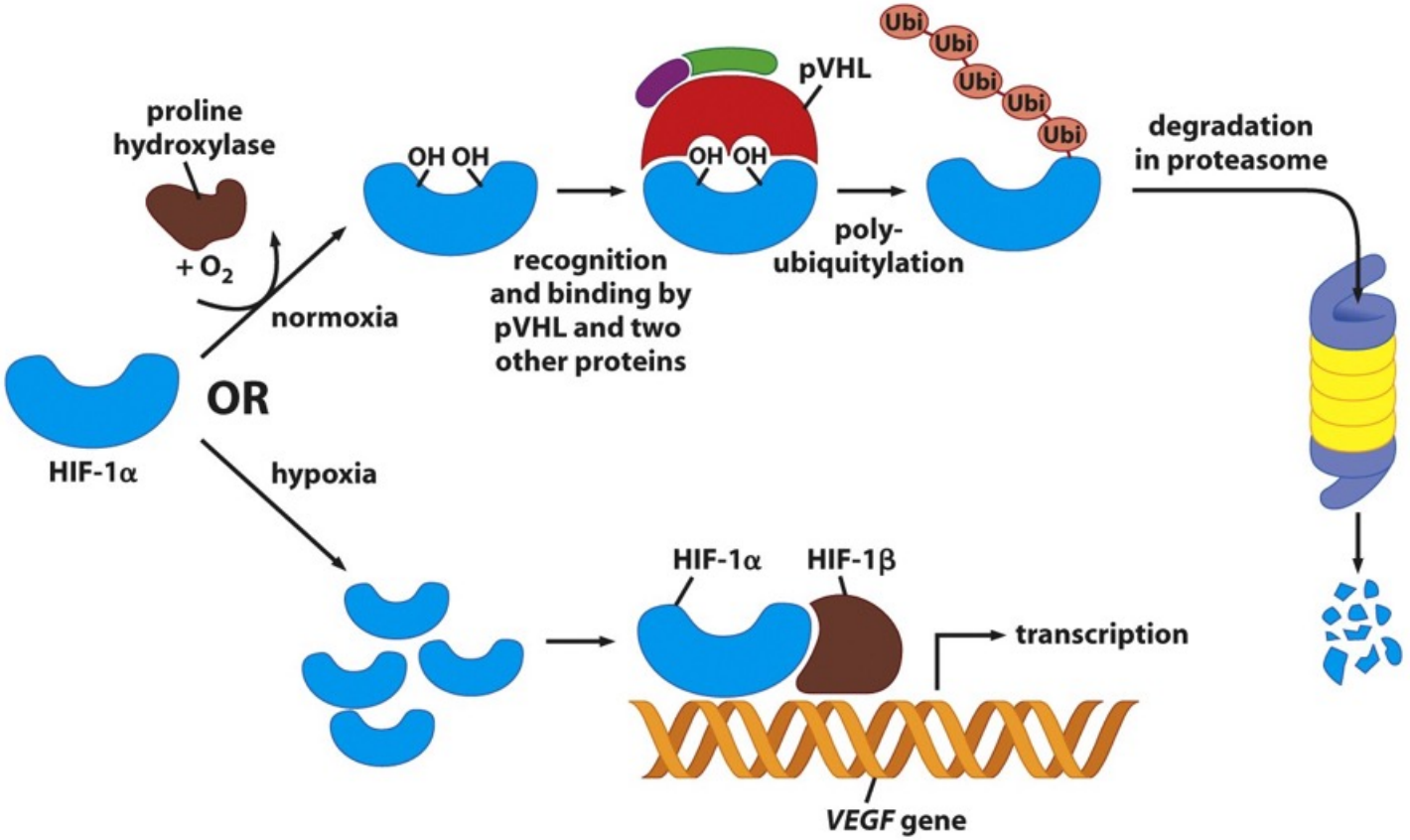
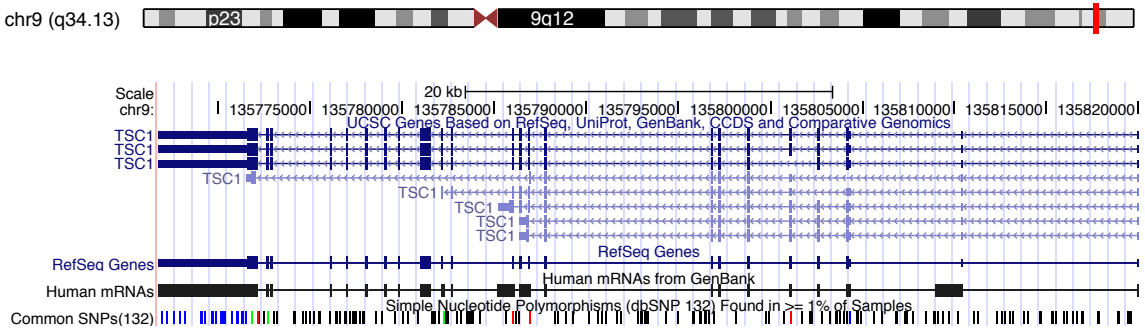


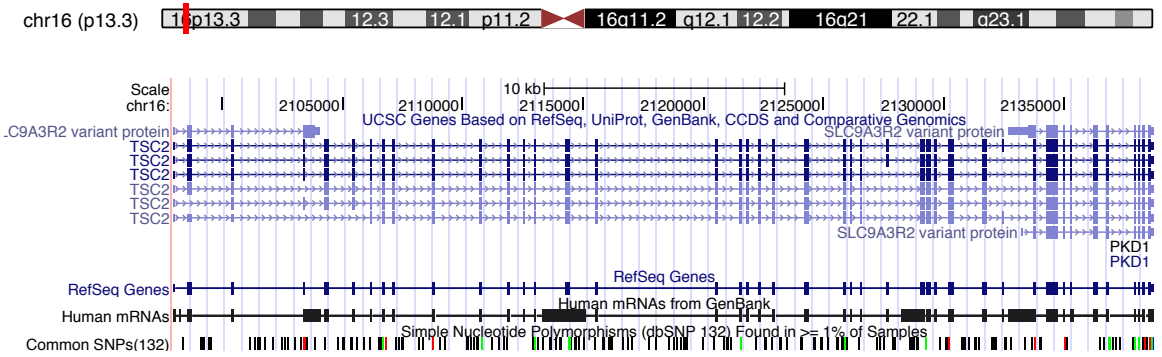
Figure 7.28a *The Biology of Cancer* (© Garland Science 2007)

Tuberous Sclerosis (TSC)

