

# Atypical GISTs

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# Atypical GISTs

- Hereditary GISTs
  - Familial GISTs
  - GISTs associated with other hereditary syndromes
    - GISTs associated with neurofibromatosis type I (NF1-GISTs)
    - Carney-Stratakis hereditary syndrome
- Pediatric and young adults GISTs
  - Carney Triad

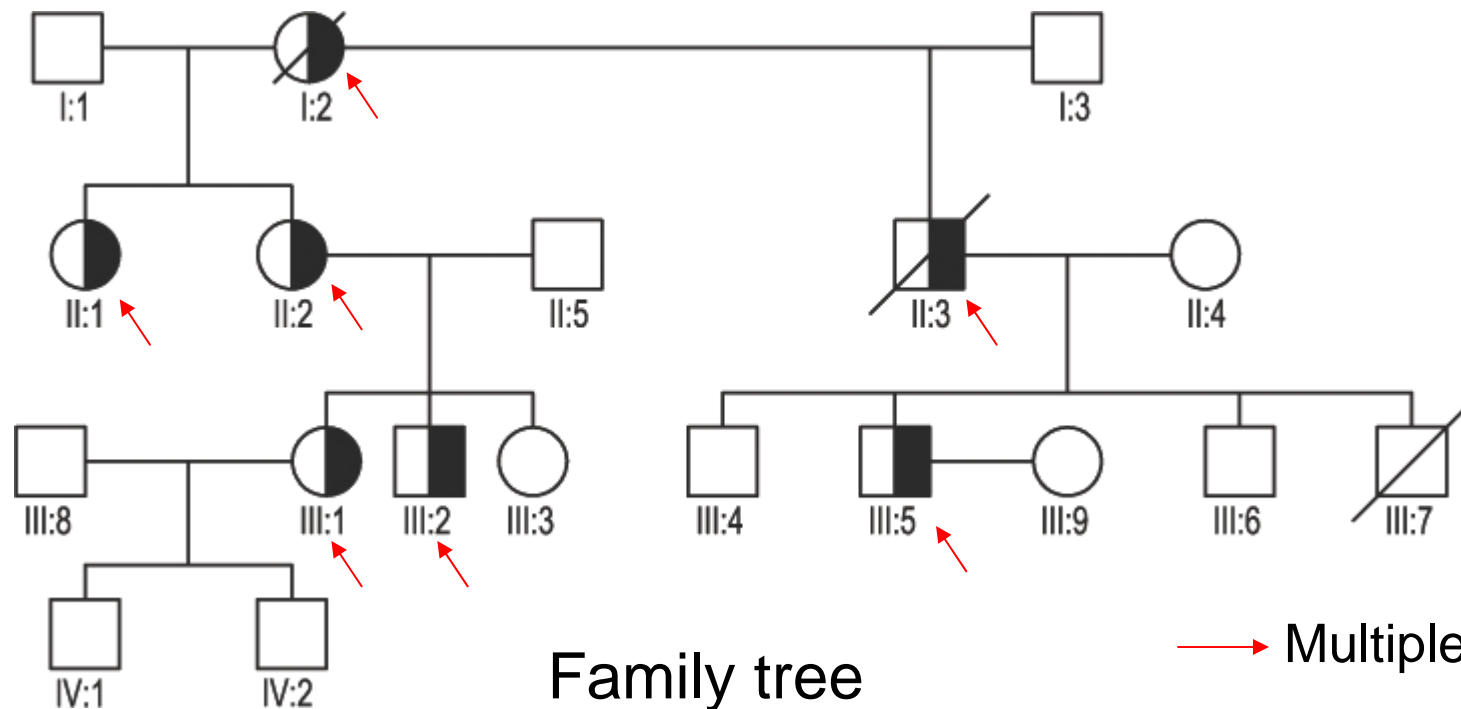
# Familial GIST syndrome

- Rare hereditary condition
  - only 22 families have been reported world wide
- Caused by germ-line *KIT* or *PDGFRA* genes mutations
- An autosomal dominant pattern of inheritance with a high penetrance

Familial GISTs associated with  
germ-line *KIT* mutation

# Familial GIST syndrome associated with germ-line *KIT* K642E mutation

- An autosomal dominant pattern of inheritance
  - 50% risk of mutation transmission
- A high penetrance
  - ~100% risk of tumor development



