SDH-Deficient GIST-A Newly Identified GIST Subtype

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On behalf of the Consortium for Pediatric & wildtype GIST Research

NATIONAL CANCER INSTITUTE

CPGR Consortium for Pediatric & wildtype GIST Research

the NIH Pediatric & Wildtype GIST Clinic

Pediatric ONCOLOGY BRANCH

Wild-Type GIST

- **85% of GIST occurring in young population is lacking mutations in *KIT* or *PDGFRA***
- **Stomach location, epithelioid histology**
- **May be syndromic (Carney Triad, Stratakis-Carney Syndrome)**
- **Tyrosine kinase inhibition is less effective compared to *KIT* or *PDGFRA* mutant tumors**

the NIH Pediatric & Wildtype GIST Clinic

An international clinic twice a year

115 patients have been seen in 10 clinics since 2008.

Objectives of the Wildtype Clinic at NIH

- **To bring together healthcare providers who have the most experience treating and studying GIST**
- **To obtain clinical history, response to prior treatments, histopathologic results, radiographic assessments and genetic/molecular analyses**
- **Continue long-term follow-up for these patients**

Report on First 78 Patients Characterized

- 12 PATIENTS-KINASE TYPE (Group A)
- 22 PATIENTS-SDH DEFICIENT WITHOUT IDENTIFIED SDH MUTATION (Group B)
- 44 PATIENTS-SDH DEFICIENT WITH SDH MUTATIONS, ALL BUT 3 GERMLINE (GROUP C)

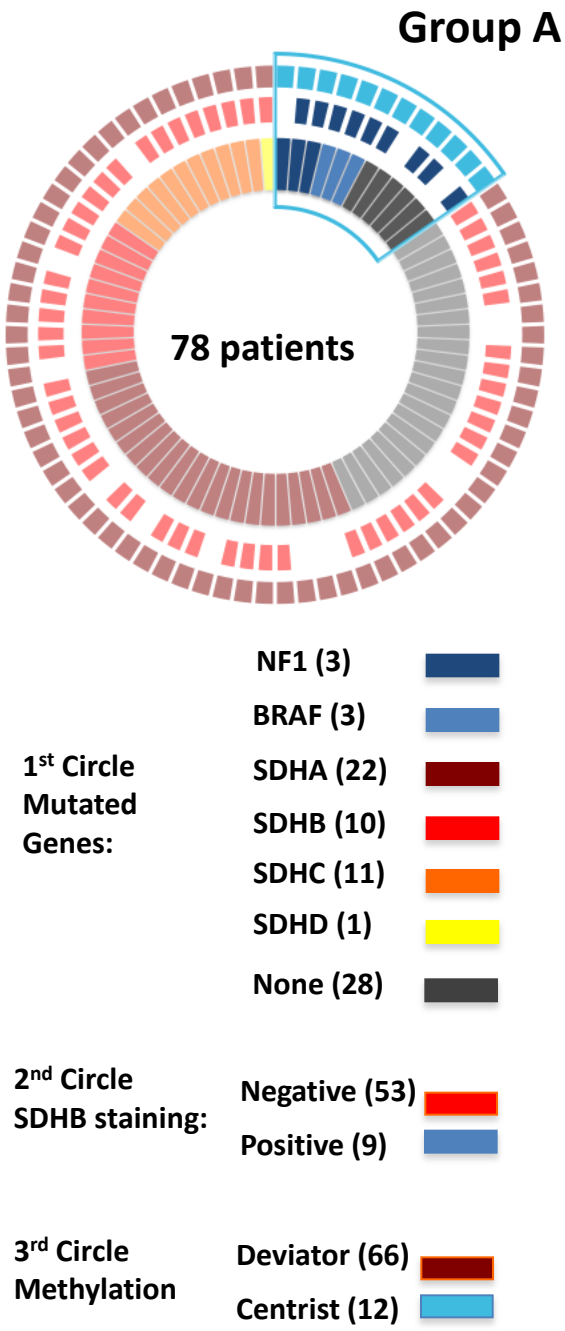
Group A (n=12)