TSC1 – 9q34



TSC2 – 16p13



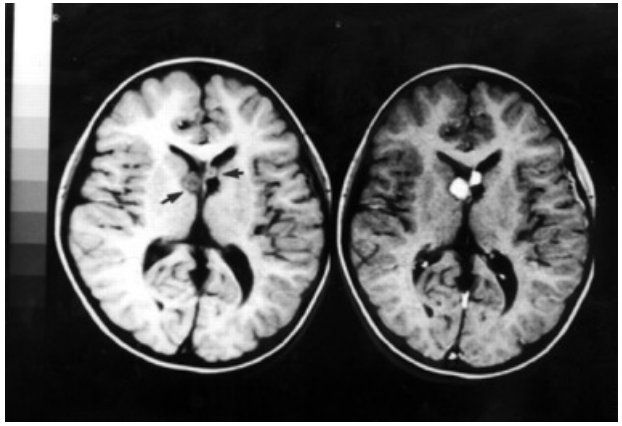
Tuberous Sclerosis (TSC)

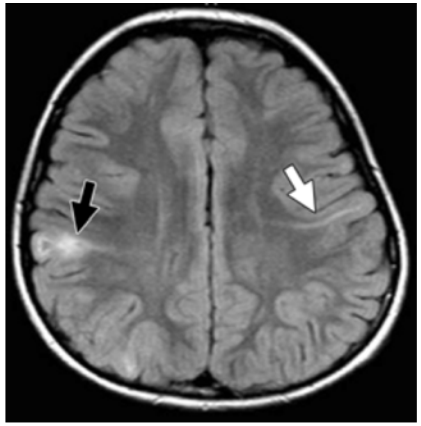
- De novo mutations
- Autosomal dominant
- Gonadal mosaicism (blood test will not reveal mutation)

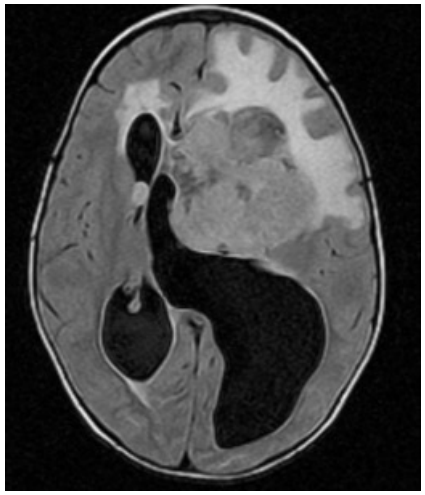
Tuberous Sclerosis (TSC)

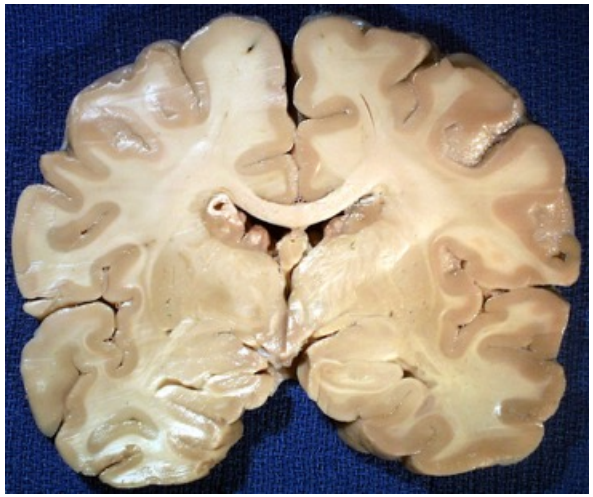
- Brain
  - Cortical tubers
  - Subependymal nodules
  - SEGA
- Renal
  - Cysts & angiomyolipomas (70-80% patients)
  - RCC, oncocytomas
  - Bleeding from cysts and AML
- Cardiac rhabdomyomas
- Skin
  - Hypomelanic macules (ash leaf spots)
  - Facial angiofribromas (also called adenoma sebaceum)
  - Forehead plauqes
  - Shagreen patches (lower back or nape of neck)
  - Ungual or subungual fibromas (can cause bleeding)
- Other organs affected
  - Liver, lung, pancreas, bone cysts, rectal polyps, gum fibromas, dental pits

Tuberous Sclerosis (TSC)