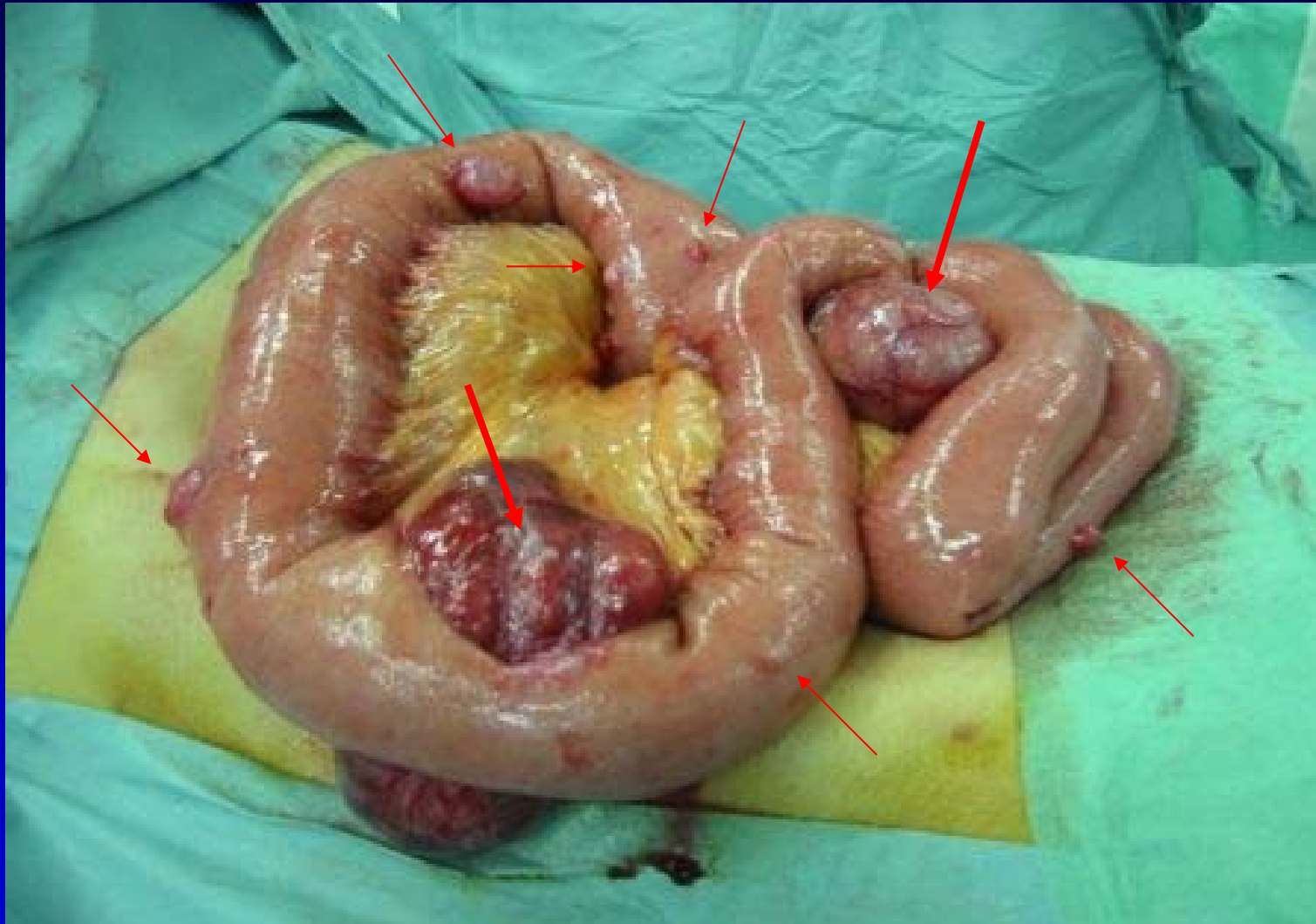
Family tree

→ Multiple tumors

## Clinical symptoms associated with germ-line *KIT* mutation

- Patients develop GISTs at younger age (median – 46 years).
- The tumors are usually
  - multiple in number (3 to >100 tumors)
  - smaller in size
  - occur in a background of polyclonal diffuse hyperplasia of Cajal cells within the myenteric plexus

Multiple intestinal tumors  
in patient with germ-line *KIT* K642E mutation



# Familial GIST syndrome associated with germ-line *KIT* mutation

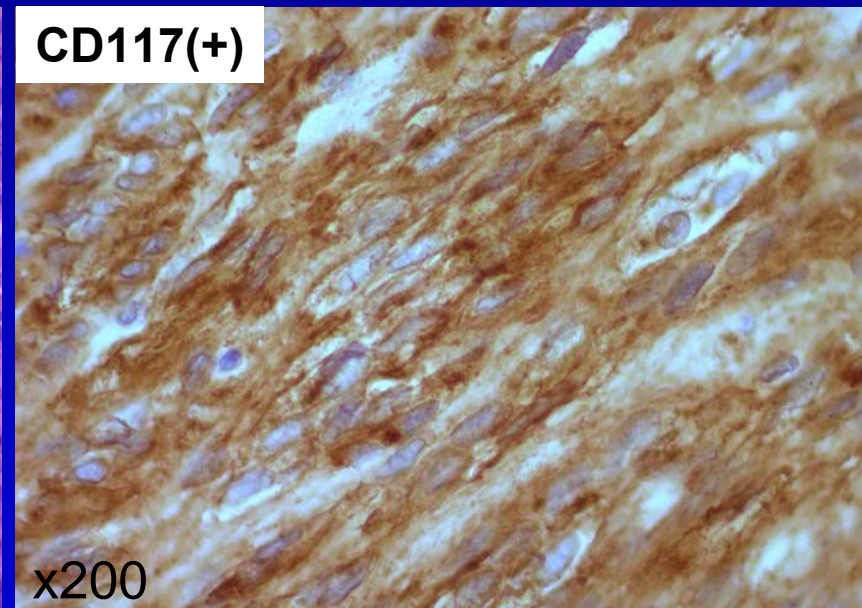
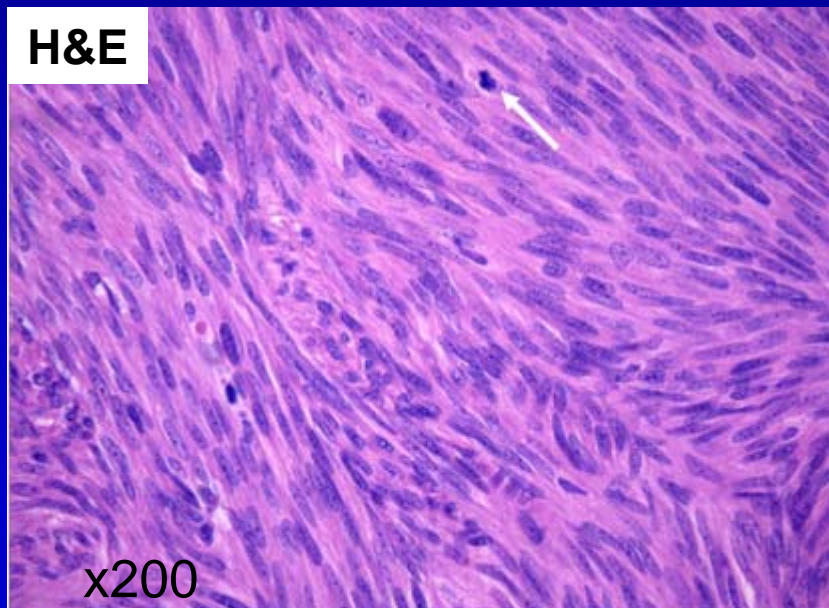
- In addition to GISTs additional abnormalities may be present, with a substantial clinical variability:
  - **Abnormalities of bowel motility and sphincter tone:** dysphagia, constipation or gastroesophageal reflux symptoms
  - Features linked with the **dysfunction of melanocytes:** cutaneous hyperpigmentation, melanocytic nevi, lentiginos, café au lait spots and vitiligo
  - **Abnormalities of mast cells:** urticaria pigmentosa or systemic mastocytosis

## Clinical symptoms associated with germ-line KIT mutation

- Symptoms associated with GI bleeding (anaemia and melanea) are common and may be the only manifestation of the disease.

# Familial GIST syndrome associated with germ-line *KIT* mutation

- Histopathology
  - GISTs: gastric and/or intestinal, spindle type, KIT immuno(+), CD34 (+/-)
  - Hyperplasia of Cajal cells



# Cytogenetic and molecular features of GISTs associated with germ-line *KIT* mutation

- The same as in sporadic GISTs
  - oncogenic *KIT* mutations as a cause of tumor development:
    - KIT exon 8 mutation – 5%
    - **KIT exon 11 mutation – 75%**
    - KIT exon 13 mutation – 10%
    - KIT exon 17 mutation – 10%
  - cytogenetic/genomic and gene expression profile is the same as in incidental GISTs

# Advanced GISTs associated with germ-line KIT mutation

- Response to Imatinib relates to mutational profile of the tumor and not to detectable KIT expression
  - Majority reported germ-line *KIT* mutation are sensitive to imatinib
  - Genotyping has predictive value and is mandatory for the proper management of disease
  - Genetic counseling and genetic testing of all members of affected family has preventive value

