Brigham and Women's Hospital, Harvard Medical School

Why does a MicroGIST not become a Clinical GIST?

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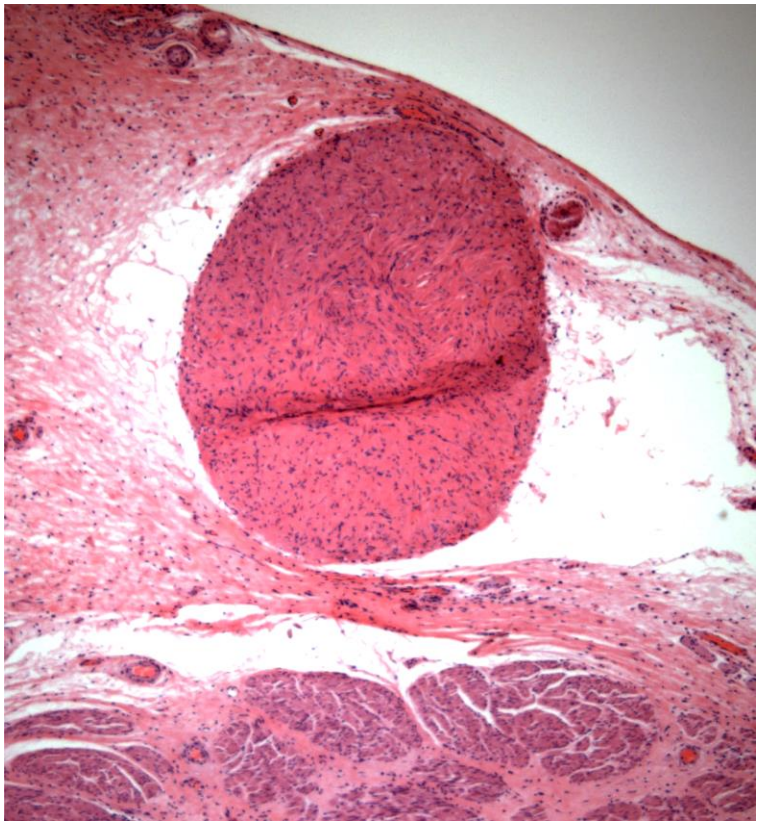
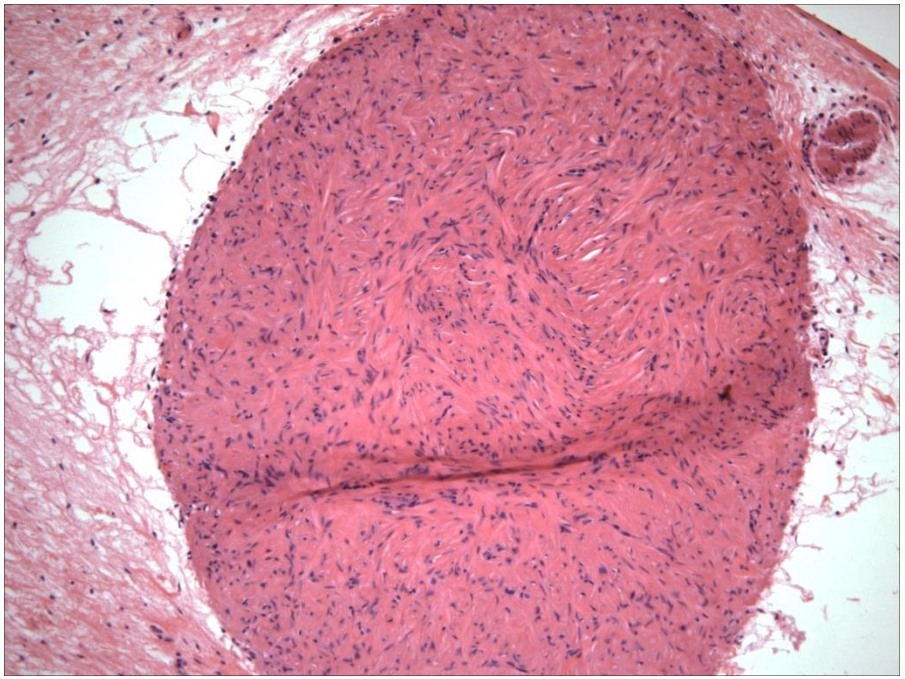
microGIST (<1cm)