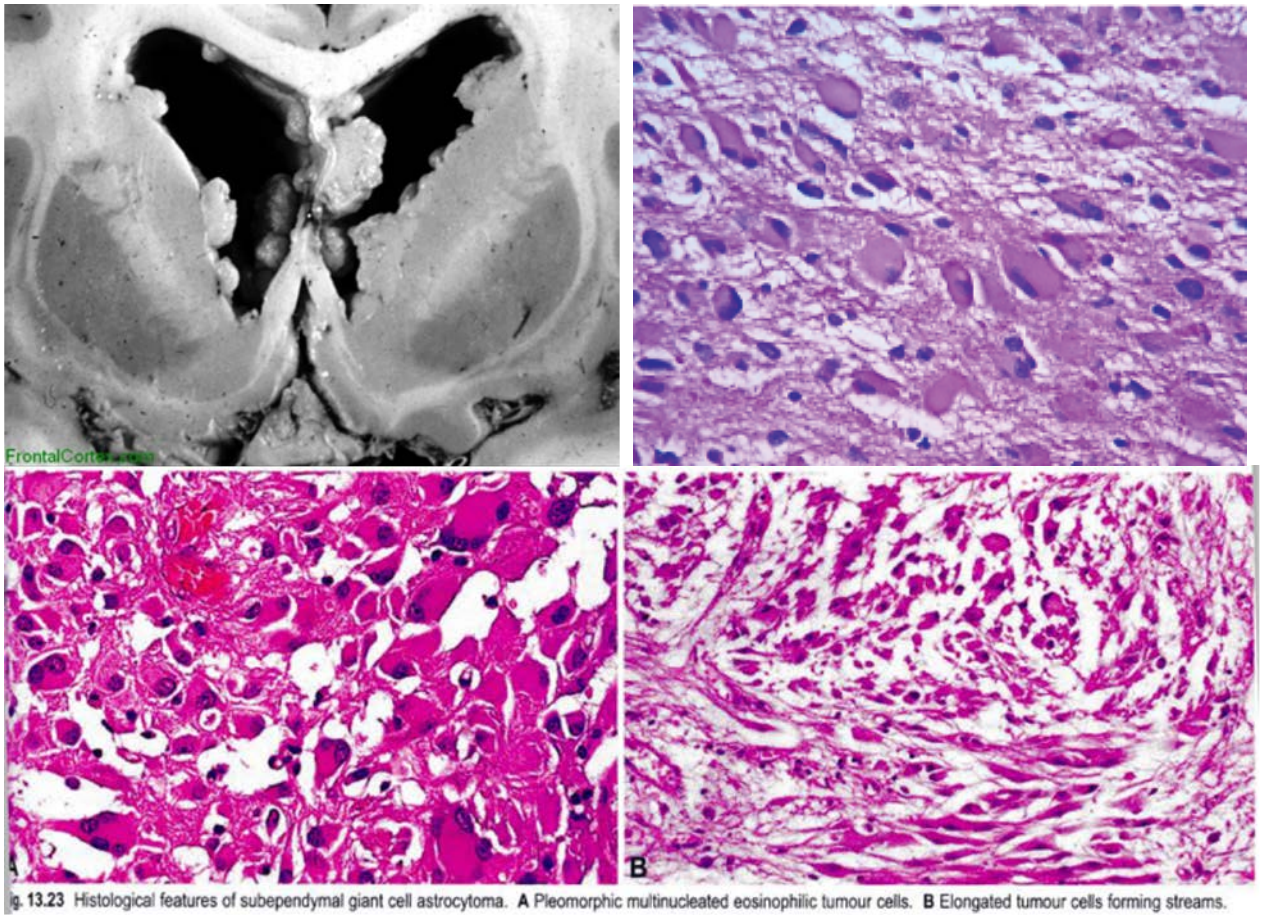






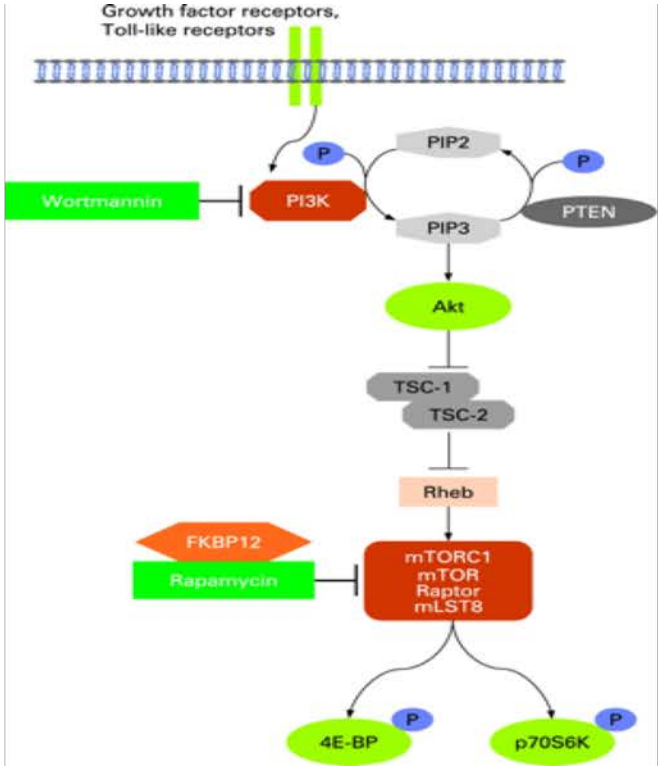


Tuberous Sclerosis (TSC)



ig. 13.23 Histological features of subependymal giant cell astrocytoma. **A** Pleomorphic multinucleated eosinophilic tumour cells. **B** Elongated tumour cells forming streams.

Tuberous Sclerosis (TSC)



Tuberous Sclerosis (TSC)

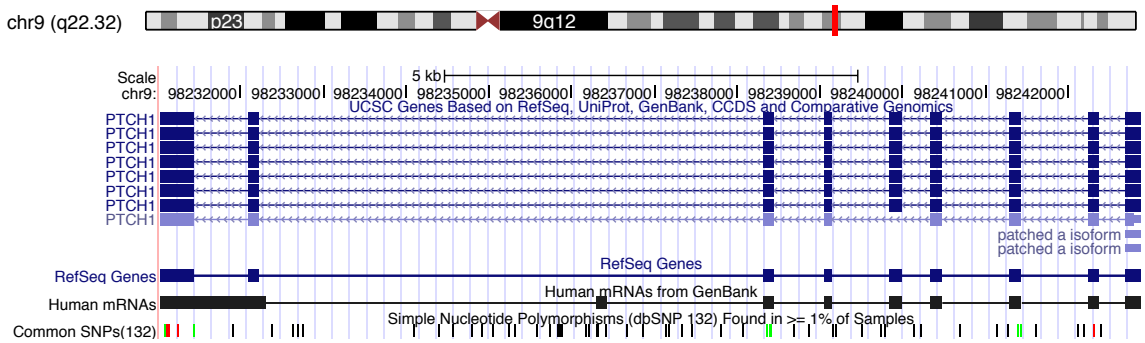
ORIGINAL ARTICLE

Everolimus for Subependymal Giant-Cell Astrocytomas in Tuberous Sclerosis

Darcy A. Krueger, M.D., Ph.D., Marguerite M. Care, M.D.,
Katherine Holland, M.D., Ph.D., Karen Agricola, F.N.P., Cynthia Tudor, P.N.P.,
Prajakta Mangeshkar, M.S., Kimberly A. Wilson, M.S., Anna Byars, Ph.D.,
Tarek Sahmoud, M.D., Ph.D., and David Neal Franz, M.D.

Gorlin Syndrome (Nevoid Basal Cell Carcinoma Syndrome - NBCCS)

- PTCH1 - 9q22

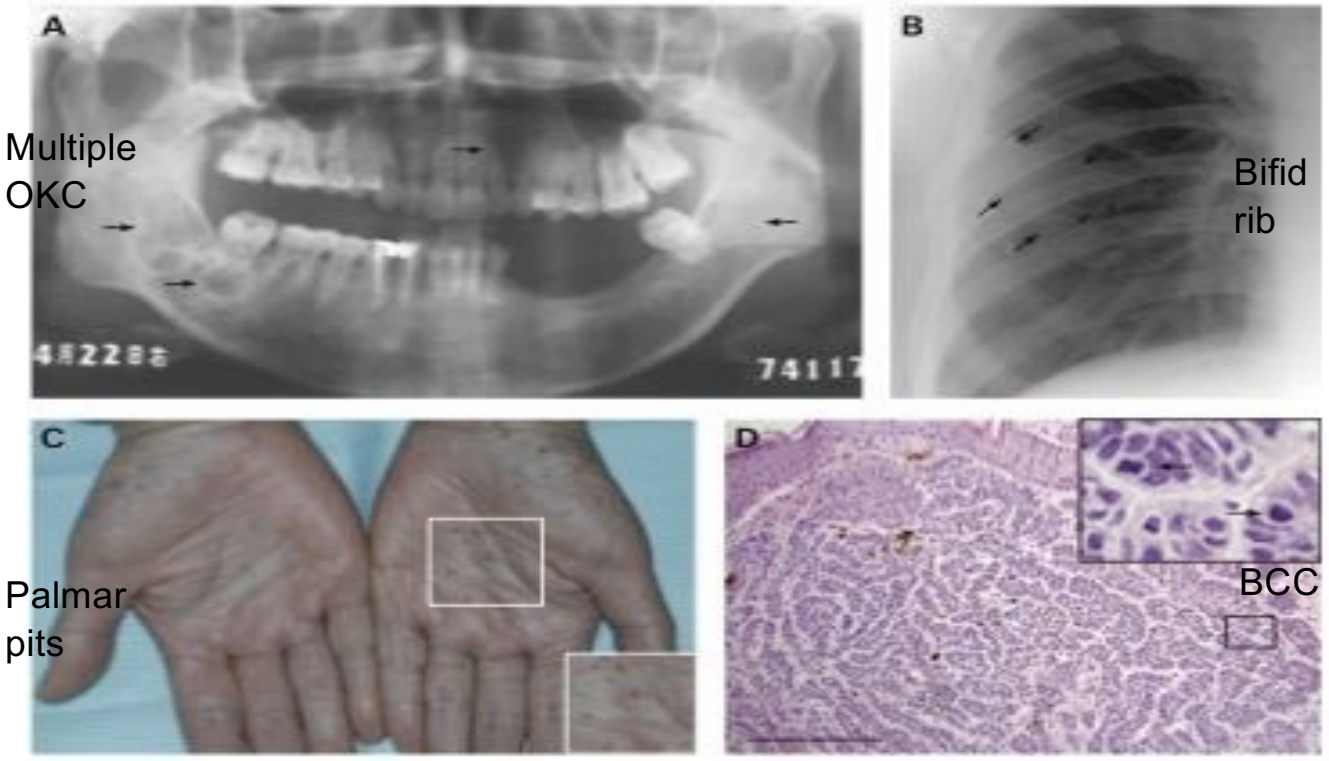


- Autosomal dominant
- 160kd

Gorlin Syndrome (NBCSS)