Familial GIST syndrome associated  
with germ-line *PDGFRA* mutation

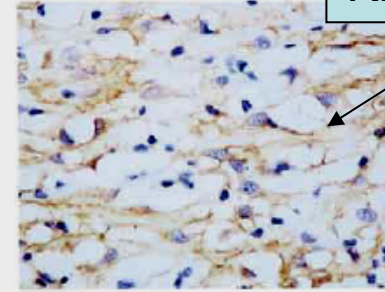
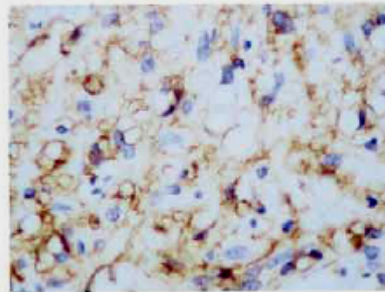
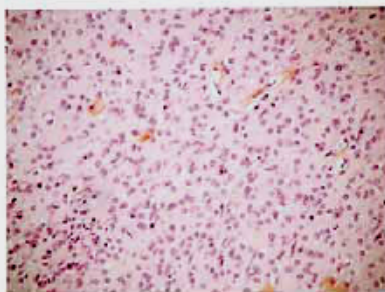
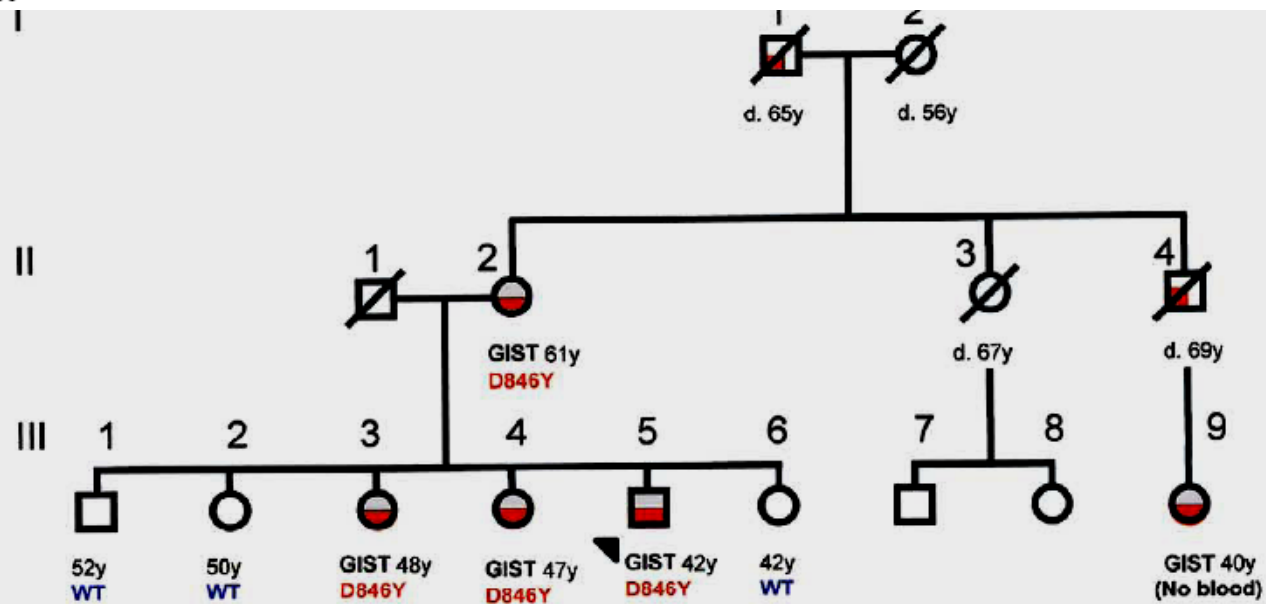
## Familial GIST syndrome associated with germ-line *PDGFRA* mutation

- Only three families described
  - Adult onset
  - Multiple gastric and/or intestinal tumors
  - GI symptoms (GI bleeding, constipation, bloating)
  - No other symptoms such as dysphagia, hyperpigmentation, or mast cell abnormalities
  - Unusually large hands

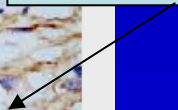
# PDGFRA Germline Mutation in a Family With Multiple Cases of Gastrointestinal Stromal Tumor

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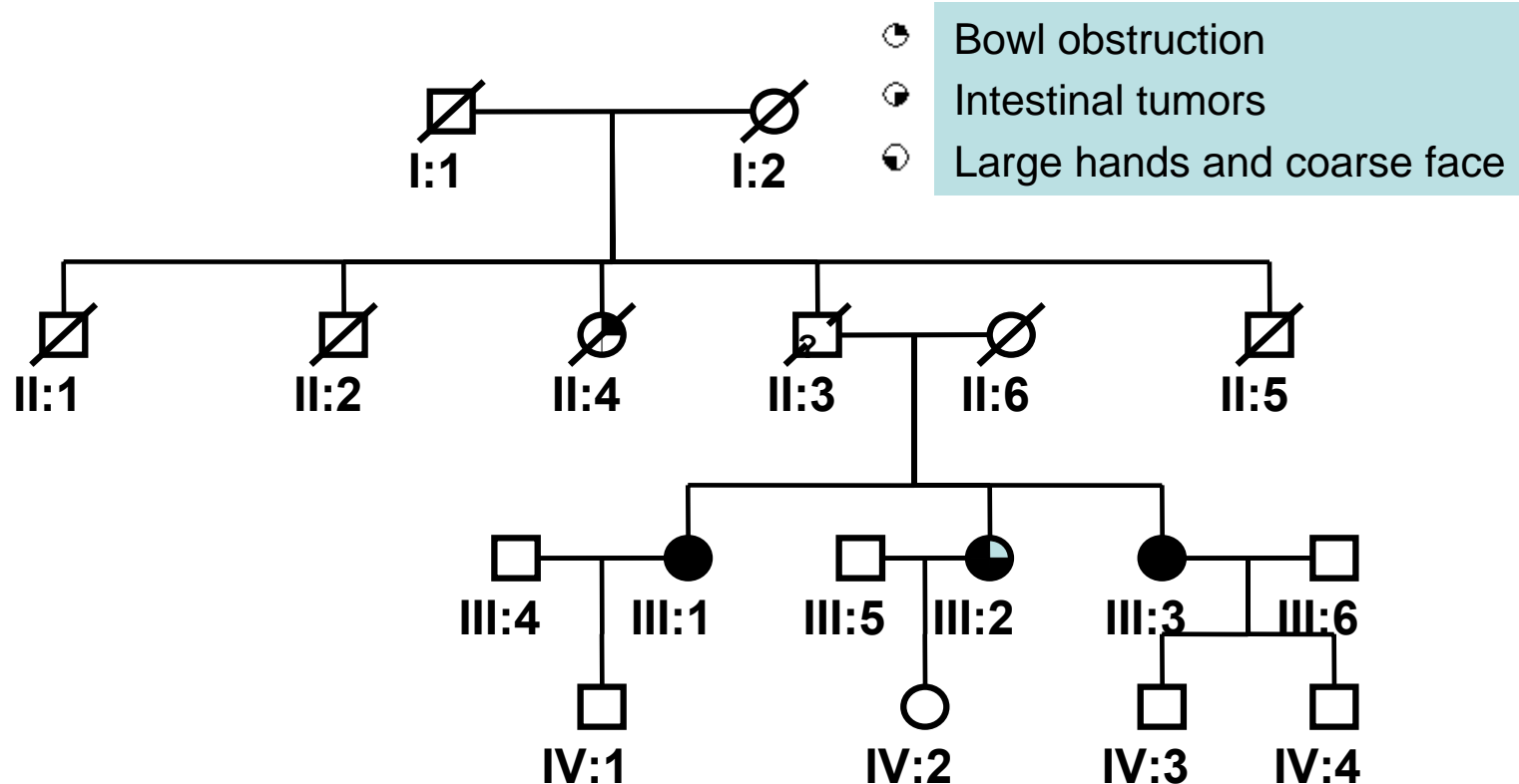
Departments of \*Medicine, †Genetics, and §Pathology, Institut Gustave Roussy, Villejuif, France; and ¶Clinique Pasteur, Vitry sur Seine, France



