Less Familiar Cancer Genes and Syndromes

Mark H. Greene, M.D.

Chief, Clinical Genetics Branch

Division of Cancer Epidemiology & Genetics

National Cancer Institute

Ataxia-Telangiectasia

- Incidence: 1 in 40,000 to 1 in 100,000
- Autosomal recessive inheritance
- Caused by mutations in the *ATM* gene, found on the long arm of chromosome 11 (11q22.3)
- Diagnostic testing
  - Serum AFP
  - Colony survival assay
  - Karyotyping (translocation 7;14)
  - Immunocompetence assays

Ataxia-Telangiectasia

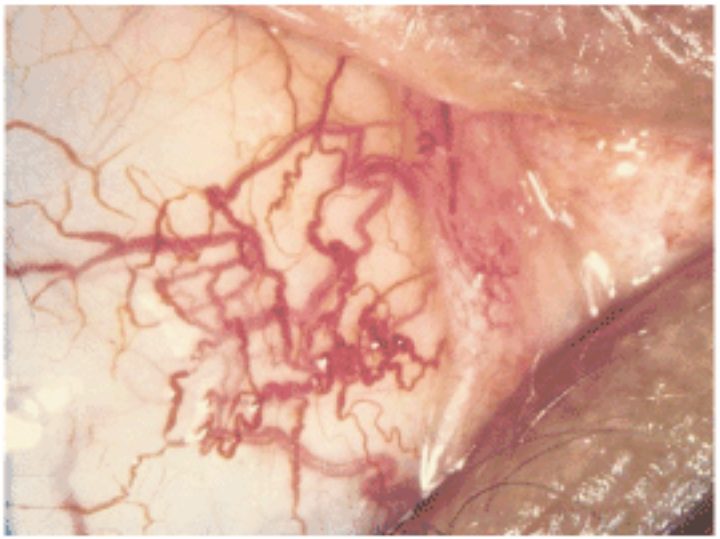
- Clinical features
  - Progressive cerebellar ataxia
  - Facial and conjunctival telangiectasia
  - Combined immunodeficiency
  - Growth retardation
  - Usually normal intelligence
- Associated malignancies
  - Lymphoma/leukemia (in ~40%)
  - Increased risk for solid tumors (e.g., ovary, breast, melanor stomach)

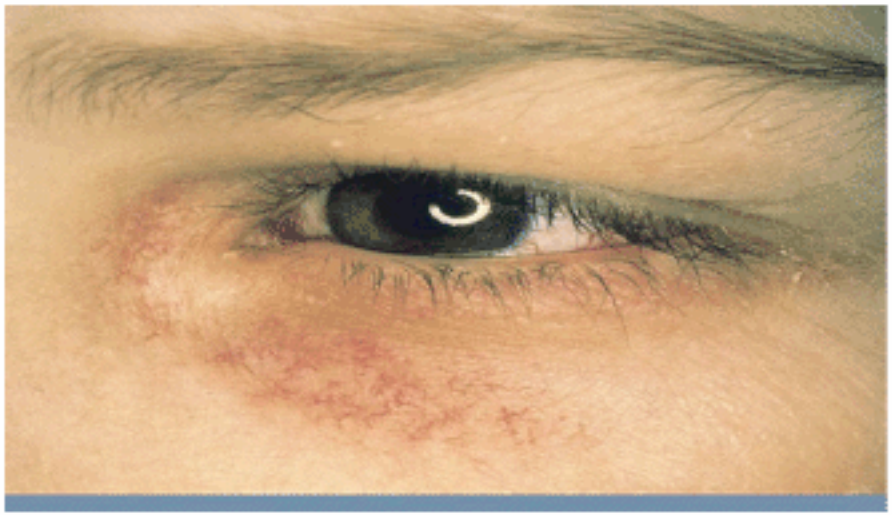
Jones KL. In: *Smith's Recognizable Patterns of Human Malformation.* 5th ed. Philadelphia: WB Saunders Co; 1997: 196-197.

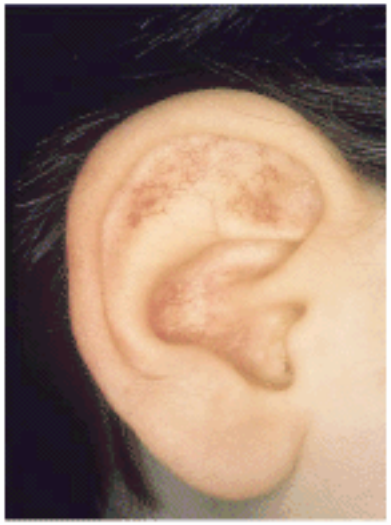
Olsen JH, et al. *J Natl Cancer Inst.* 2001;93:121-127.

Swift M, et al. *N Engl j Med.* 1991;1831–1836.

Ataxia-Telangiectasia *(cont.)*







Photos courtesy of Yossi Shiloh, PhD

Heterozygous *ATM* Mutation Carriers

- Ataxia-telangiectasia is an autosomal recessive condition
- *ATM* gene on chromosome 11 cloned in 1995
- Early studies suggested that female carriers have an elevated risk of breast cancer
- Two *ATM* mutations identified in Australia: T7271G, IVS10-6T → G
  - 15.7-fold elevated risk of breast cancer in carriers
  - Found in families with multiple cases of breast cancer