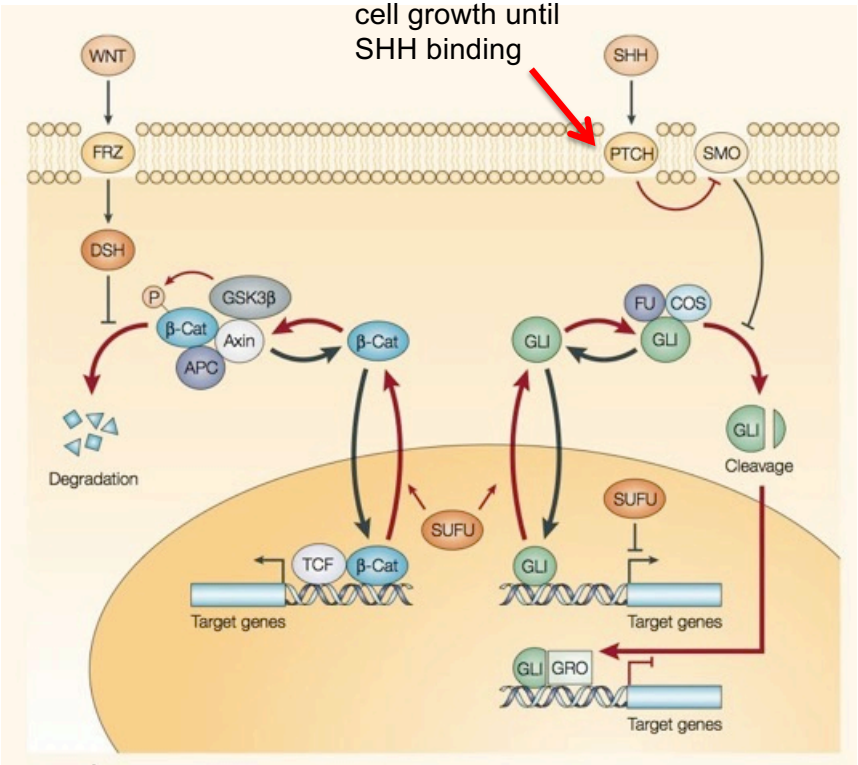
- Prevalence 1:57000
- Medulloblastoma (desmoplastic variant)
- Basal cell carcinomas
  - Face, chest, back
  - Number of tumour varies between affected patients
- Keratocystic odontogenic tumours of the jaw
- Ovarian fibromas (fertility)
- Cardiac fibromas
  - Outflow obstruction, arrhythmia

Gorlin Syndrome - NBCCS



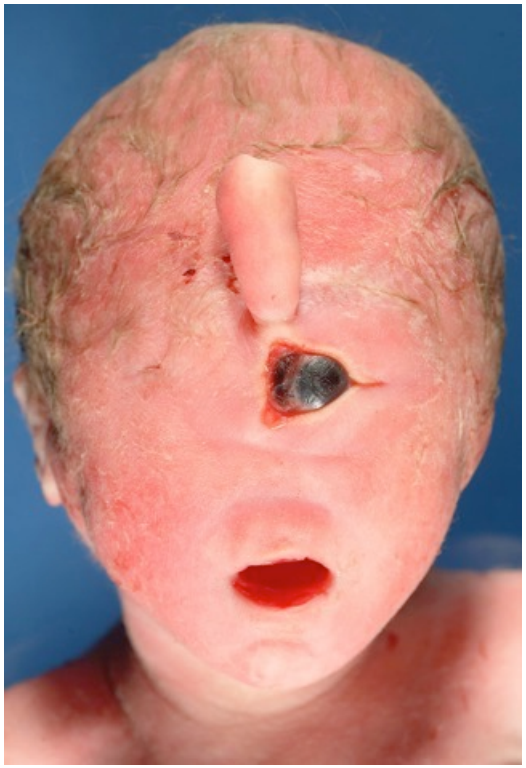
Gorlin Syndrome - NBCCS

PTCH suppresses cell growth until SHH binding



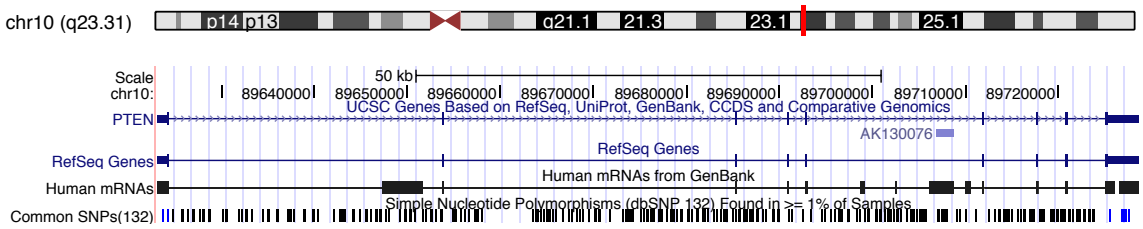
PTCH1 is also involved in holoprosencephaly

Cyclopia, proboscis, nasal agenesis



Lhermitte- Duclos Syndrome (Cowden disease)