Positive SDHB IHC
Normal Methylation pattern

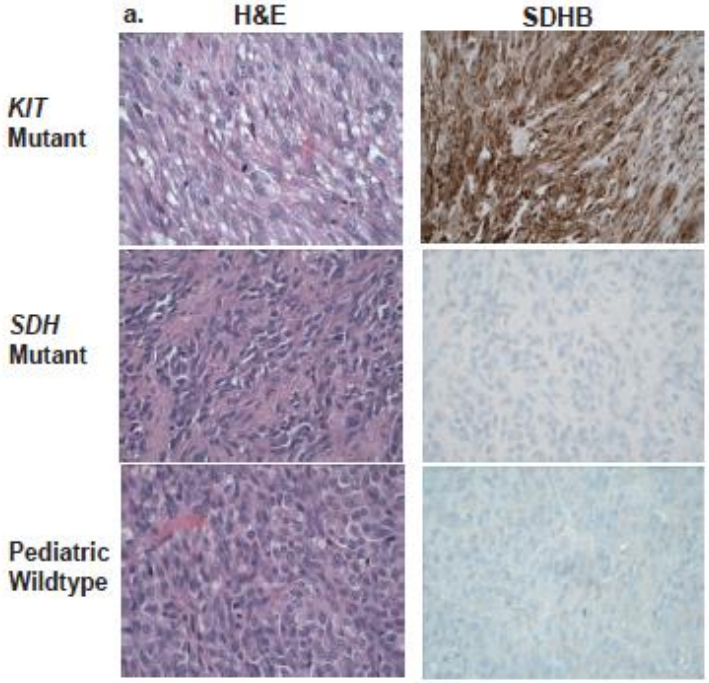
<u>Mutations in NF1, BRAF or other unknown genes</u>