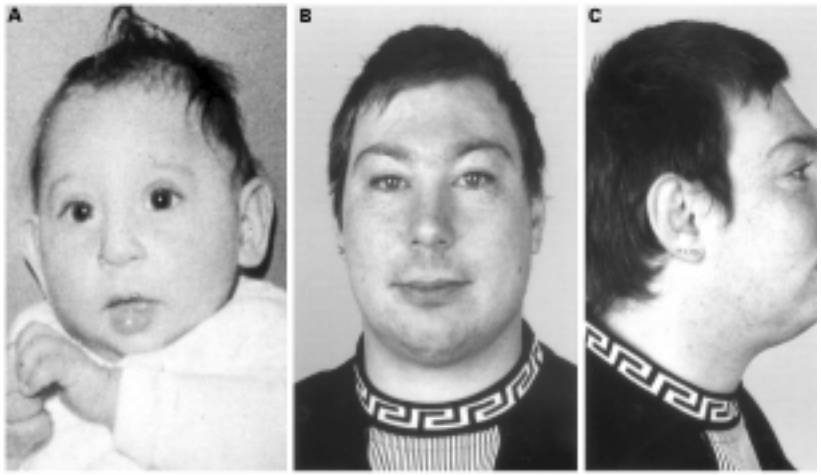
Chenevix-Trench G et al. *J Natl Cancer Inst.* 2002;94:205-215.
Khanna KK. *J Natl Cancer Inst.* 2000;92:795-802.
Savitsky K et al. *Science.* 1995;268:1749-1753.

Heterozygous *ATM* Mutation Carriers

- This issue is of importance in view of the frequency of *ATM* heterozygotes in the general population, estimated as ~ 2-3%
- The summary estimated relative risk of breast cancer in *ATM* heterozygotes is ~4 (D Easton: Int J Radiat Biol 1994; 66 [Suppl 6]:177-182)
- If both estimates are correct, 3-4% of all breast cancer might be attributable to *ATM* heterozygosity
- Problem: more recent epi studies have yielded conflicting results regarding whether this risk estimate is correct (RM Tamimi et al: Breast Cancer Res 2004; 6:R16-R22)
- The strongest data in support of there being a relationship between *ATM* and breast cancer risk are found in studies targeting female family members from AT kindreds (JH Olsen et al: JNCI 2001; 93:121-127)

Nijmegen Breakage Syndrome

- Clinical features
  - Microcephaly
  - Growth retardation/short stature
  - Mental retardation
  - Irregular pigmentation
  - Immunodeficiency
  - 1° ovarian failure
  - Congenital malformations
- Associated malignancies
  - Lymphoma, especially B cell
  - Other lymphoreticular cancers



Concannon PJ, Gatti RA. GeneTests [database online]. Available at: http://www.geneclinics.com. Accessed November 11, 2002.

The International Nijmegen Breakage Syndrome Study Group. *Arch Dis Child*. 2000 82:400-406. Photos reprinted with permission fro BMJ Publishing Group.

OMIM™. Available at: http://www.ncbi.nlm. nih.gov/omim. Accessed November 11, 2002.

Nijmegen Breakage Syndrome *(cont.)*

- Incidence: ~1 in 100,000
- Autosomal recessive inheritance
- Associated with mutations in *NBS1* (8q21.3)
  - Almost 100% of Slavic patients and ~70% of North America patients are 657del5 homozygotes
  - Clinical testing available for 657del5
- Gene product is nibrin, which complexes with the protein products of *hMre11* and *hRAD50* to aid in DNA repair

Carney JP et al. *Cell.* 1998;93:477-486.

Concannon PJ, Gatti RA. GeneTests [database online]. Available at: http://www.geneclinics.com. Accessed November 11, 2002.

Varon R et al. *Cell.* 1998;93:467-476.

Heterozygous *NBS* Mutation Carriers

- Two founder mutations in NBS occur in Poland, permitting genetic studies to be more efficiently accomplished
- 23 of 1289 (1.8%) subjects with various cancers carried one of the founder mutations, versus 14/1620 (0.9%) controls
  - significantly increased risks of melanoma, NHL and colon cancer were seen
  - (J Steffen et al: Int J Cancer 2004; 111:67-71)
- Another Polish study:
  - 0.6% of 1500 controls were carriers
  - 7% of 305 prostate cancer cases were carriers (OR = 3.9)
  - 9% of 56 familial prostate cancer cases were carriers (OR = 16)
  - (C Cybulski et al: Cancer Res 2004; 64:1215-1219)

Bloom Syndrome

- Clinical features
  - Prenatal and postnatal growth delay/short stature
  - Spotty hypo- and hyperpigmentation
  - Facial telangiectatic erythema
  - Photosensitivity
  - Microcephaly
  - Immunoglobulin deficiency

Bloom Syndrome. In: Gorlin RJ, Cohen MM Jr, Levin LS, eds. *Syndromes of the Head and Neck.* 3rd ed. New York: Oxford University Press; 1990:297-300. Photo reprinted with permission from Oxford University Press.

Bloom Syndrome *(cont.)*

- Incidence: rare in most ethnic groups; 1 in 100,000 in Ashkenazi Jews
- Autosomal recessive inheritance
- High rate of chromosomal instability
  - Elevated sister chromatid exchange (pathognomonic)

Wamen S et al. *Proc Nat Acad Sci U S A.* 1581;78:3133–3137.
Roa BB, et al. *Genet Test.* 1999;3:219-221.

Bloom Syndrome *(cont.)*

- Gene mutated is *RECQL3 (BLM)* at locus15q26.1
  - 2281delta6ins7 is a founder mutation in Ashkenazi Jews (~1% are carriers)
- Gene product is a helicase involved in DNA repair

Ellis NA et al. *Cell.* 1995;83:655–666.

Imamura O et al. *Oncogene*. 2001;20:1143-1151.

Marsh DJ, Zori RT. *Cancer Lett*. 2002;181:125-164.

Roa BB et al. *Genet Test.* 1999;3:219-221.