Kit positive ICC



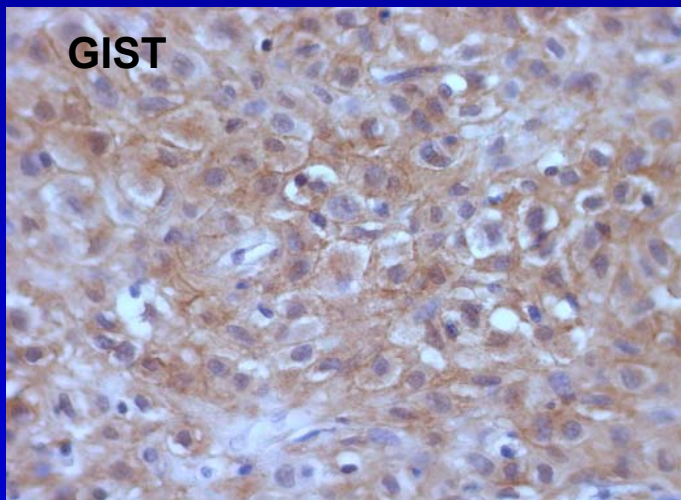
# Familial GIST syndrome associated with germ-line *PDGFRA* Y555C mutation



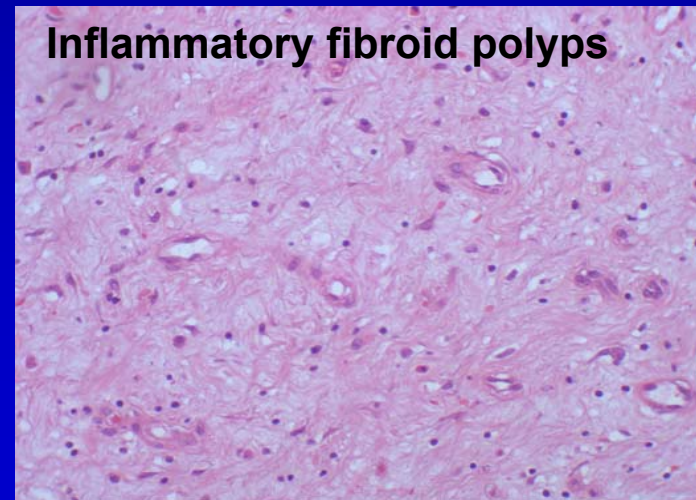
- Autosomal dominant inheritance pattern
- Incomplete penetrance (variable expression)

# Familial GIST syndrome associated with germ-line PDGFRA mutation

- Histopathologic features
  - GIST: epithelioid or spindle cell tumors  
[CD117(+),CD34(+/-)]
  - Tumors with atypical phenotype [CD117(-), CD34(-)]
    - Neurofibroma-like
    - Inflammatory fibroid polyps



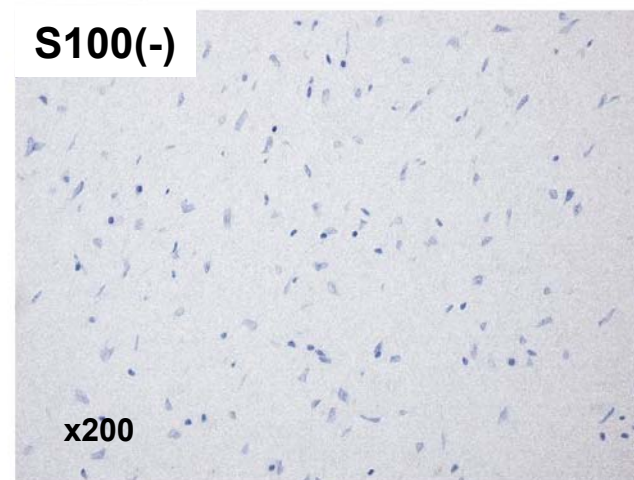
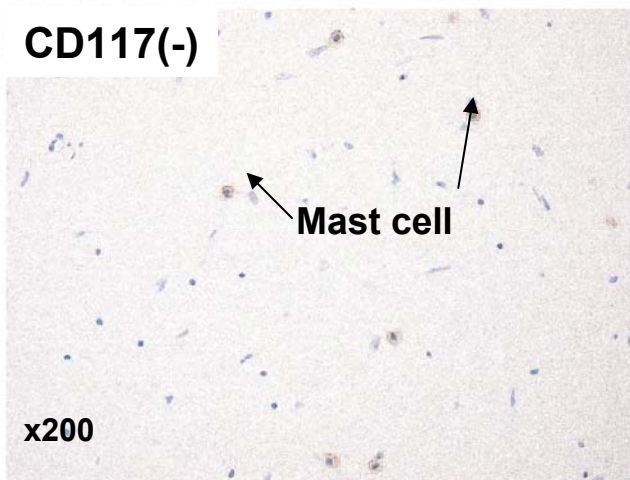
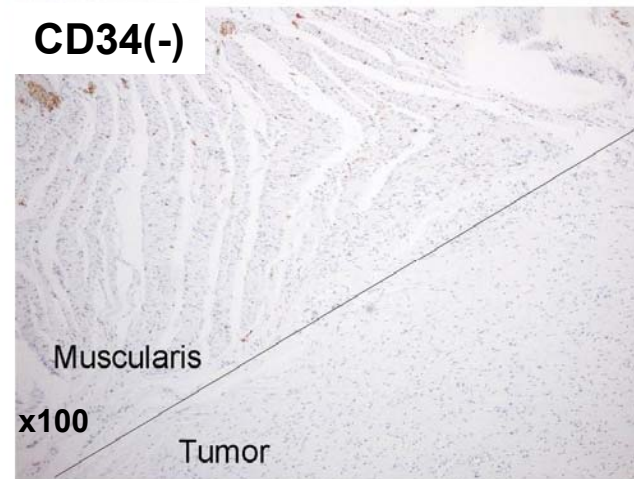
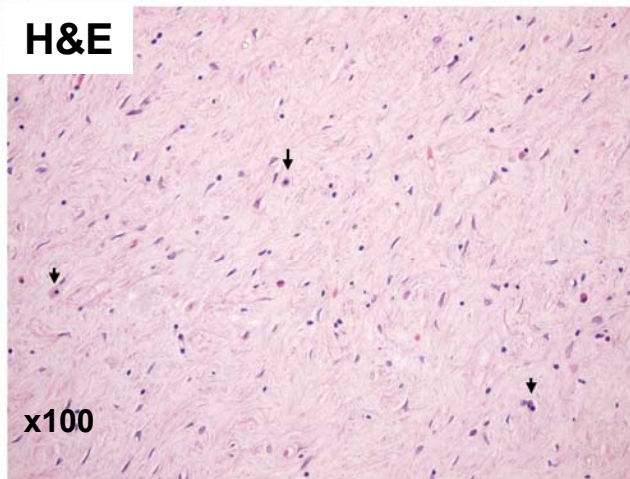
KIT / CD117 imuno(+)