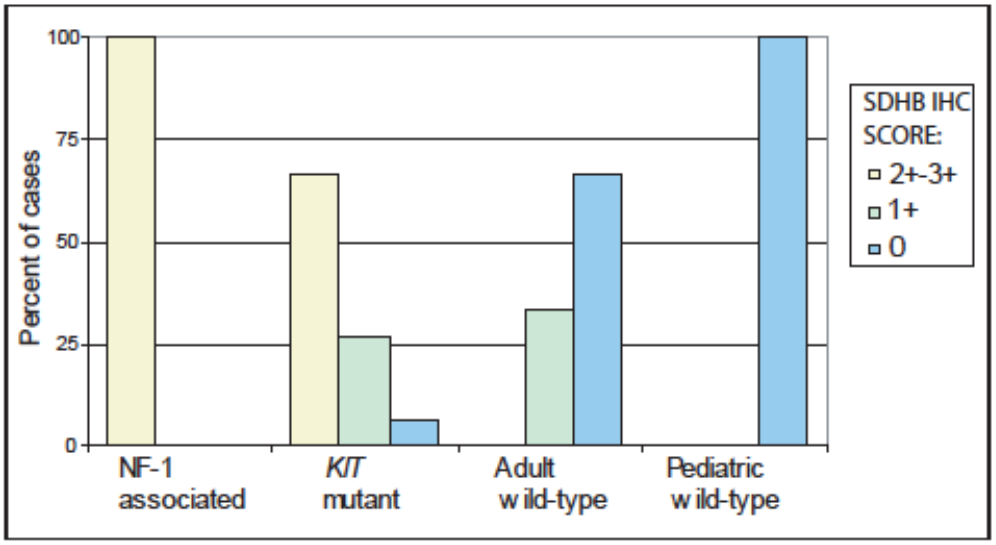
These are Kinase-type GIST

Remaing 66-SDH deficient



Loss of SDHB Protein Abundance



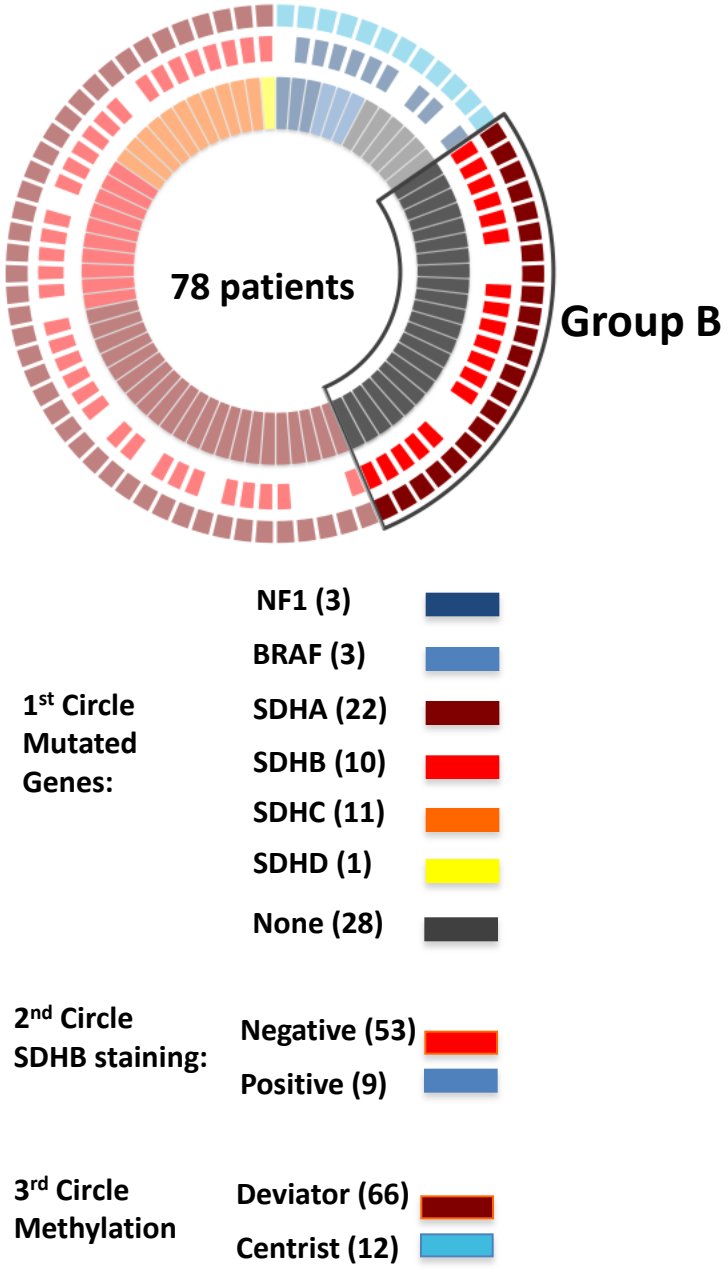


Janeway and Kim, et al. 2011 PNAS 108:314

Group B (n=22)

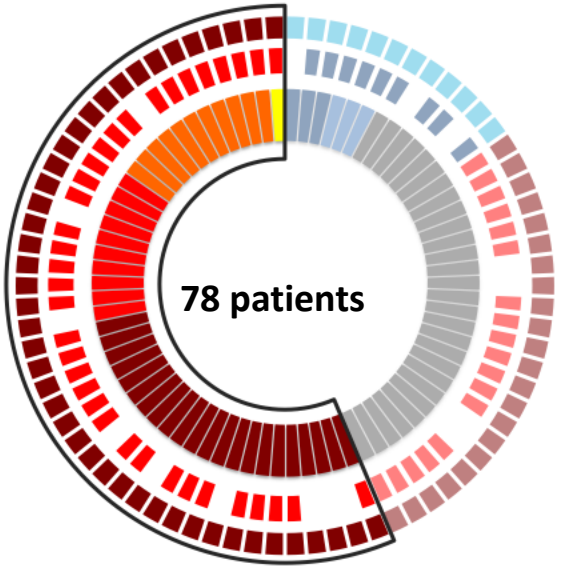
Negative SDHB staining by IHC
Hypermethylation (Deviator)

<u>No indentified mutations-early data suggest a mechanism of SDH deficiency</u>



Group C (n=44)

Group C



Negative SDHB staining by IHC
Hypermethylation (Deviator)