Found in 30% of the general population





EG junction, spindle cell type

Dr. Cher-Wei Liang

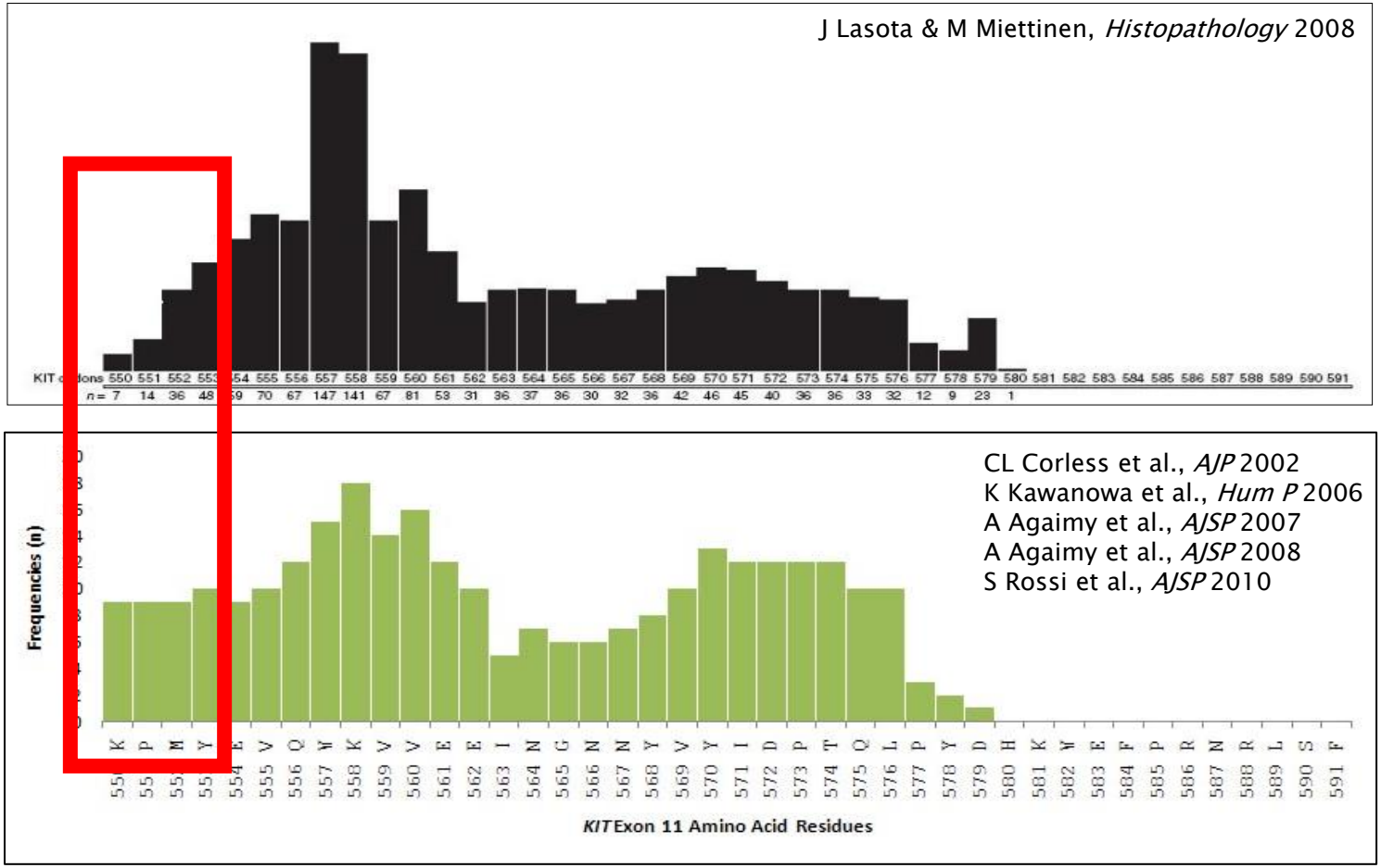
Mutation Status in Small (<2cm) vs. Clinically-overt GISTs

Genotype	Small GISTs (N = 135)	Overt GISTs (N = 101)	P value
Mutant	74%	84%	0.078
KIT exon 11	46%	61%	0.025