H&E

# Neurofibroma-like GIST strictly limited to the intestine associated with germ-line *PDGFRA* Y555C mutation

Absence of typical GIST immunohistochemical markers



# Familial GIST syndrome associated with germ-line PDGFRA mutation

- Generally **indolent clinical course** (absence of metastases in most individuals)
- Genetic counseling and **family testing** for hereditary form of disease is **mandatory**
- The multi-focality of the disease suggests that **surgical intervention should be avoided** in the absence of complications or large size tumors

## Summary:

familial GISTs associated with germline *KIT* or *PDGFRA* mutations

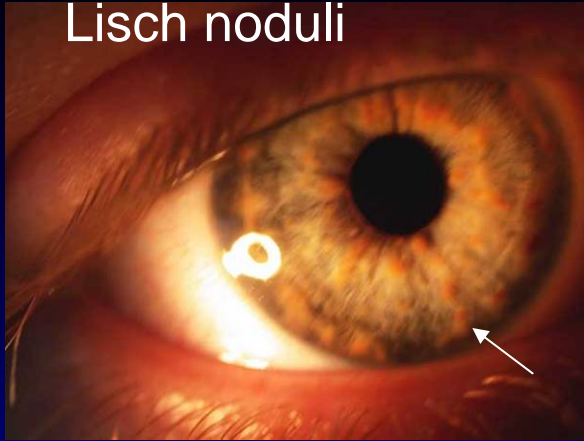
- Clinical symptoms relates to the type of mutation
- Genotyping is necessary for the proper management of disease
- The careful monitoring for the development of tumors is indicated
- **Imatinib may be effective in the prevention of development as well as in the treatment of familial GISTs**

GISTs associated with  
neurofibromatosis type I  
(NF1-GISTs)

# Neurofibromatosis type 1

- Caused by germ-line *NF1* mutation
- Autosomal dominant inheritance pattern
- Most frequent human hereditary disease: 1/3000
- Abnormalities
  - Melanocytes
  - Schwann cells
  - Glial cells – astrocytes – neurons – IC of Cajal
  - Cells of hematologic origin (eg. mast cells)
- Familial tumor syndrome
  - Benign Neurofibromas
  - Malignant Peripheral Nerve Sheet Tumors (MPNST)
  - Gliomas
  - GISTs
  - Juvenile Monocytic Leukemia

Lisch noduli



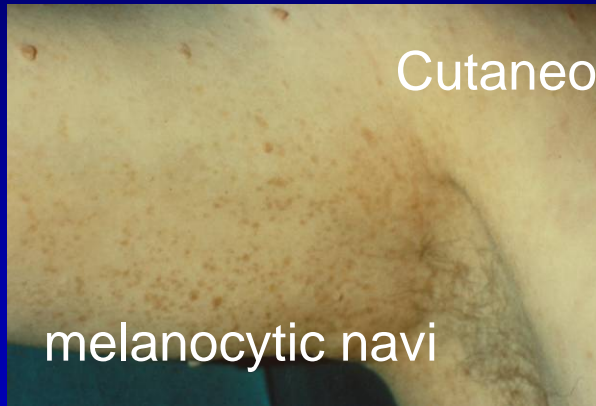
Benign tumors along nerves  
(neurofibromas)



Café au lait spots  
(changes in skin pigmentation)



Cutaneous hyperpigmentation



melanocytic navi

Optic gliomas  
(eye tumors)



Skin freckling



neurofibromas



Large head  
(macrocephalia)



# GISTs associated with neurofibromatosis type I (NF1-GISTs)

- Adults with NF1 have a **7% risk** of developing GISTs
- **Multiple** tumors located predominantly **within the small intestine**
- NF1-GISTs usually show low cell proliferation (growth) indicators and they **rarely metastasize**
- Abdominal pain, bowel obstruction and gastrointestinal bleeding are the most common clinical manifestations

## GISTs associated with neurofibromatosis type I (NF1-GISTs)

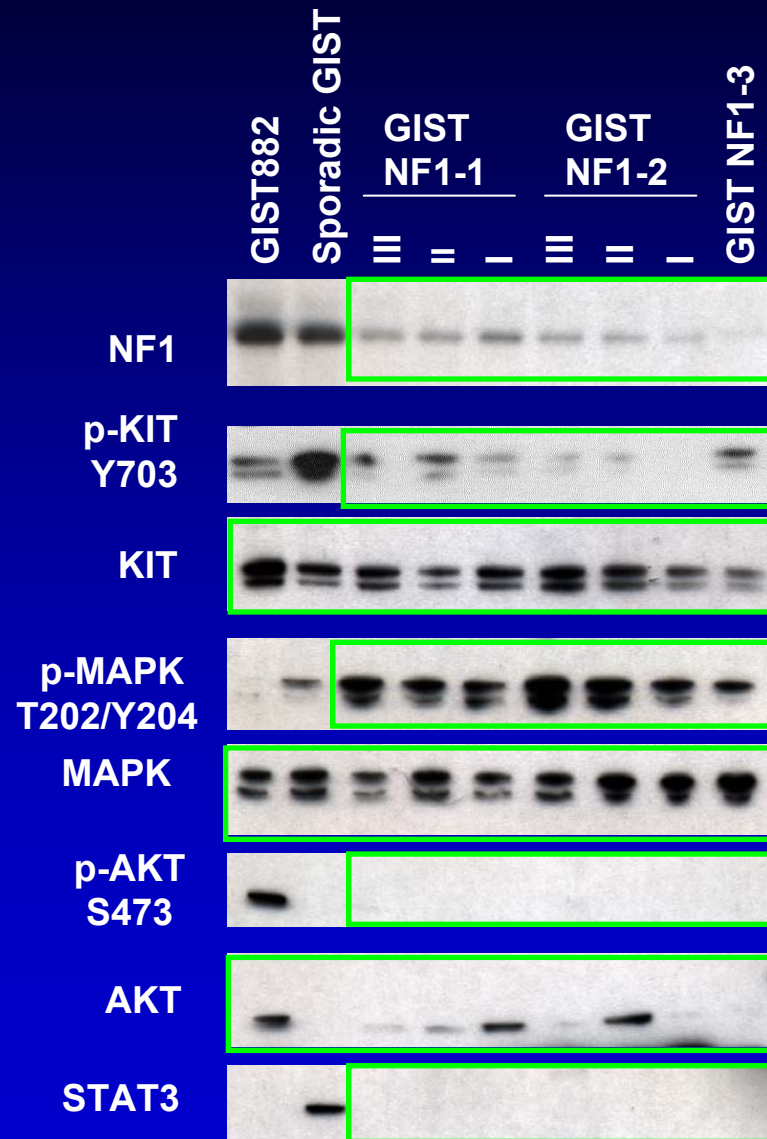
- Morphologically and cytogenetically GISTs occurring in the NF1 setting were found to be similar to sporadic *KIT*- and *PDGFRA*-mutant GISTs
- NF1-GISTs are *KIT* and *PDGFRA* wild-type (they do not carry *KIT* or *PDGFRA* mutations)