- PTEN – 10q23

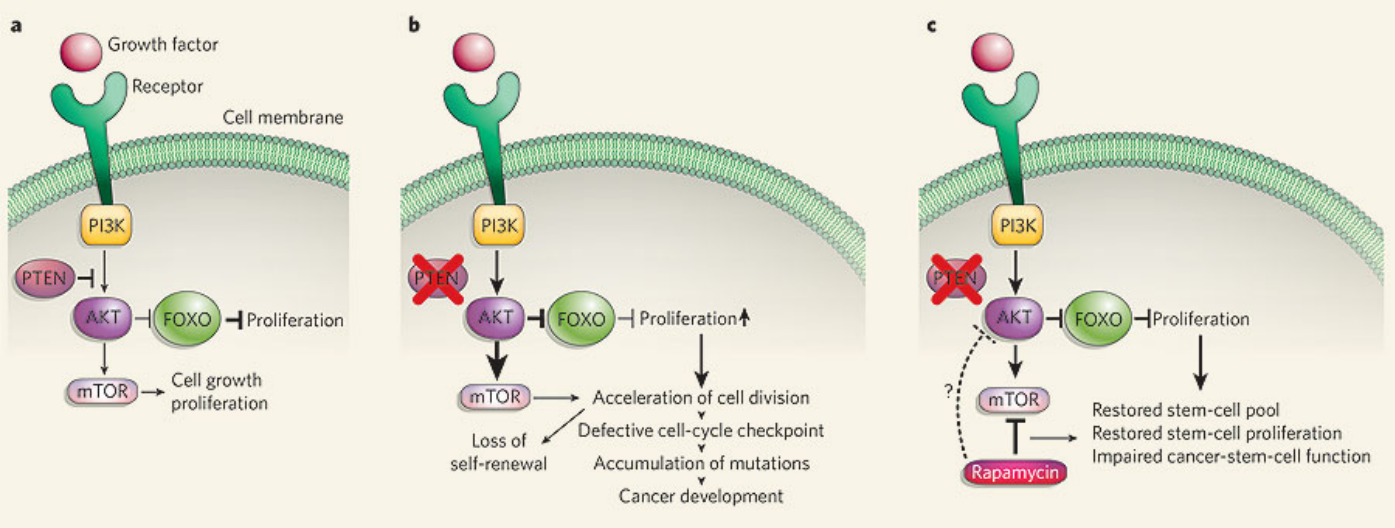


- Autosomal dominant
- Bannayan-Riley-Ruvalcaba Syndrome
  - Triad of macrocephaly, lipomatosis, angiomatosis
- Macrocephaly

Lhermitte- Duclos Syndrome (Cowden disease)

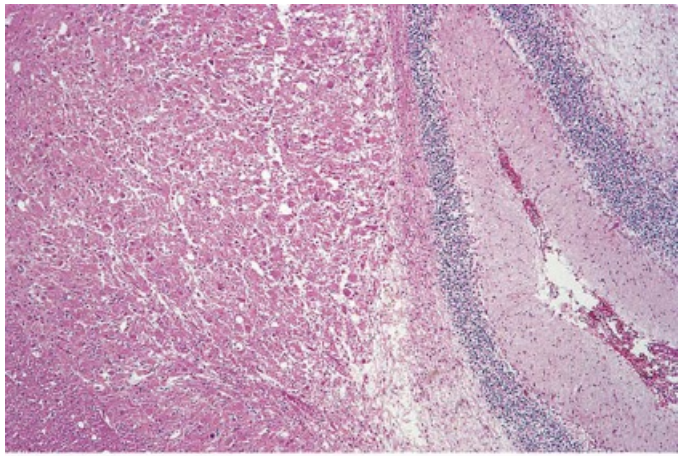
- Incidence of Cowdon syndrome is 1: 250,000
- Multiple hamartomas in tissues from all 3 germ layers
- Trichilemmoma, adult-onset dysplastic gangliocytoma of CBx are pathognomonic for germline mutations in *PTEN*
- Increased risks of cancers
  - Breast, non- medullary thyroid, endometrial
- 1.2 kb transcript – 47 kd
- 30-40% germline mutations in exon5 – abrogate PTPase function (65% mutations in exons 5, 7, 8)

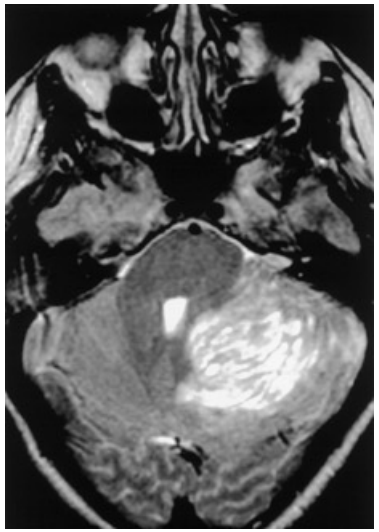
Lhermitte-Duclos disease (PTEN)

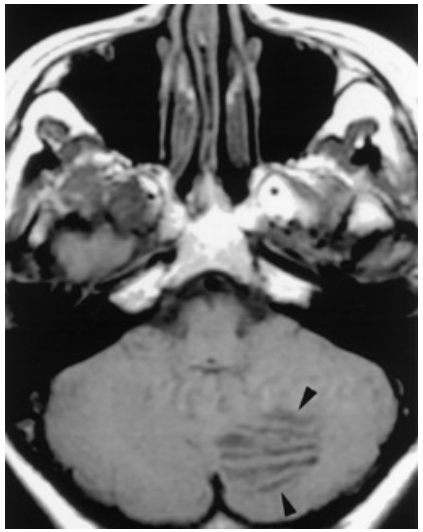


PTEN normally regulates signals promoting cell growth and proliferation

Lhermitte-Duclos disease (PTEN)



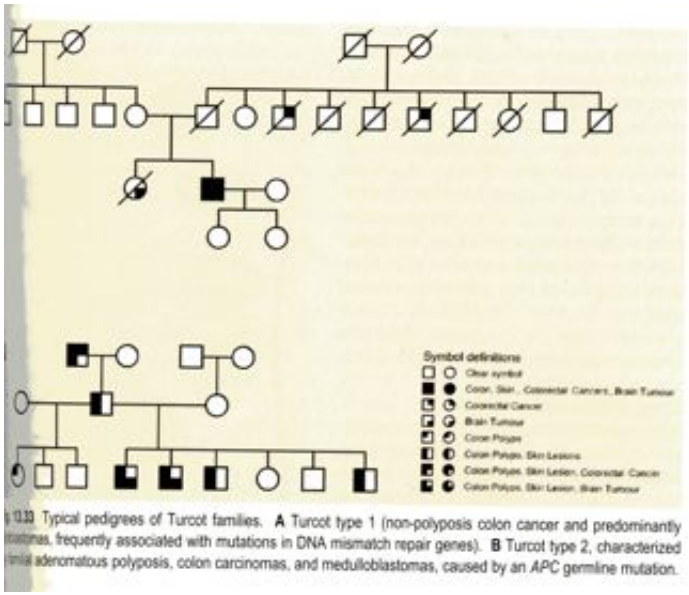




WHO I

Distortion but not destruction of CBx architecture
Loss of PTEN expression (IHC)
Increased pAKT and S6
Hypertrophy rather than hyperplasia