Bloom Syndrome *(cont.)*

- Associated malignancies
  - Very high rate of cancer
  - Acute leukemia, lymphoma
  - Solid tumors in adults

    tongue — breast
    esophageal — others
    colon
  - Solid tumors in children

    medulloblastoma — osteosarcoma
    Wilms tumor — others

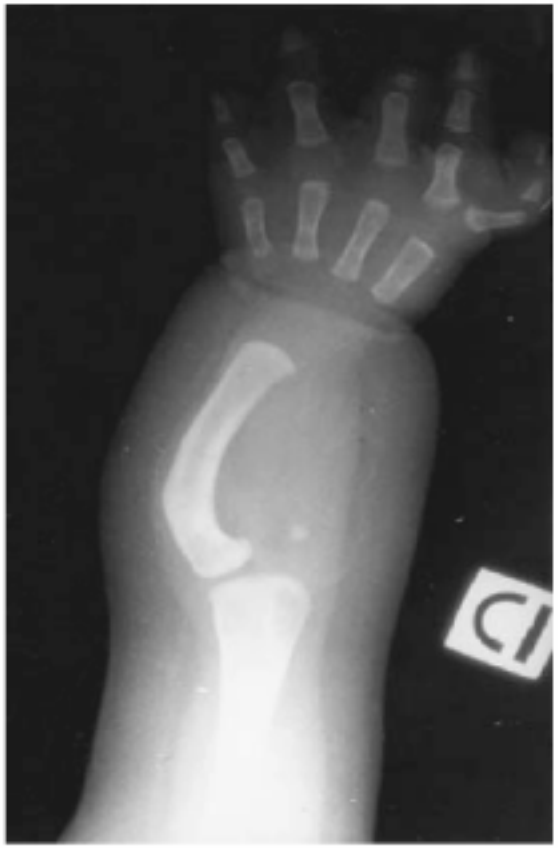
German J. *Cancer Genet Cytogenet.* 1997;93:100-106.
OMIM™. Available at: http://www.ncbi.nlm.nih.gov/omim. Accessed November 1, 2002.

Heterozygous *BLM* Mutation Carriers

- **Case (n=1244) – control (n=1839) study of colon cancer risk in *BLM* Heterozygotes in Subjects of Ashkenazi Jewish heritage**
- **Facilitated by the AJ *BLM* founder mutation**
- **Colorectal cancer subjects were 2.45 times more likely to carry the AJ BLM founder mutation than were controls**
  (SB Gruber et al: Science 2002; 297:2013)
- **Emerging concept: "HAPLOINSUFFICIENCY"**
  - **For some genes, a half-dose of its protein is not adequate for full gene function**
  - **May be a particular issue for genes involved in maintenance of genomic integrity**
  - **Subnormal levels of protein lead to genomic instability, increased mutation rate in affected cells, and an increased risk of malignant transformation**
    - **Examples: *ATM, NBS, XP, FA***

Fanconi Anemia

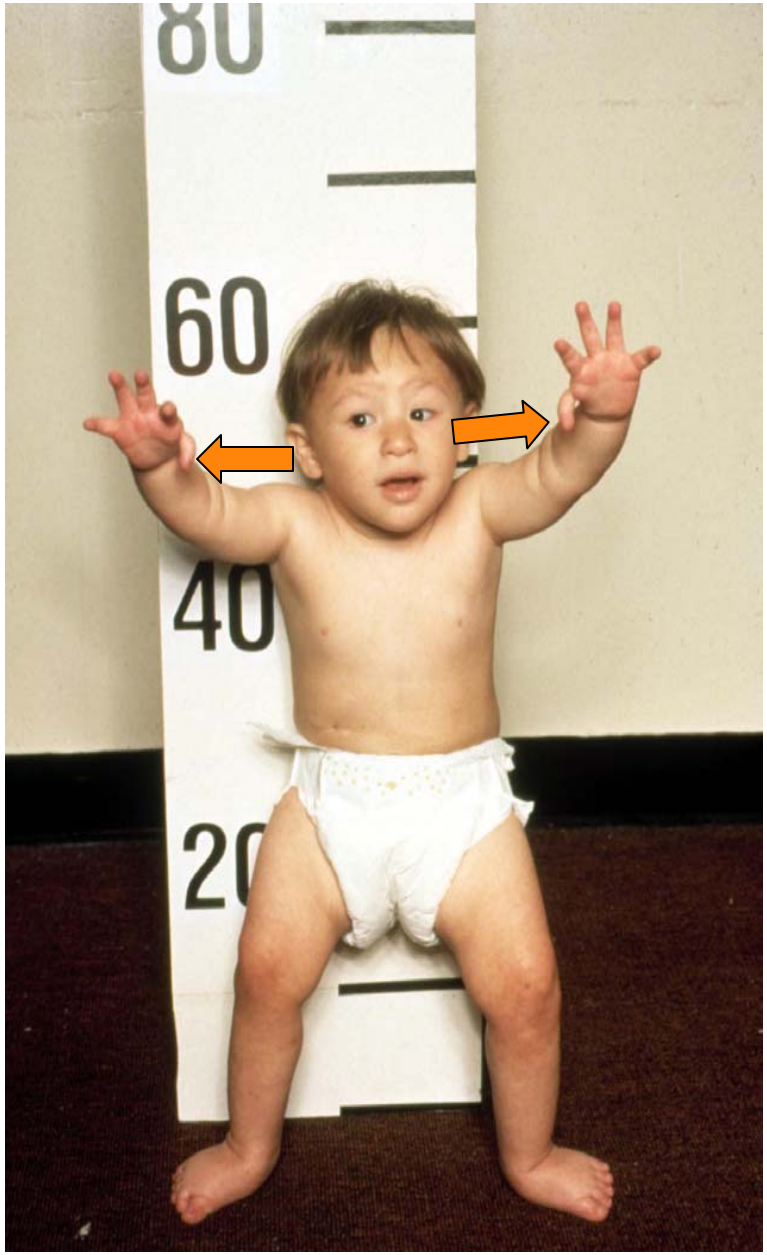
- Clinical features
  - Short stature
  - Abnormal pigmentation
  - Thumb abnormalities; radial hypoplasia (see radiograph)
  - Other multisystem congenital anomalies
  - Hearing loss
  - Progressive bone marrow failure with pancytopenia