# NF1 GISTs: NF1 mutation analysis

patient	tumor	material	NF1	
			Germline	somatic
NF1-1	I	F	4269+1G>T	ND
	II	F		5242C>T (R1748X)
	III	F		5546+2T>A
NF1-2	I	F	6792insA	279T>A (C93X)
	II	F + ICC		7846C>T (R2616X)
	IV	F + ICC		LOH
NF1-3	I	F	7807delG	LOH

Somatic (acquired), inactivating mutation of the wild-type *NF1* allele in precursor cells is leading to tumor development

# NF1-GISTs: Western analysis



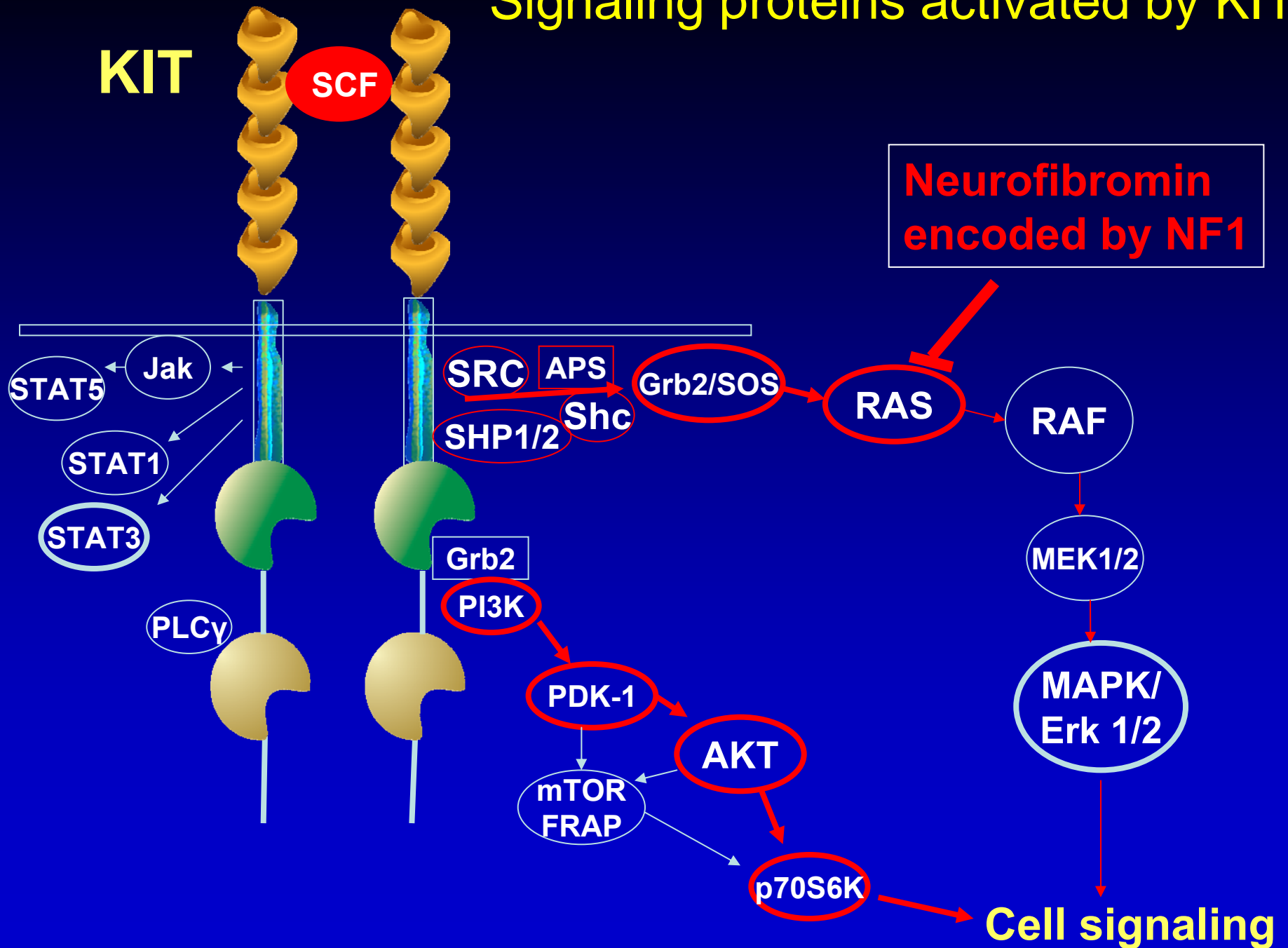
- \* NF1 expression: rudimentary
- \* KIT expression: normal
- \* KIT phosphorylation: low level
- \* MAPK phosphorylation: strong
- \* AKT: variable, no phosphorylation
- \* no STAT3 expression