<u>SDHA, B, C, D mutations</u>

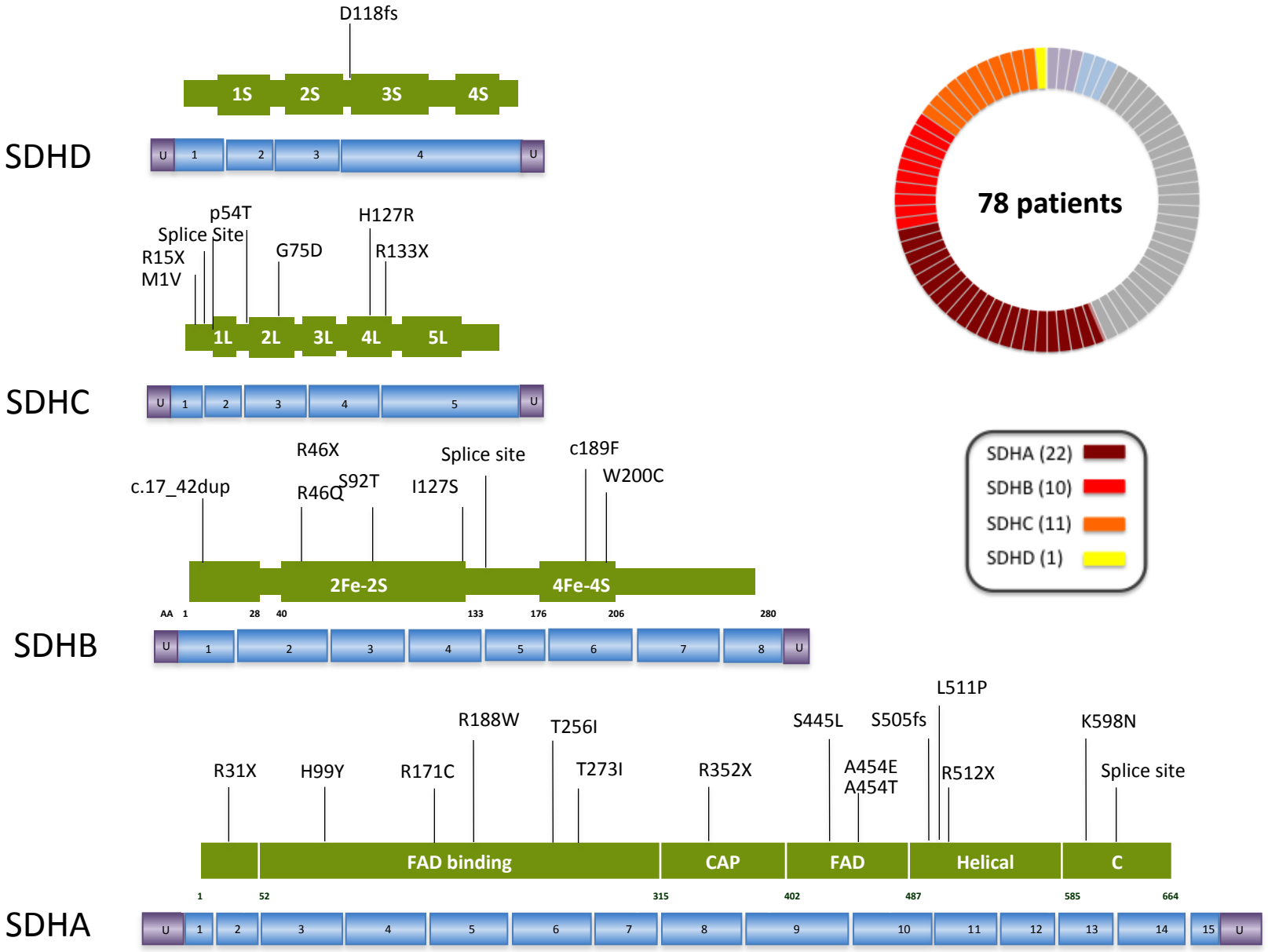
<u>To date, all but 3 are germline mutations</u>

1st Circle Mutated Genes:
- NF1 (3)
- BRAF (3)
- SDHA (22)
- SDHB (10)
- SDHC (11)
- SDHD (1)
- None (28)

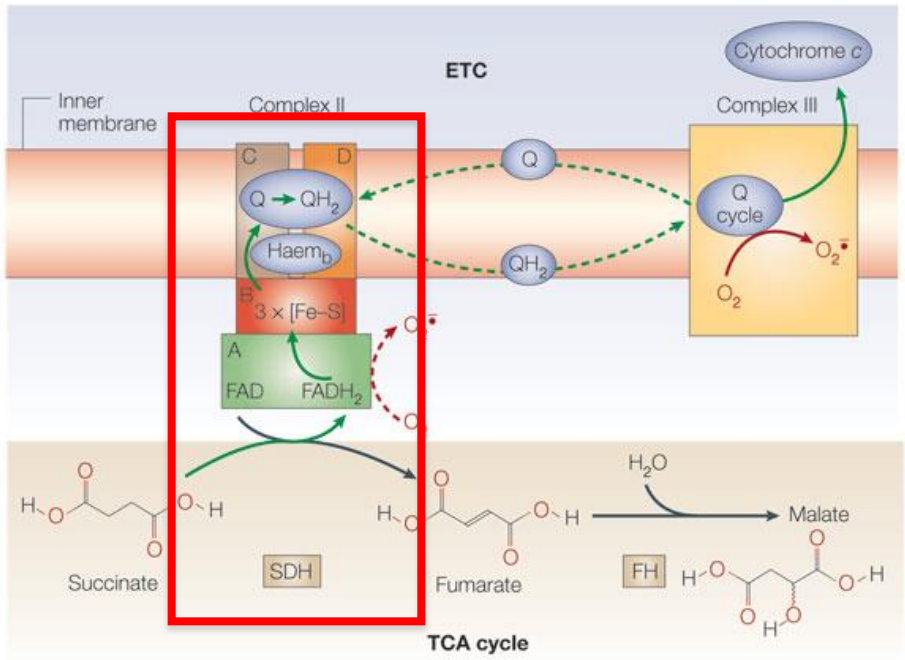
2nd Circle SDHB staining:
- Negative (53)
- Positive (9)