Mode of transmission of Turcot Disease

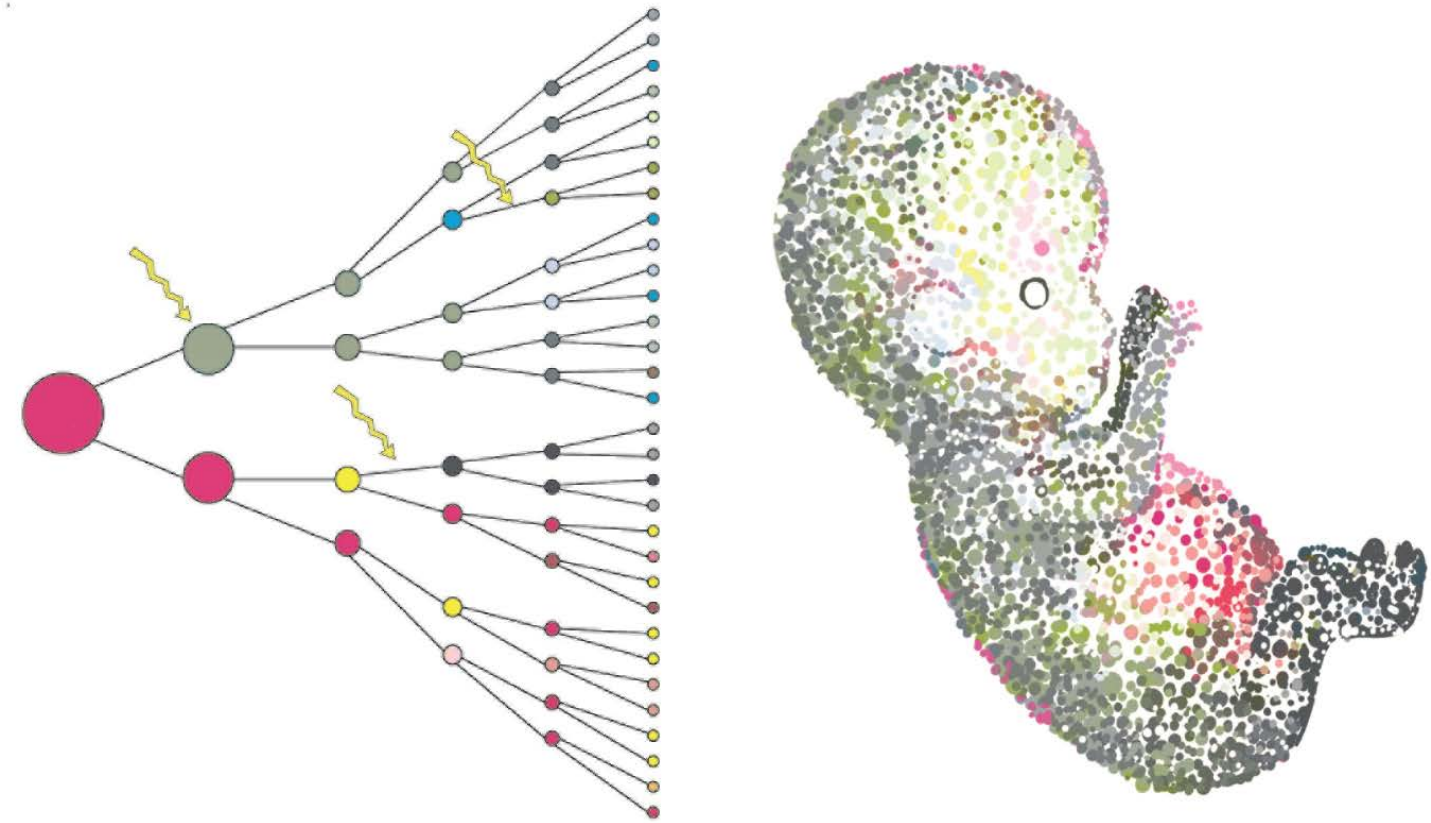


Typical pedigrees of Turcot families. **A** Turcot type 1 (non-polyposis colon cancer and predominantly ...omas, frequently associated with mutations in DNA mismatch repair genes). **B** Turcot type 2, characterized ...milial adenomatous polyposis, colon carcinomas, and medulloblastomas, caused by an *APC* germline mutation.

Turcot Type 1
MSH genes
NPCC
Colorectal Ca & GBM

Turcot Type 2
APC gene
FAP, Colorectal Ca,
Medulloblastoma

Somatic mosaicism



http://sangerinstitute.wordpress.com/2014/04/28/single-cell-genomics-thinking-small/

Parents

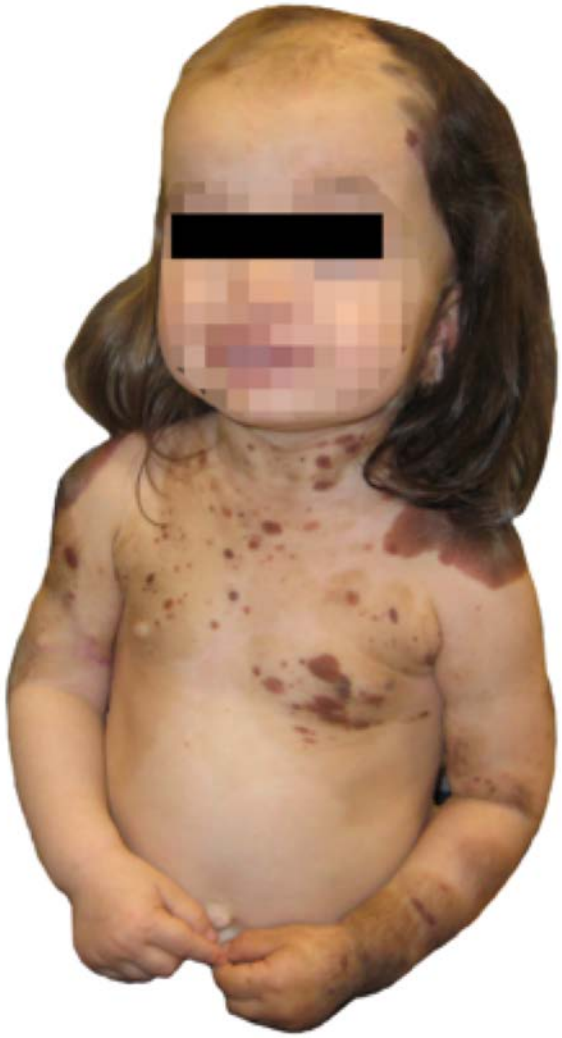
- Healthy, non-consanguinous couple
- Uneventful full-term pregnancy

At birth

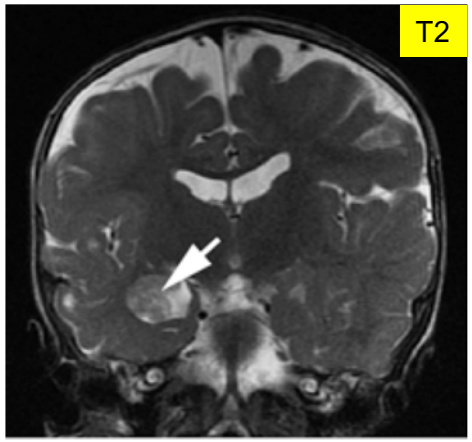
- Multiple hairy melanocytic lesions
- Intradermal and compound nevi with congenital features