# Signaling proteins activated by KIT

**KIT**

**SCF**

**Neurofibromin  
encoded by NF1**

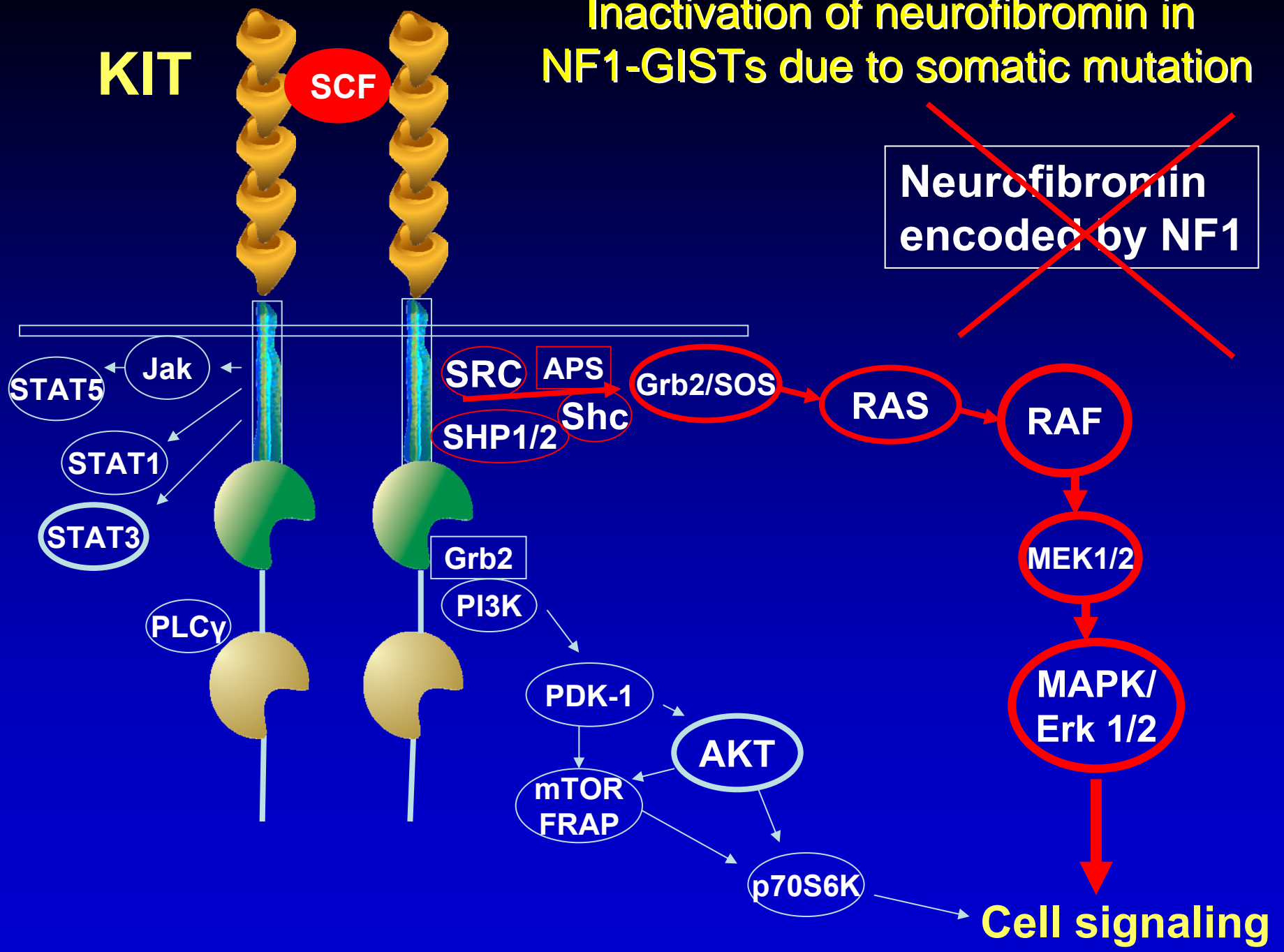


# Inactivation of neurofibromin in NF1-GISTs due to somatic mutation

## KIT

SCF

~~Neurofibromin encoded by NF1~~



# Summary: NF1-GISTs

- NF1-GISTs are usually **clinically indolent**
- NF1-GISTs are *KIT*- and *PDGFRA*-wild-type (WT) - **imatinib is less effective in NF1-GISTs** than in *KIT*- and *PDGFRA*-mutant GISTs
- **Somatic *NF1* inactivation** is underlying pathogenetic mechanisms
- Dual inhibitors of KIT/PDGFR $\alpha$  and MAPK pathways (such as Sorafenib) might be more effective in advanced disease

# Carney-Stratakis syndrome (Carney dyad)

- **Familial syndrome**, transmitted as autosomal dominant trait
- Females and males **equally affected**
- **Early onset** (< 23 years old)
- Multicentric **paragangliomas** and multifocal, gastric, CD117(+) **GISTs**

# Sporadic or familial paragangliomas

- Catecholamine-producing tumors derived from chromaffin cells of adrenal gland or extra-adrenal ganglions
- Usually benign tumors but may develop into malignant disease
- Sporadic or associated with familial paraganglioma hereditary syndrome
- Hereditary condition are caused by germ-line inactivating mutations of *SDH genes*

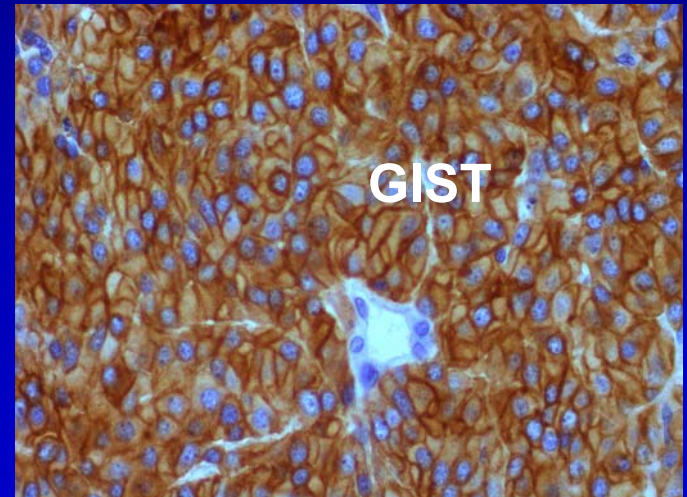
# Carney-Stratakis syndrome (Carney dyad)

- Hereditary condition, caused by **germ-line inactivating mutations of *SDHB* (10%), *SDHC* (80%) or *SDHD* (10%) genes** (the same mutations are found in paraganglioma hereditary syndrome)
- Multifocal, gastric GISTs **do not carry *KIT* or *PDGFRA* mutations** (WT GISTs)
- **Imatinib treatment might be less effective** than in sporadic *KIT*-mutant GISTs

# Pediatric and young adults GISTs

# Pediatric and young adults GISTs

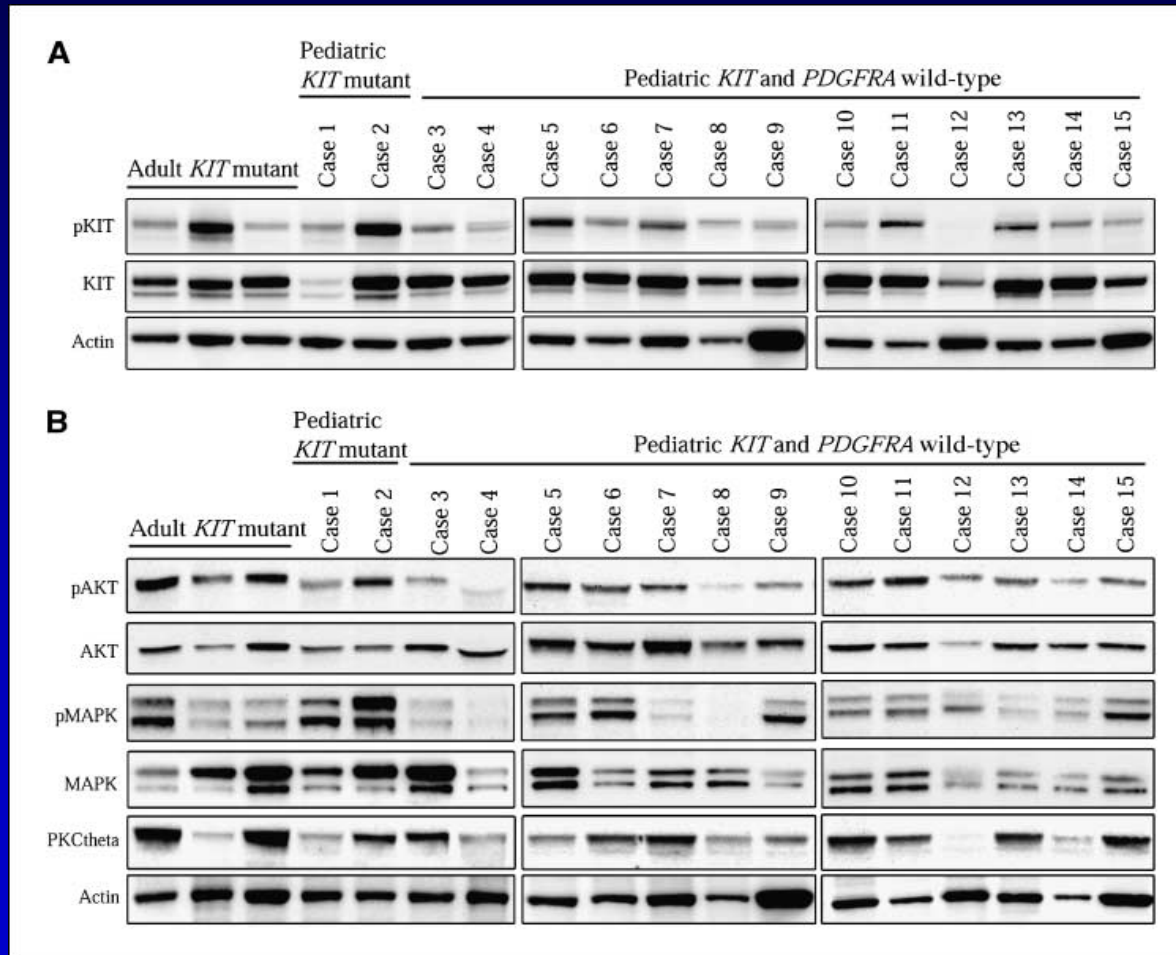
- *Histopathology*: gastric, multifocal, epithelioid type
- *Tumor genotype*: *KIT*- and *PDGFRA*-Wild-Type (WT GISTs)
- Mainly in females
- Clinically less aggressive, but with malignant potential