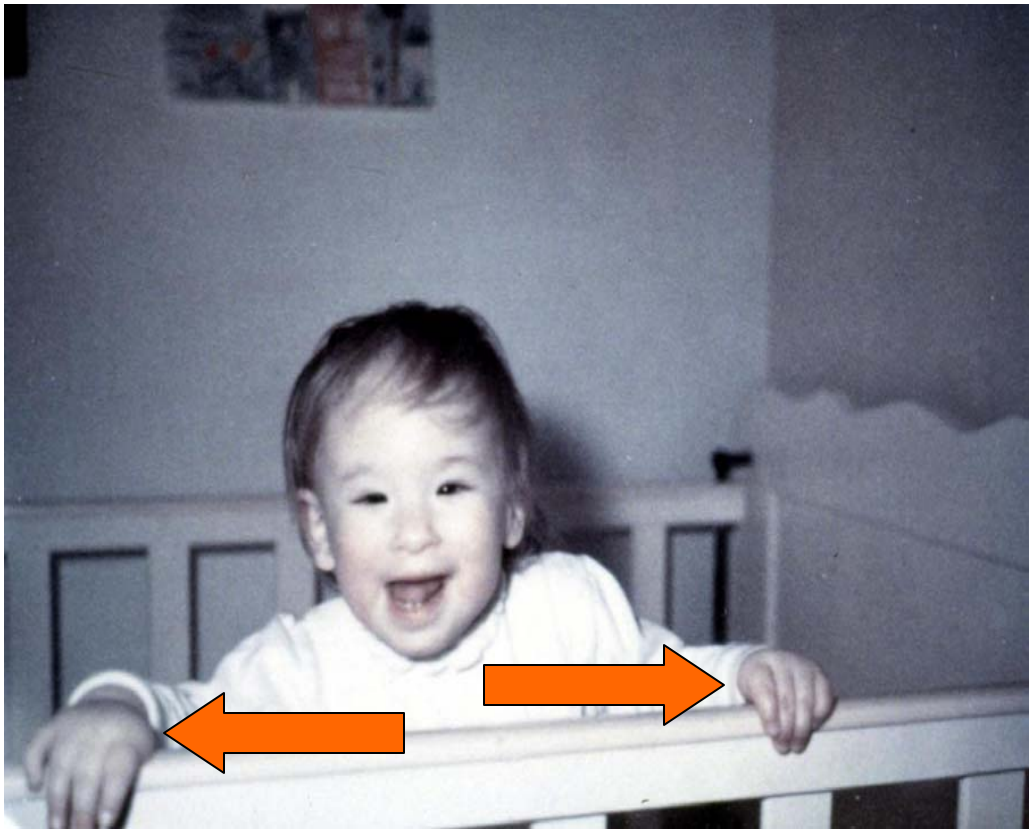


De Kerviler E et al. *Clin Radiol.* 2000;55:340-345. Figure reprinted with permission from Elsevier.

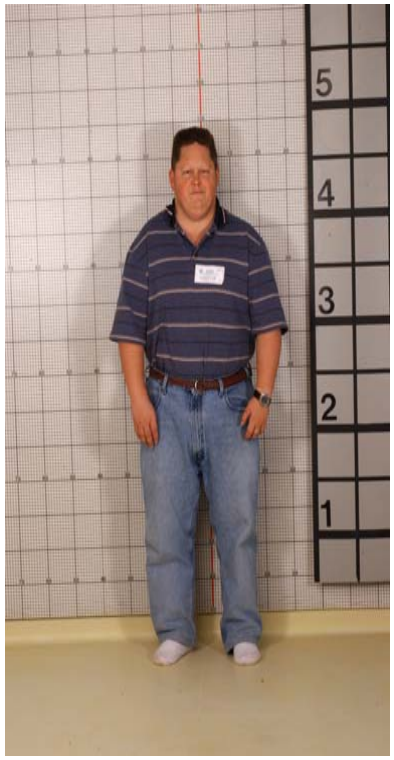
Giampietro PF et al. *Am J Med Genetics.* 1997;68:58-61.

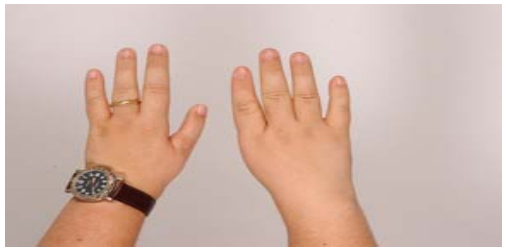
Cousins with Fanconi's Anemia





Case 1



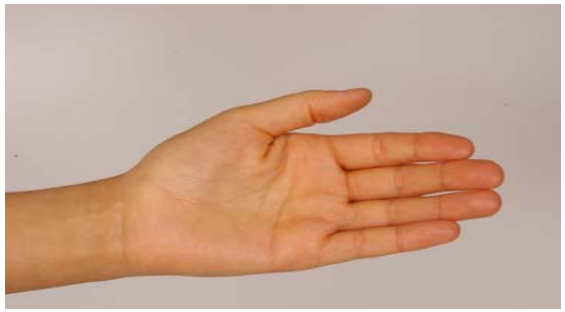


Absent thumbs,
L pollicization

Wrist Splint

Case 2

Café-au-lait spot



Flat thenar eminence

Fanconi Anemia *(cont.)*

- Associated neoplasias
  - Myelodysplasia
  - Acute myelogenous leukemia
  - Solid tumors
    - **Vulvar Cancer: O/E = 4300**
    - **Esophageal Cancer: O/E = 2400**
    - **Head/Neck Cancer: O/E = 700**
      - **Beware the atypical presentation in young adults!**

Butturini A et al. *Blood.* 1994;84:1650-1655.
Giampietro PF et al. *Am J Med Genetics.* 1997;68:58-61.