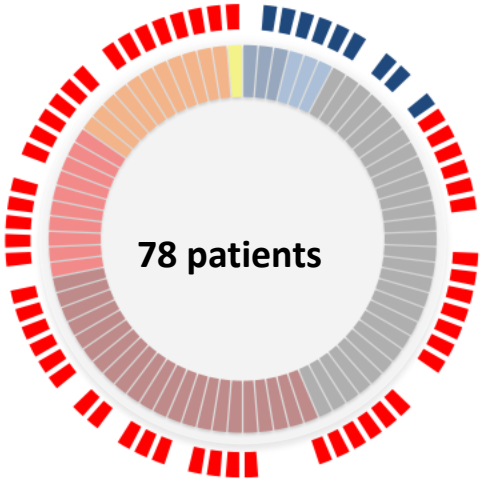
3rd Circle Methylation
- Deviator (66)
- Centrist (12)

Mutations Distributed across all exons-90% Germline



- **Tumors with SDHA, B, C, D mutations have always negative SDHB staining.**





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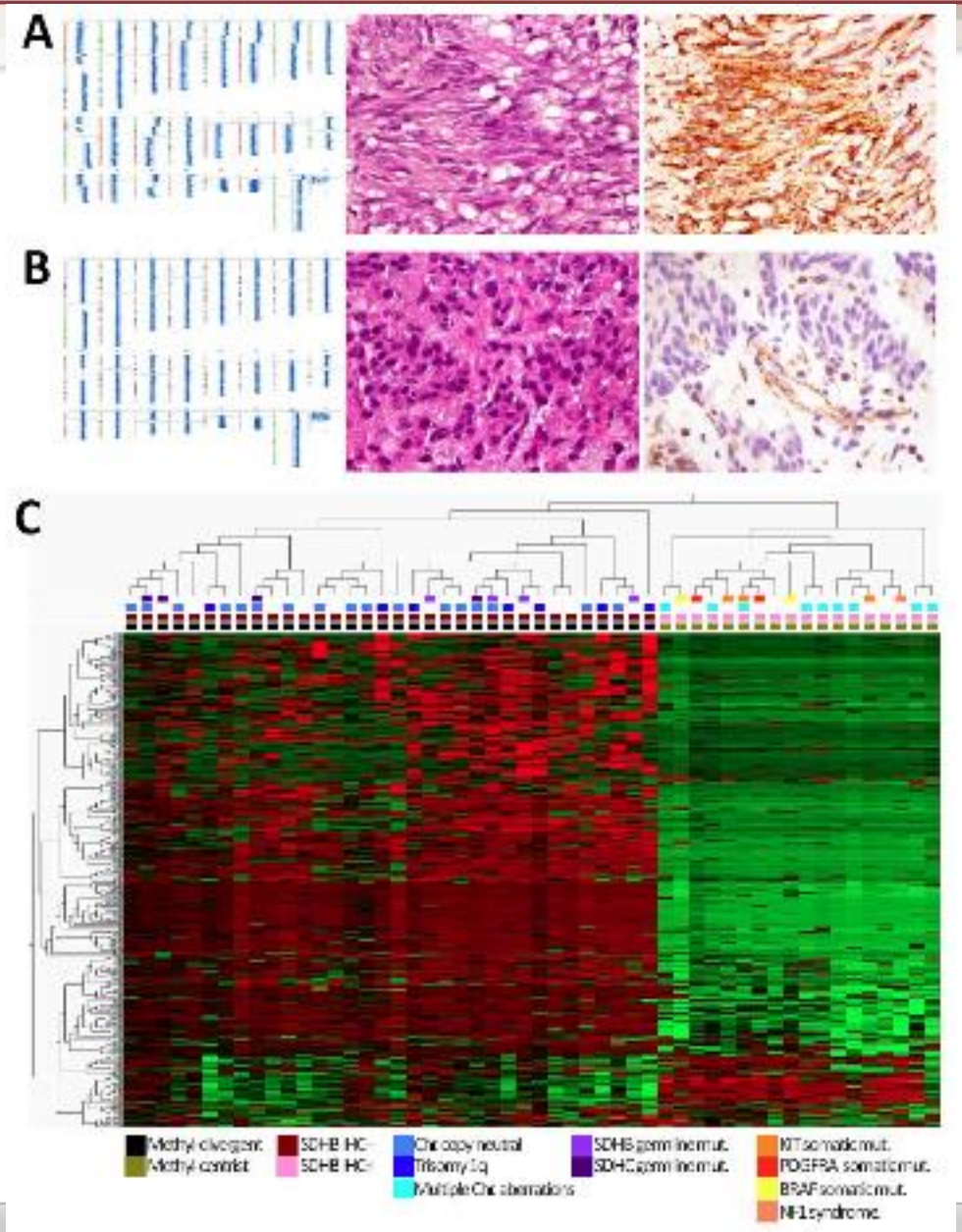
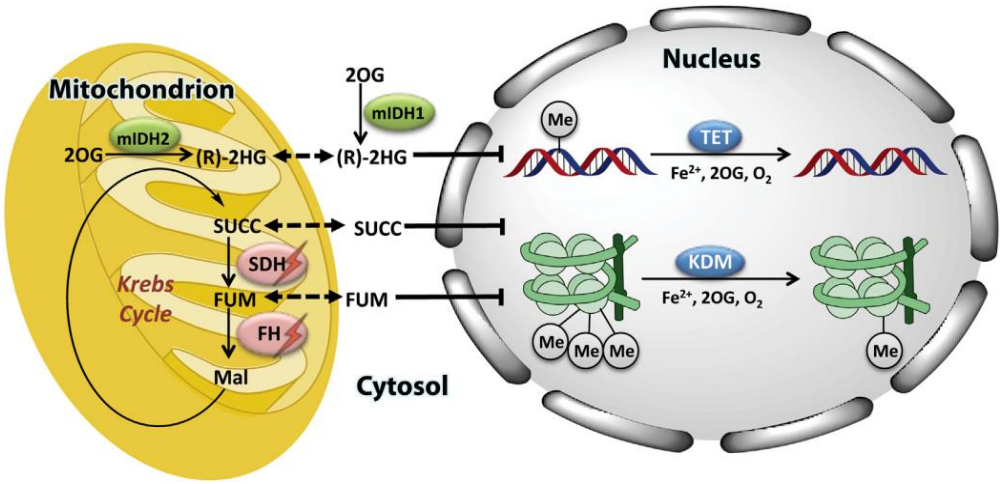
SDH Deficient GIST Have Global Hypermethalyation