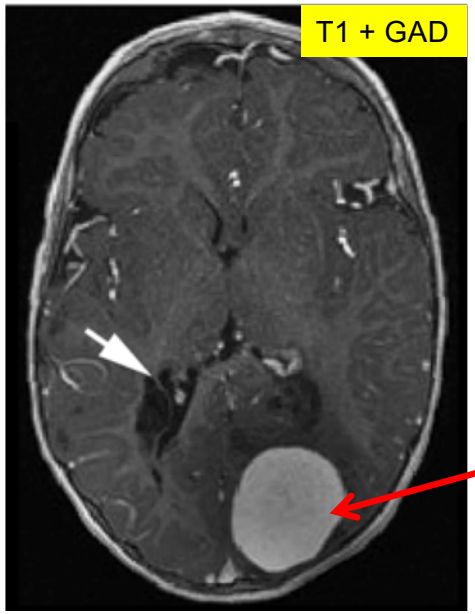
2 months of age

- Macrocephalic (97th percentile)
- Episodes of seizure
- MRI show multiple solid and cystic intracerebral lesions some with features of melanin deposition



Shih F, Yip S, McDonald PJ, Chudley AE, Del Bigio MR. Oncogenic codon 13 NRAS mutation in a primary mesenchymal brain neoplasm and nevus of a child with neurocutaneous melanosis. Acta neuropathologica communications. 2014;2(1):140.





<u>14 months of age</u>

- Right choroid plexus tumour

<u>23 months of age</u>

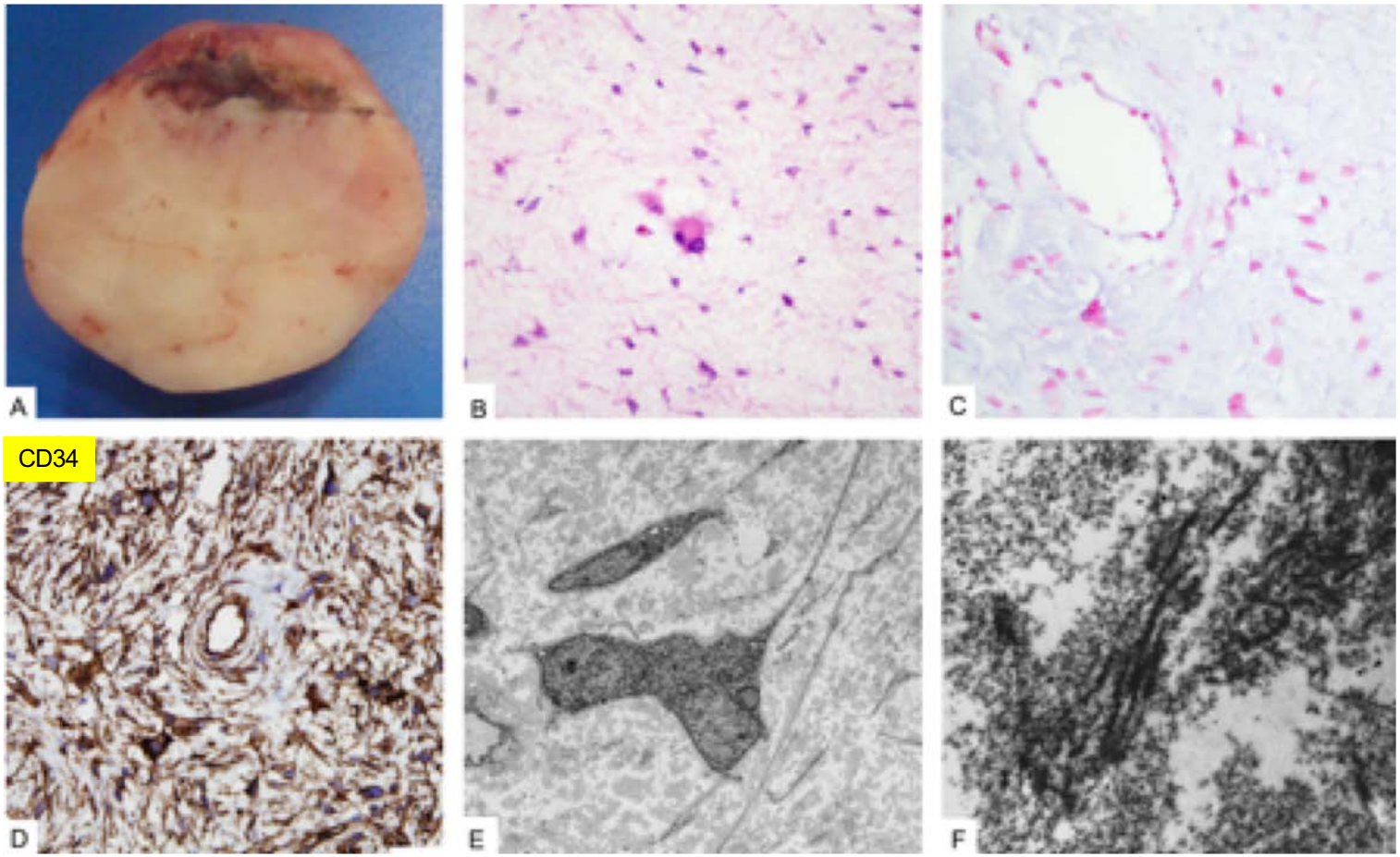
- Left occipital lobe tumour, expanding
- Right periventricular cysts adjacent to occipital horn

<u>24.5 months of age</u>

- Left occipital craniotomy
- Tumour away from dura, single vascular pedicle
- Easily defined tumour/brain interface

Shih F, Yip S, McDonald PJ, Chudley AE, Del Bigio MR. Oncogenic codon 13 NRAS mutation in a primary mesenchymal brain neoplasm and nevus of a child with neurocutaneous melanosis. Acta neuropathologica communications. 2014;2(1):140.

Left occipital tumour resected at 24.5 months of age



Shih F, Yip S, McDonald PJ, Chudley AE, Del Bigio MR. Oncogenic codon 13 NRAS mutation in a primary mesenchymal brain neoplasm and nevus of a child with neurocutaneous melanosis. Acta neuropathologica communications. 2014;2(1):140.

Left occipital tumour resected at 24.5 months of age

- Stellate and elongated cells in a myxoid background
- NO PIGMENTED CELLS
- Immunopositive for CD34 and vimentin

- Dx – Myxoid mesenchymal brain tumour of uncertain growth potential

Shih F, Yip S, McDonald PJ, Chudley AE, Del Bigio MR. Oncogenic codon 13 NRAS mutation in a primary mesenchymal brain neoplasm and nevus of a child with neurocutaneous melanosis. Acta neuropathologica communications. 2014;2(1):140.