Rosenberg P et al: Blood 2003; 101:822-826

Fanconi Anemia *(cont.)*

- Incidence: 1 in 100,000 live births
- Autosomal recessive inheritance
  - Carrier frequency: 1 in 300; ~1 in 100 in Ashkenazi Jews (IVS4 +4 A→T founder mutation)
- Diagnosis based on chromosomal breaks and other aberrations detected using diepoxybutane or mitomycin C in culture

Auerbach AD. *Genet Test.* 1997;1:27-33.

Fanconi Anemia *(cont.)*

- **ELEVEN** complementation groups identified (A, B, C, D1, D2, E, F, G, **I, J, L)**
  - FA-A subtype present in >65% affected patients
- **NINE** genes have been identified, including *BRCA2* (FA-I
  - Clinical testing available only for FA-C and FA-D1 group gene mutatio (includes Ashkenazi carriers)
- Gene products complex together and interact with other proteins such as those of the *BRCA1* and *BRCA2* genes to regulate DNA repair and genomic stability

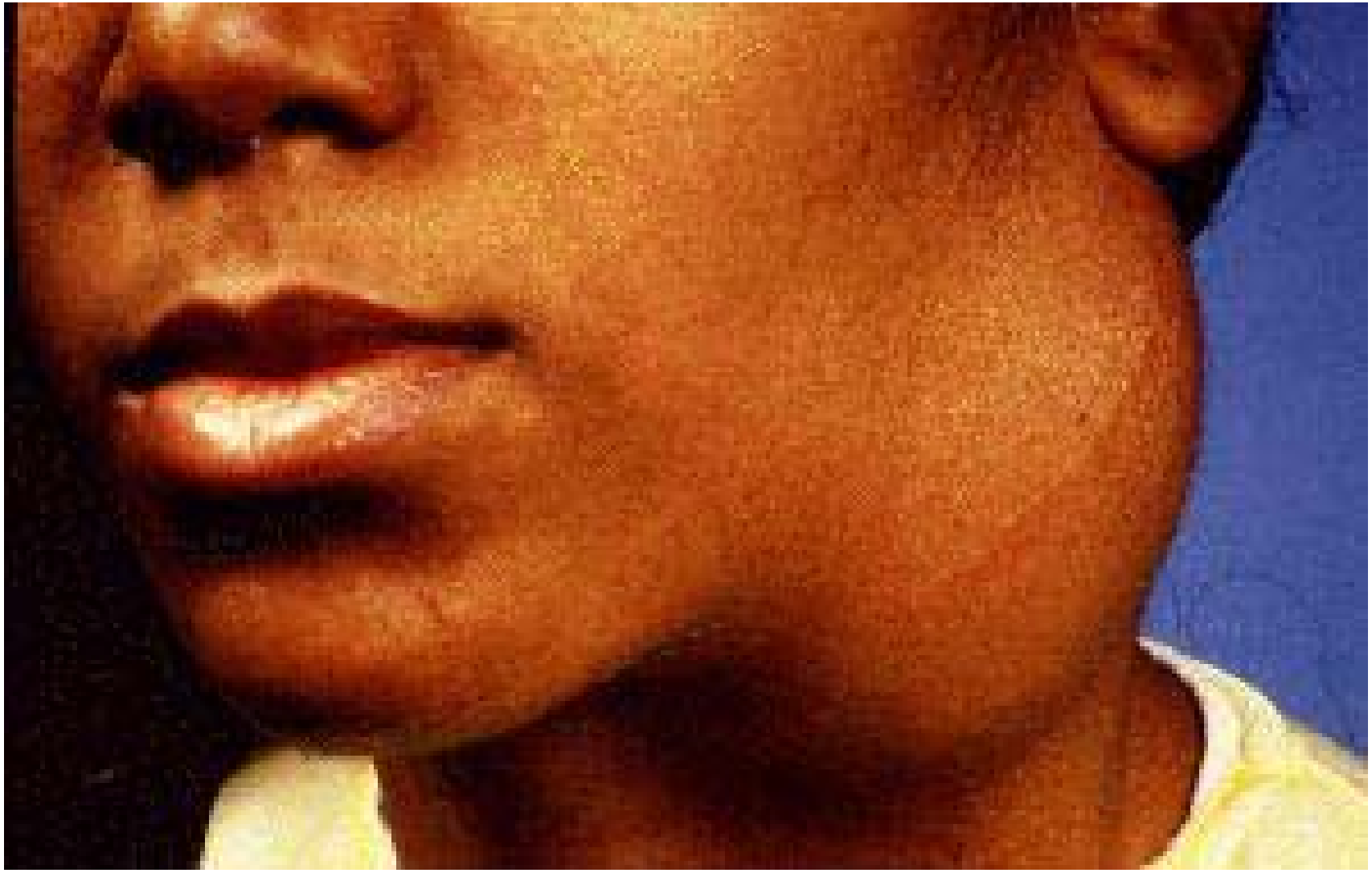
Howlett NG et al. *Science*. 2002;297:606-609.

Shimamura A et al. GeneTests [database online]. Availableat: http://www.geneclinics.com. Accessed August 27, 2002.