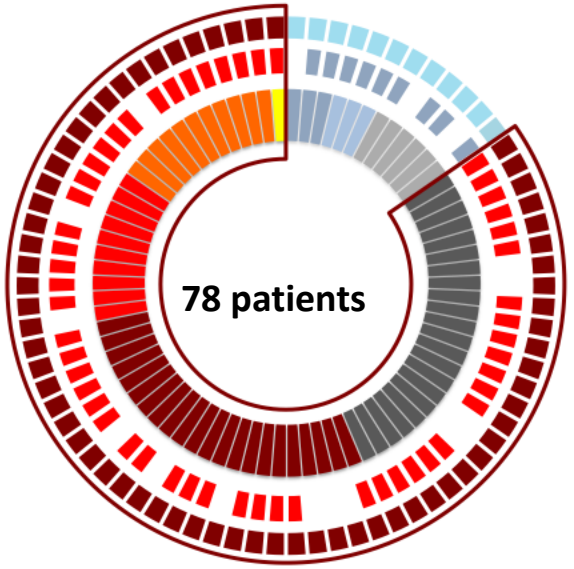
18 SDH mutations found

Killian K et al.
Cancer Discovery 2013

SDH loss leads to succinate inhibition of demethylases TET2 and KDM



Yang M, Pollard PJ Cancer Cell 2013



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- Deviator (66)
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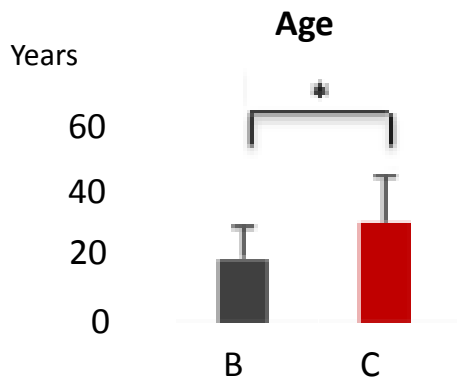
Comparison of Group B and C

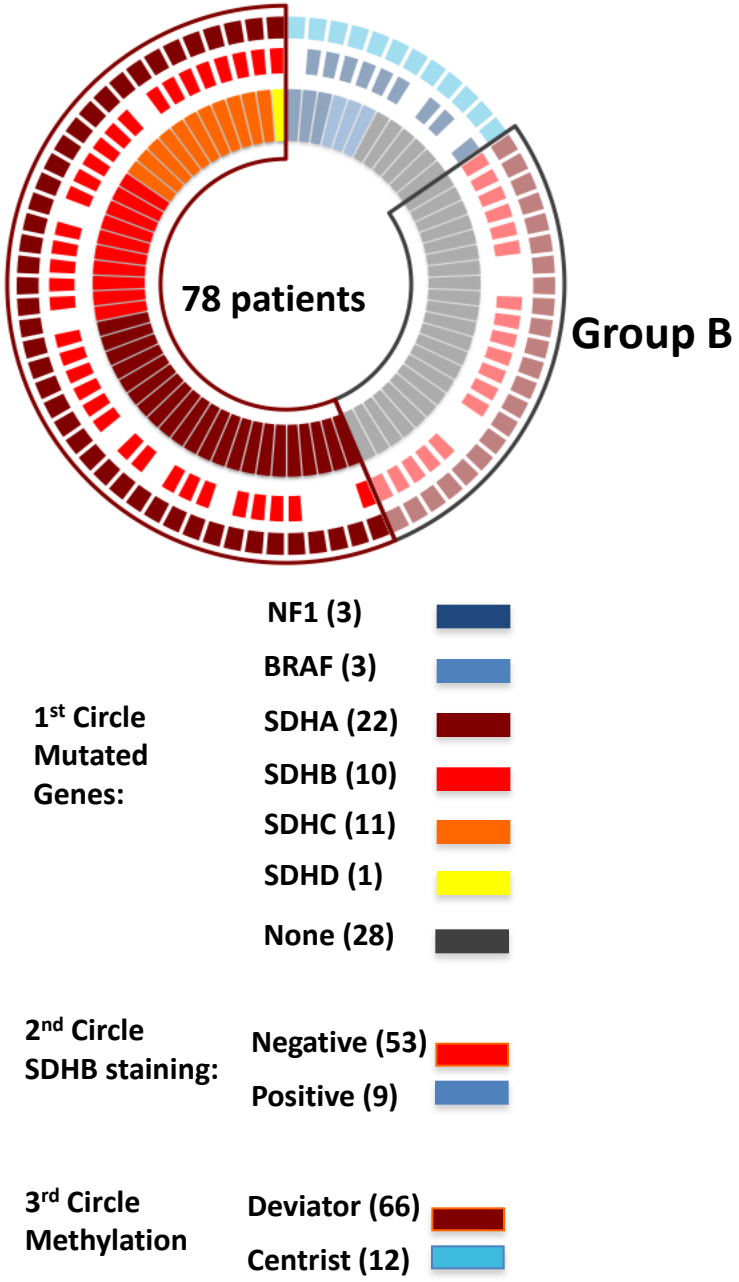
1. Group B=young age



2. All patients in Group B are females while in Group C 65% are females.

We have Carney Triad patients (chondroma, paraganglioma) or Carney-Stratakis Syndrome patients (paraganglioma) in both groups B and C.

At the moment we have no statistically significant differences in overall Survival, Recurrence free Survival.