Neurocutaneous Melanosis

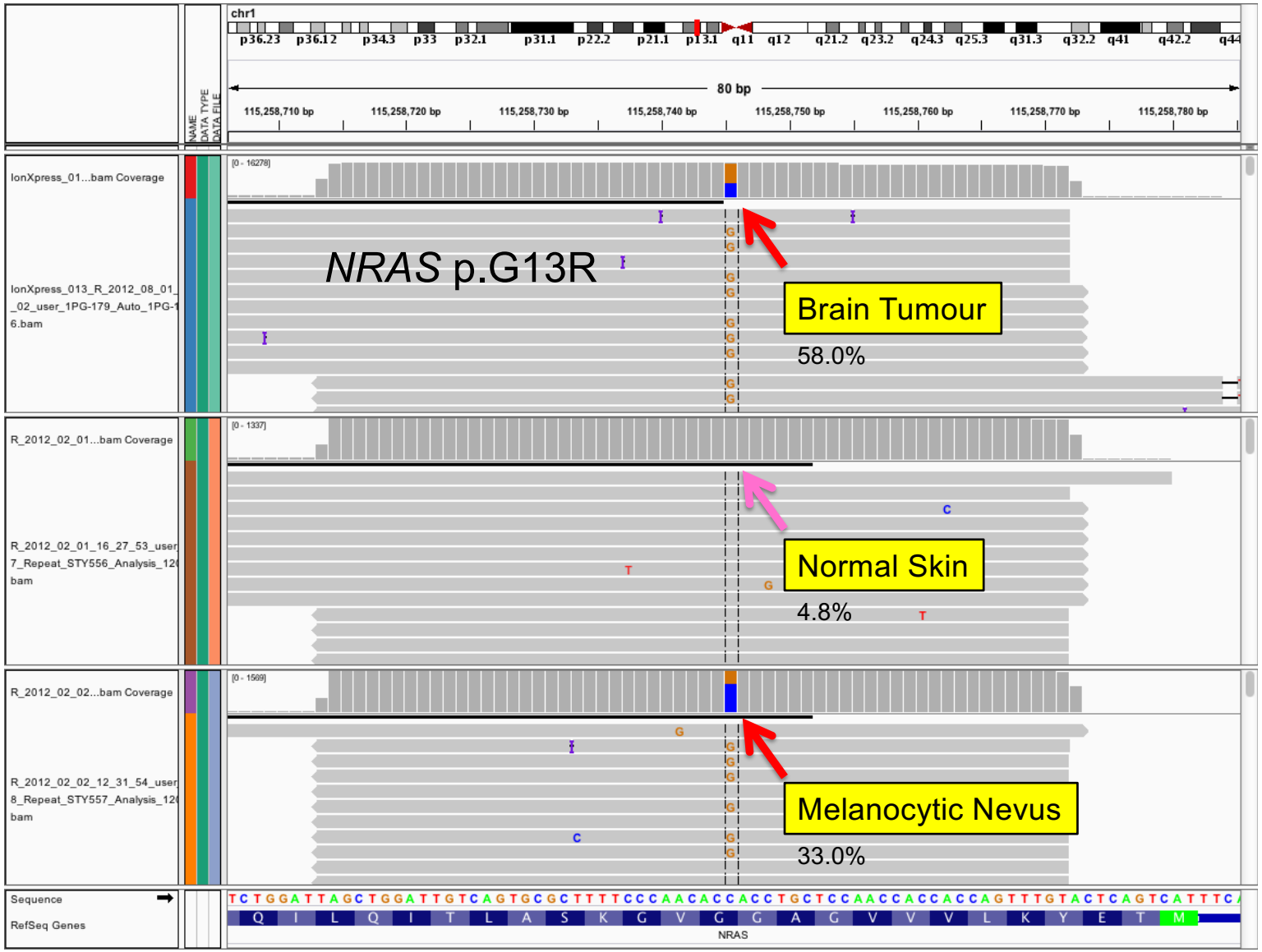
- Multiple giant cutaneous melanocytic nevi with 5% lifetime risk of transformation

- Extensive leptomeningeal melanosis (30%)
- Epilepsy (50%)
- Dandy Walker Malformation

- Approximately 100 cases described in literature

- Somatic *NRAS* codon 61 mutation
- Activation of RAS/MAPK pathway

Dessars B et al. Genotypic and gene expression studies in congenital melanocytic nevi: insight into initial steps of melanotumorigenesis. J Invest Dermatol 2009: 129; 139-147.


chr1
p36.23 p36.12 p34.3 p33 p32.1 p31.1 p22.2 p21.1 p13.1 q11 q12 q21.2 q23.2 q24.3 q25.3 q31.3 q32.2 q41 q42.2
80 bp
115,258,710 bp
115,258,720 bp
115,258,730 bp
115,258,740 bp
115,258,750 bp
115,258,760 bp
115,258,770 bp
115,258,780 bp
NAME
DATA TYPE
DATA FILE
IonXpress_01...bam Coverage
IonXpress_013_R_2012_08_01_
_02_user_1PG-179_Auto_1PG-1
6.bam
NRAS p.G13R
Brain Tumour
58.0%
R_2012_02_01...bam Coverage
R_2012_02_01_16_27_53_user
7_Repeat_STY556_Analysis_12
bam
Normal Skin
4.8%
R_2012_02_02...bam Coverage
R_2012_02_02_12_31_54_user
8_Repeat_STY557_Analysis_12
bam
Melanocytic Nevus
33.0%
Sequence
RefSeq Genes
NRAS

Allelic frequency of *NRAS* mutation

Gene	*NRAS*	*BRAF*
Chr: Position (hg19)	1:115258745	7:140481411
Nucleotide change	c.37G>C	c.1397G>T
Amino Acid change	p.Gly13Arg	p.Gly466Val
Brain Tumour	58.00	0.00
Melanocytic Nevus	33.00	32.00
Normal Skin	4.76	0.00
Patient buccal swab	2.69	0.00
Mother buccal swab	0.00	0.00
Father buccal swab	0.00	0.00

Shih F, Yip S, McDonald PJ, Chudley AE, Del Bigio MR. Oncogenic codon 13 NRAS mutation in a primary mesenchymal brain neoplasm and nevus of a child with neurocutaneous melanosis. Acta neuropathologica communications. 2014;2(1):140.

Allelic frequency of *BRAF* mutation

Gene	*NRAS*	*BRAF*
Chr: Position (hg19)	1:115258745	7:140481411
Nucleotide change	c.37G>C	c.1397G>T
Amino Acid change	p.Gly13Arg	p.Gly466Val
Brain Tumour	58.00	0.00
Melanocytic Nevus	33.00	32.00
Normal Skin	4.76	0.00
Patient buccal swab	2.69	0.00
Mother buccal swab	0.00	0.00
Father buccal swab	0.00	0.00

Somatic mosaicism

- Not all cells in the body are genetically identical
- Assaying one tissue will not reflect the genetic state of the diseased tissue
- Can be a mechanism of disease with characteristic features (syndromic)
  - Proteus, Maffucci, CLOVES, Sturge-Weber
- Genomic
  - Mutations and copy number changes
- Epigenomic
  - Methylation, chromatin marks
- Low frequency events can be difficult too resolve using traditional techniques

Familial brain tumour syndromes

Autosomal dominant transmission

Tumour suppressor gene – Dominant negative effect

Often involves other systems esp. phakomatosis

General cancer vs brain tumour predisposition syndromes

Unique pathways affected could be targeted with selective inhibitors