FA Complementation Groups/Genes

Group	Locus	cDNA	Exons	AA	%
A	16q24.3	5.5	43	1455	~70
B	Xp22.31	2.8	10	859	Rare
C	9q22.3	4.6	14	558	~10
D1/BRCA2	13q12.3	11.4	27	3418	Rare
D2	3p25.3	5	44	1451	Rare
E	6p21-22	2.5	10	536	~5
F	11p15	1.3	1	374	Rare
G	9p13	2.5	14	622	~10
I	-	-	-	-	Rare
J	-	-	-	-	Rare
L	2p15-16.1	1.7	14	375	Rare

Carotid body is the most common location of PGL tumors

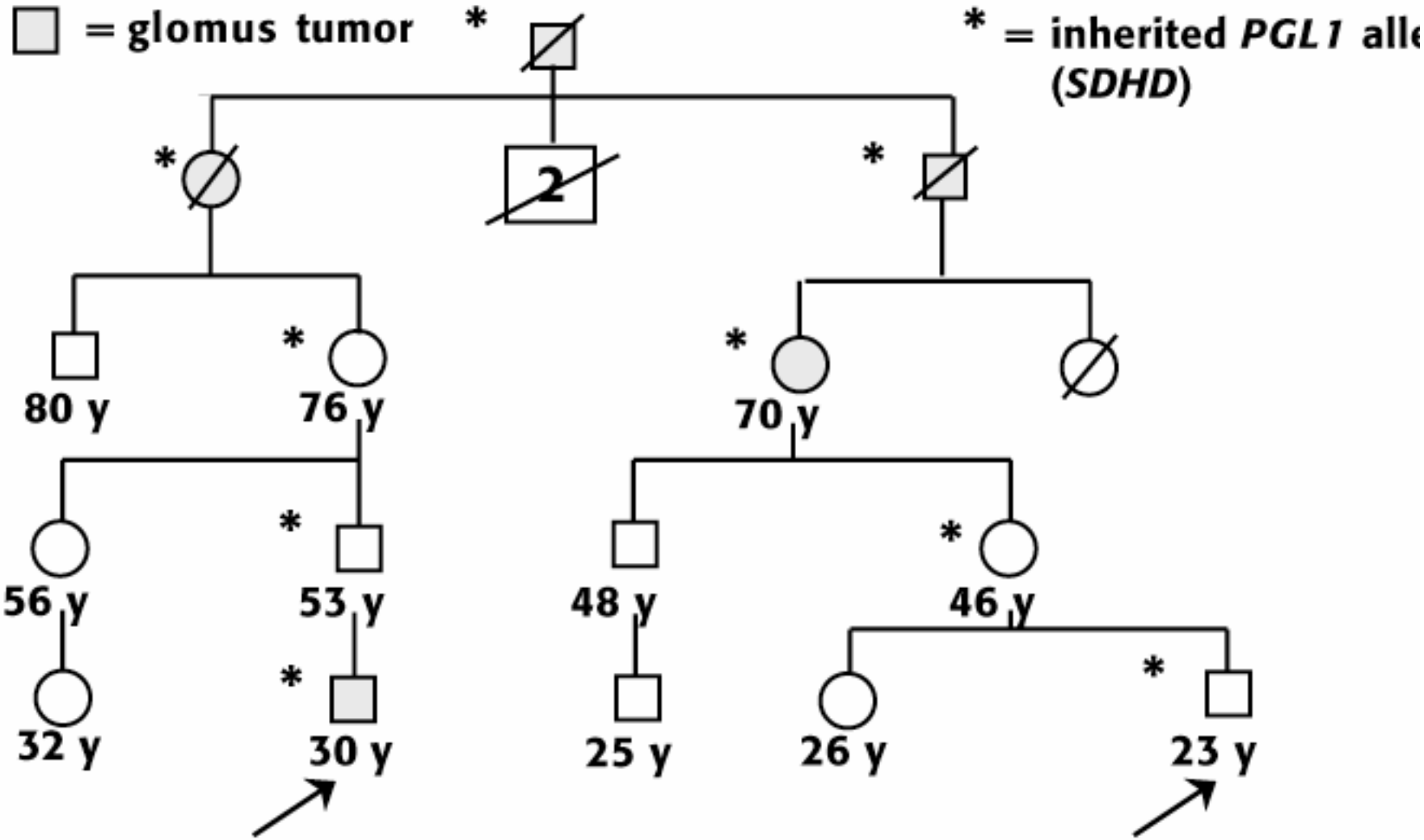


Hereditary Paraganglioma

- Genes: *SDHB*, *SDHC*, and *SDHD* (encode subunits of mitochondrial complex II)
- Inherited as an autosomal dominant disorder
- Characterized by imprinting: affected individua inherit the gene from their fathers
- Genetic heterogeneity:
  - *SDBH:* chromosome 1p36.1-35
  - *SDHC:* chromosome 1q21
  - *SDHD:* chromosome 11q23

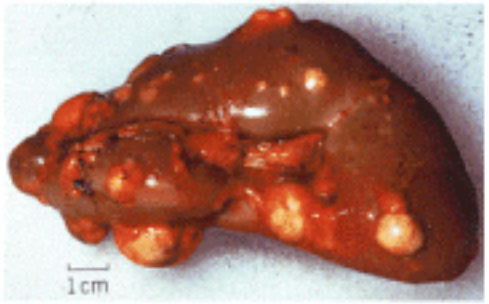
Baysal BE et al. *J Med Genet.* 2002;39:178-183.