Drs. Sabrina Rossi, Roberta Maestro, Paolo dei Tos, AJSP, 2010

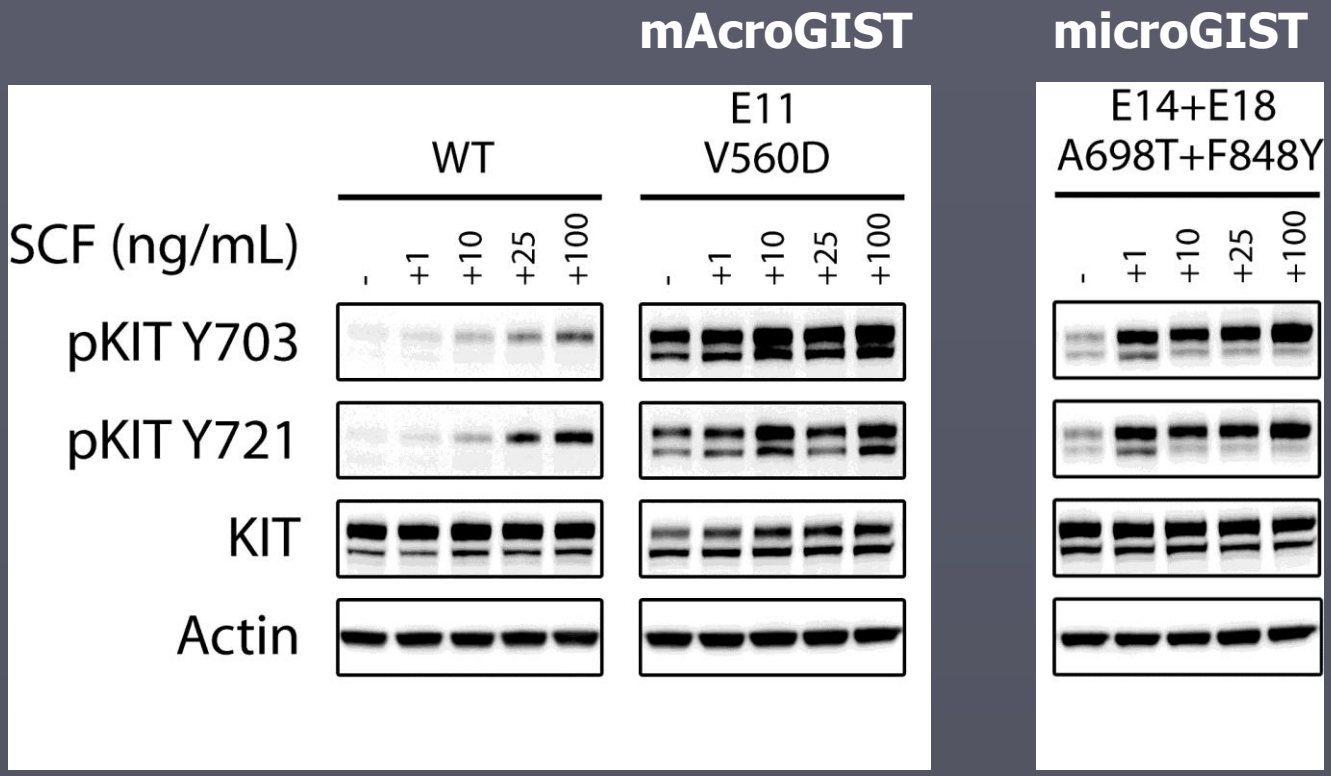
KIT exon 11 deletions in clinical GISTs vs. microGISTs

Distribution of *KIT* E11 Deletion, clinical GISTs



Distribution of *KIT* Ex11 deletions, microGISTs (34 cases from present series, and 76 cases from previously published series)