KIT/CD117 imuno(+)

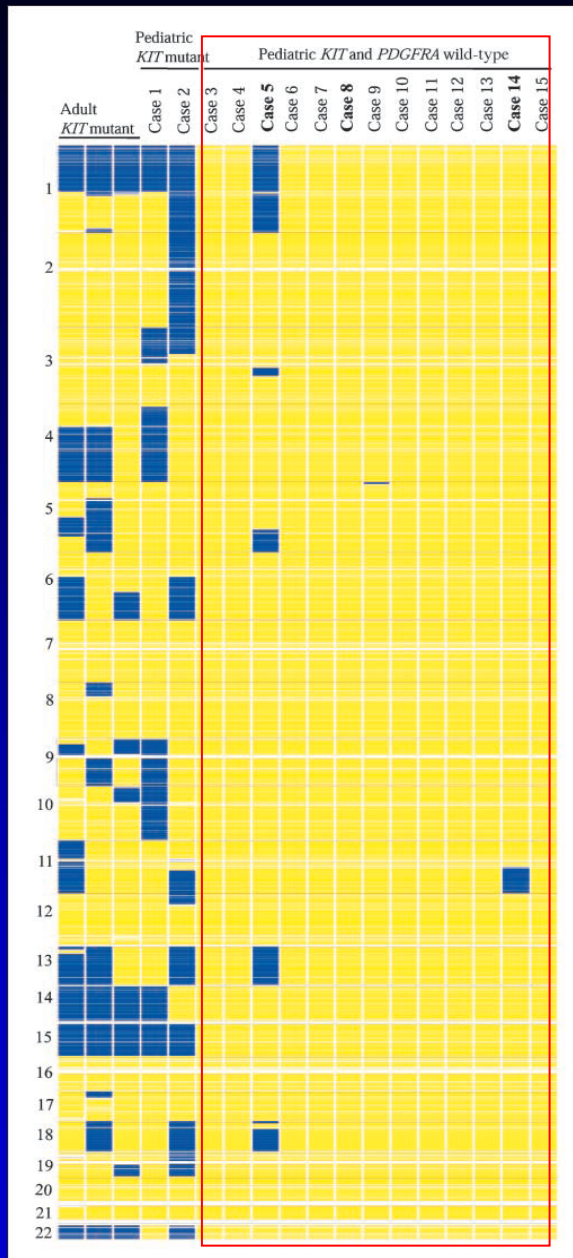
# Pediatric and young adults GISTs

KIT activation similar to levels in adult *KIT*-mutant GISTs



Janeway et al., Cancer Res 2007; 67: (19), 2007

# SNP Affimetrix



## Pediatric and young adults GISTs

GISTs progress to malignancy without acquiring large-scale chromosomal aberrations

Janeway et al., Cancer Res 2007; 67: (19), 2007

# Pediatric and young adults GISTs

Expression profile different than adult *KIT*- or *PDGFRA*-mutant GISTs

Gene	Gene Title	Fold Change	Chromosomal Location
CRLF1*	cytokine receptor-like factor 1	186.2	19p12
BAALC*	brain and acute leukemia, cytoplasmic	40.93	8q22.3
FGF4*	fibroblast growth factor 4	18.88	11q13.3
PLAG1*	pleomorphic adenoma gene 1	16.63	8q12
IGF1R*	insulin-like growth factor 1 receptor	10.96	15q25-q26
FGF3	fibroblast growth factor 3	9.913	11q13
RB1	retinoblastoma 1	6.641	13q14.2
FGF18	fibroblast growth factor 18	5.589	5q34

Angaram et al., Clin Cancer Res 2008.

# Pediatric and young adults GISTs

- Imatinib less effective than for sporadic *KIT*- or *PDGFRA*-mutant GISTs
- Clinical evidence - Sunitinib more effective than Imatinib
- Building knowledge about pediatric GISTs is important for finding new possible molecular targets for the therapy

# Carney triad

- **Non-familial association** of different tumor types
- Affecting **mostly females**
- Association of
  - **pulmonary chondromas** (usually multiple)
  - gastric, multifocal, epithelioid type of **GISTs**, frequently CD117-immunonegative
  - **pheochromocytomas (PHEO)**  
(cortisol-producing tumors and other nonfunctioning adrenocortical adenomas)
- 20% all three components, 80% only two components (usually gastric GIST and PHEO)

# Carney triad

- Pathogenesis unknown
- GISTs in patients with Carney Triad are similar to pediatric GISTs:
  - Multifocal, gastric tumors, do not carry *KIT* or *PDGFRA* mutations (WT GISTs)
  - Progress to malignancy without acquiring large-scale chromosomal aberrations
  - *KIT* activation similar to levels in adult *KIT*-mutant GISTs
  - *IGF1R* strongly expressed and a possible target for a therapy
  - Imatinib less effective than for sporadic *KIT*- or *PDGFRA*-mutant GISTs

# Challenges in ensuring patients with atypical GIST to get optimal treatment

1. Heterogeneous pathogenesis and biology (hereditary vs. non-hereditary)
2. In familial forms of disease – genetic counseling and family testing is mandatory for the proper management of disease
3. In familial forms associated with *KIT* or *PDGFRA* germ-line mutations – treatment with imatinib is an option
4. Management of advanced disease by a specialized centers / interdisciplinary team of specialists, particularly for the treatment of pediatric GISTs

**THANK YOU!**

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