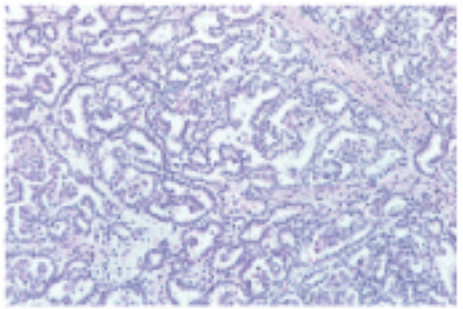
Hereditary Paraganglioma: Autosomal dominant inheritance with imprinting (affected individuals inherit the disease gene from their fathers)



Hereditary Papillary Renal Cell Carcinoma

- Young age at diagnosis (median age is 45 years)
- **Up to 3000 tumors per kidney! Difficult to detect by US, CT - hypovasc**
- Primarily type 1 papillary RCC
- Multiple affected family members





Figures courtesy of Jberton Zbar, MD, National Cancer Institute.

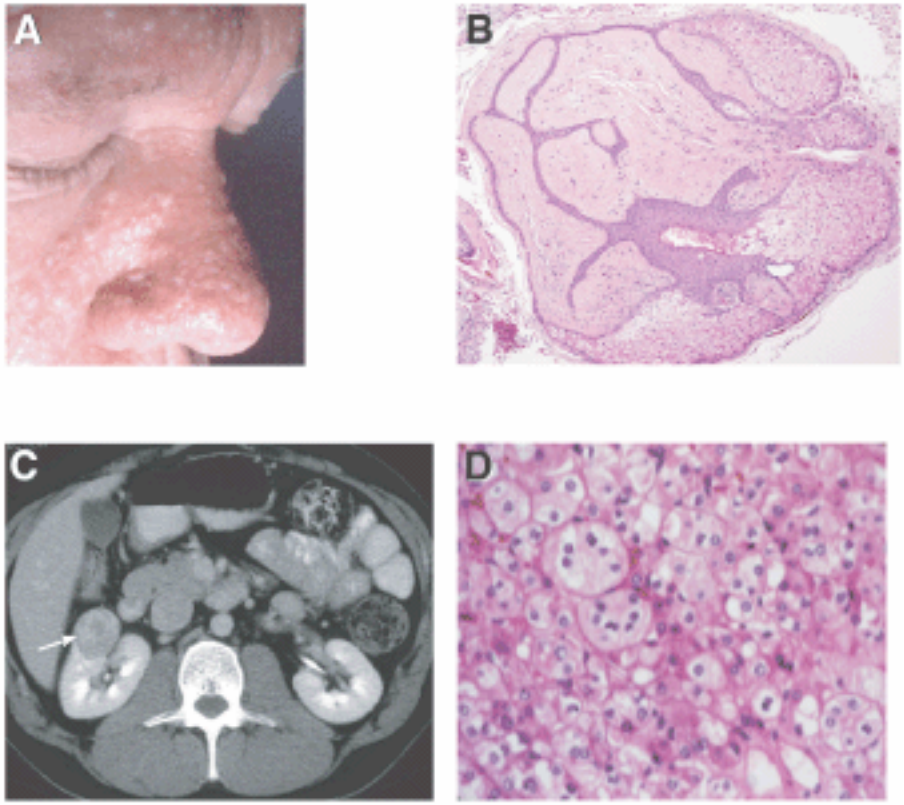
- ***Met* Proto-oncogene**
- **Encodes hepatocyte growth factor**

Schmidt L et al. *Nat Genet*. 1997;16:68-73.

Birt-Hogg-Dubé Syndrome

- Rare syndrome characterized by
  - Chromophobe renal cancer (and other histologies)
  - Fibrofolliculoma
  - Spontaneous pneumothorax
- Autosomal dominant
- Gene on chromosome 17p11.2
- **Protein Product:**

  FOLLICULIN



Figures courtesy of Jorge Toro, MD, National Cancer Institu

Nickerson M et al. *Cancer Cell*. 2002;2:157-164.

Birt-Hogg-Dubé Syndrome, con't

- Germline mutations in *BHD* found in 51/61 (84%) US families
  - 45% of mutation-positive families had ≥ 1 renal cell cancer
- Mutation hotspot in exon 11
  - 27/51 (53%) of mutations occurred in this exon
  - significantly fewer tumors with deletion mutations than insertion mutations
- 3 families affected by renal oncocytomas, first genetic association for this histologic variant of kidney cancer
- VHL, PRCC and BHD managed with observation for tumors < 3cm, partial neprectomy when larger

(LS Schmidt et al: Amer J Hum Genet 2005; 76:1023-1033)