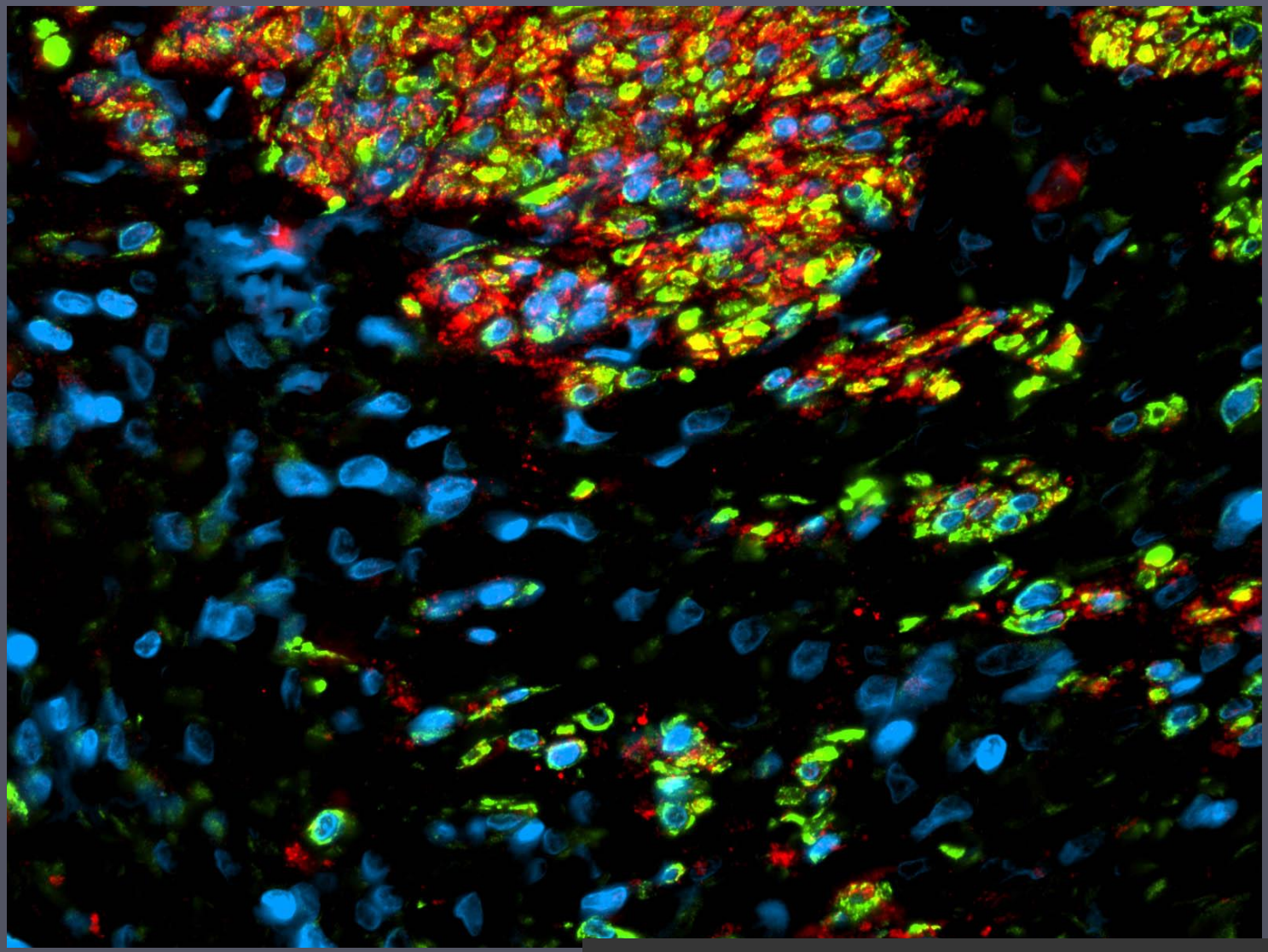
MicroGIST Mutations Expressed in KIT-negative GIST48B



SCF (KIT-LG) dose response

Cher-wei Liang

MicroGIST: KIT-ligand/SCF (RED) expressed highly in smooth muscle (GREEN), not in GIST cells (BLUE)