Conclusions

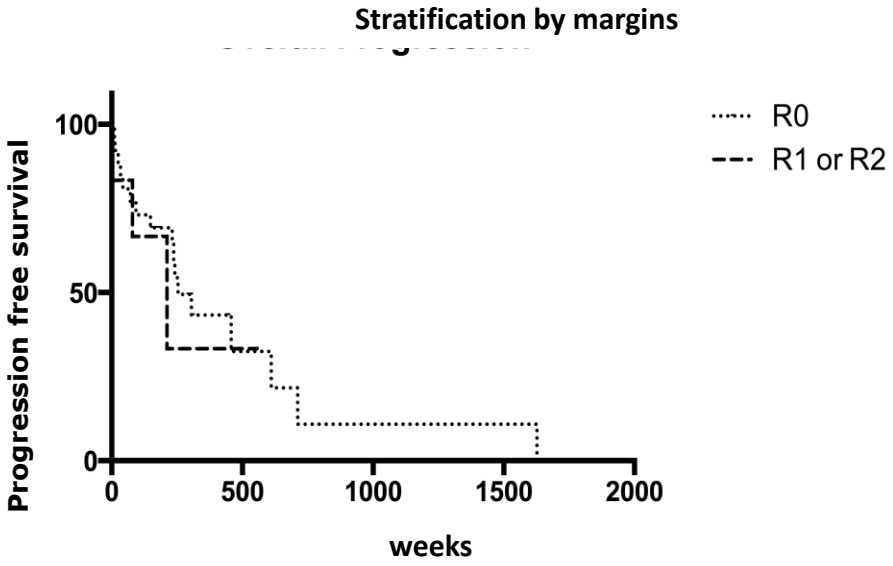
3 distinct groups of Wildtype GIST

	Group A	Group B	Group C
Mutated genes	**NF1, BRAF or other genes**	**Unknown genes**	**SDH genes**
SDHB expression by ICH	**normal**	**no**	**no**
SDH Function	**Normal**	**Impaired**	**Impaired**
Methylation Pattern	**Centrist**	**Deviator (hypermethylation)**	**Deviator (hypermethylation)**
Gender	**Both**	**Females**	**Female predominance**
Age	**Young adults, adults**	**Pediatric, young adults**	**Young adults, adults**
Location	**Gastric, small bowel**	**Gastric**	**Gastric**

Baseline patient and disease characteristics per group

		SDHB (+) N=9	SDHB (-) SDHx WT N=17	SDHB (-) SDHx mutant N=41
Age, median years (range)		44 (9-57)	16 (8-50)	24 (8-50)
Sex, n (%)	Male	3 (33.3%)	1 (5%)	14 (34%)
	Female	6 (66.6%)	16 (94%)	27 (65%)
Location of primary tumor, n (%)	Gastric	1 (11.1%)	17 (100%	41 (100%)
	Duodenum	1 (11.1%)	0	0
	Small Bowel	6 (66.6%)	0	0
	Peritoneum	1 (11.1%)	0	0
Size of primary tumor, median cm (range)		10.5 (5.6-13.5)	5.5 (2-16)	5.8 (2-21)
Multifocal Disease, n (%)	Yes	2 (22.2%)	9 (52%)	14 (40%)
	No	7 (77.7%)	7 (41%)	21 (60%)
Metastatic Disease, n (%)	At presentation	0 (0%)	5 (29%)	11 (26%)
	Later	0 (0%)	7 (41%)	19 (46%)
	Never	0 (0%)	5 (29%)	11 (26%)
Metastatic sites at presentation	Lymph Nodes	0 (0%)	1 (5%)	4 (9%)
	Small Bowel	0 (0%)	0	0
	Liver	0 (0%)	4 (23%)	9 (21%)
	Peritoneum	0 (0%)	2 (11%)	4 (9%)
Recurrence sites	Stomach	0	5 (29%)	6 (14 %)
	Small Bowel	1 (1,1 %)	0	0
	Liver	0	6 (35%)	12 (29%)
	Peritoneum	6 (66%)	4 (23%)	8 (19%)
Other tumors	Paraganglioma	0 (0%)	2 (11%)	5 (12%)
	Chondroma	0 (0)%)	4 (23%)	2 (4%)

SDH Deficient GISTS are Multi-focal



the NIH Pediatric & Wildtype GIST Clinic

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GCAF GIST Cancer Awareness Foundation

gsi GIST Support International

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Our Thanks

To GIST support group members

To the patients and their families