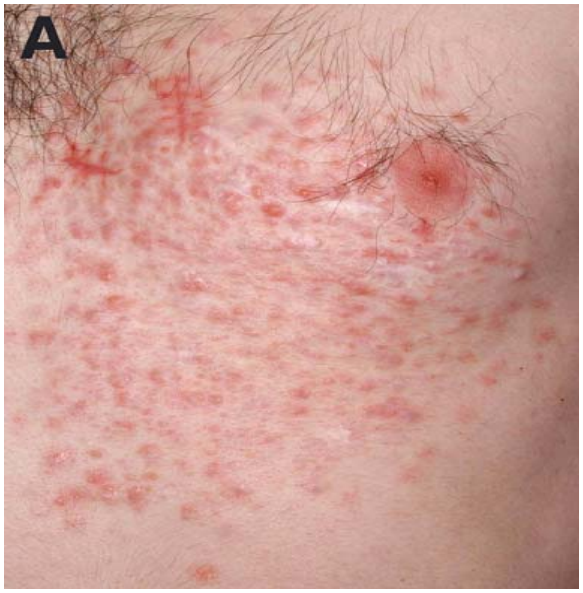
Hereditary Leiomyomatosis and RCC

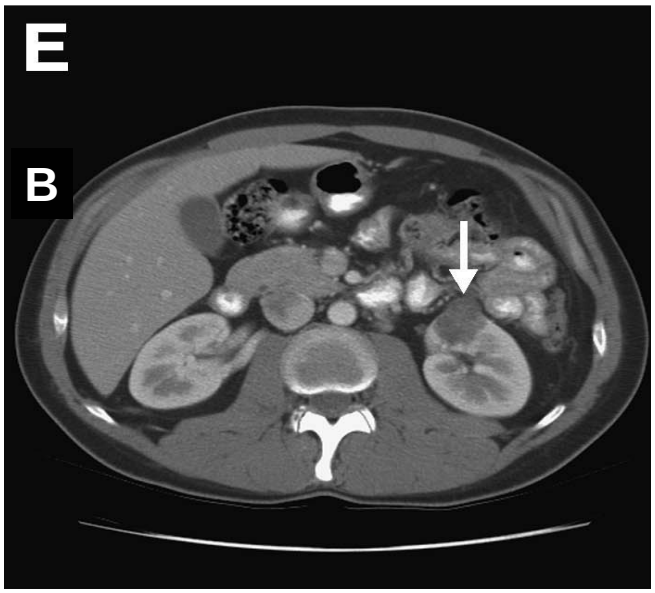
- Skin nodules (leiomyomata)
- Uterine fibroids (leiomyomas and leiomyosarcomas)
- **Unilateral, solitary, VERY aggressive; metastasize early**
- Gene on chromosome 1q42.3–43
- **Gene identified: fumarate hydratase (Krebs cycle enzyr**
- **Mutations in FH found in 31/35 (89%) families studied**
- **98% of women with skin tumors also had uterine tumor**

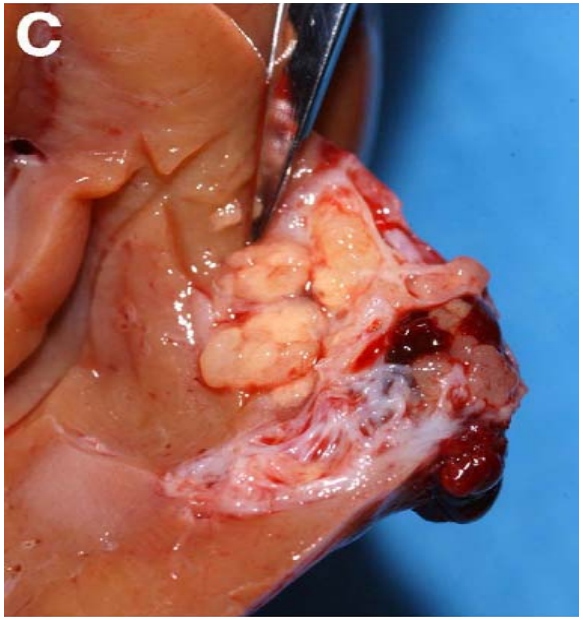
Tomlinson IP et al. *Nat Genet*. 2002;30:406-410.

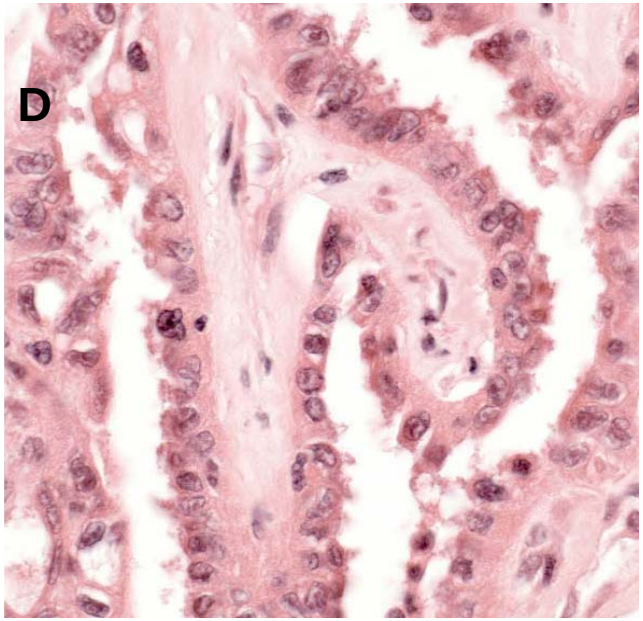
J Toro et al: Amer J Hum Genet 2003; 73:95-106

Hereditary leiomyoma renal cell carcinoma









Photographs courtesy of Dr. Jorge Toro, Genetic Epidemiology Branch, US National Cancer Institute

Histopathology of Hereditary Renal Cancers

- **Von Hippel-Lindau…….clear cell renal carcinoma**
- **Papillary Renal Cell Cancer……..type 1 papillary renal carcinoma**
- **Birt-Hogg-Dubé…….hybrid oncocytic renal tumors; chromophobe renal carcinoma**
- **HLRCC……..type 2 papillary renal carcinoma; collecting duct carcinoma**

Conclusions

- **Reviewed a series of less common genetic cancer susceptibility syndromes**
  - **Ataxia Telangiectasia**
  - **Nijmegen Breakage Syndrome**
  - **Bloom Syndrome**
  - **Fanconi Anemia**
  - **Hereditary Paraganglioma**
  - **Familial Papillary Renal Cancer Syndrome**
  - **Birt-Hogg-Dubé Syndrome**
  - **Hereditary Leiomyoma Renal Cell Cancer Syndrome**
- **Recognition of the clinical phenotype is the key**
- **Theme: potential risk of malignancy in heterozygous carriers of autosomal recessive disorders that involve maintenance of genomic integrity**
- **Novel mechanisms of inheritance (imprinting)**
- **Novel etiologic genes (fumarate hydratase; SDHB, C, D)**
- **Etiologic clues to be found in histopathologic heterogeneity**