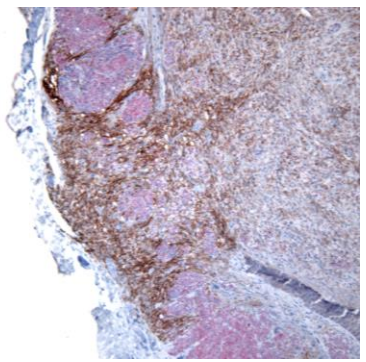


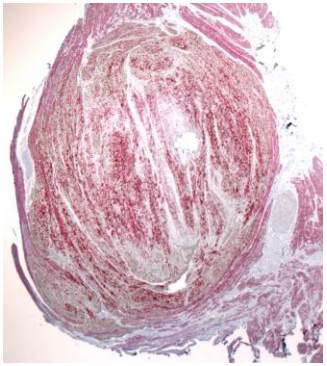
Green: Desmin Red: SCF Blue: DAPI

Dr. Jason Hornick

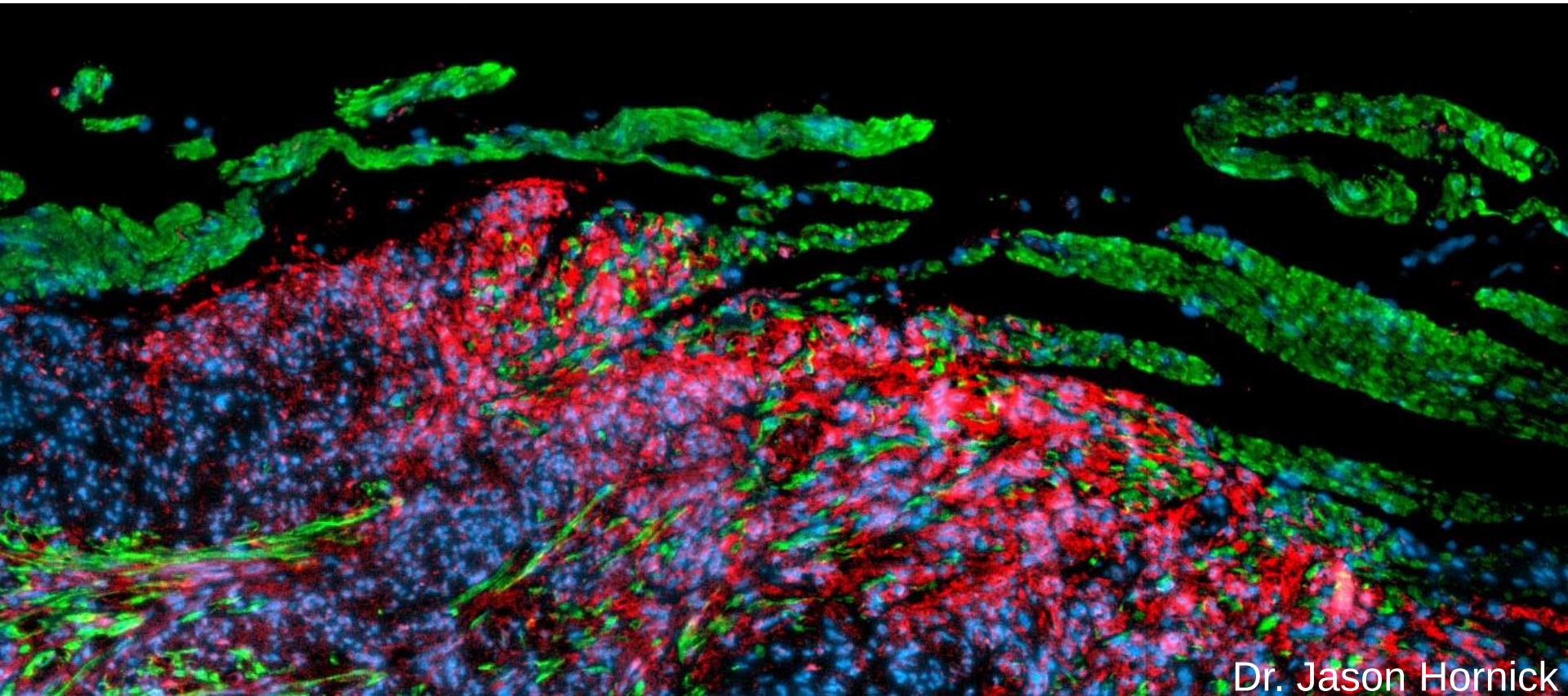
MicroGISTs have infiltrative borders and admixed smooth muscle

RED = Desmin Brown = DOG1





GREEN = Desmin RED = DOG1 BLUE = DAPI



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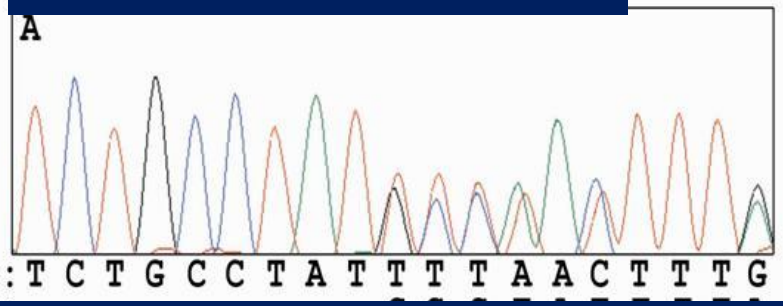
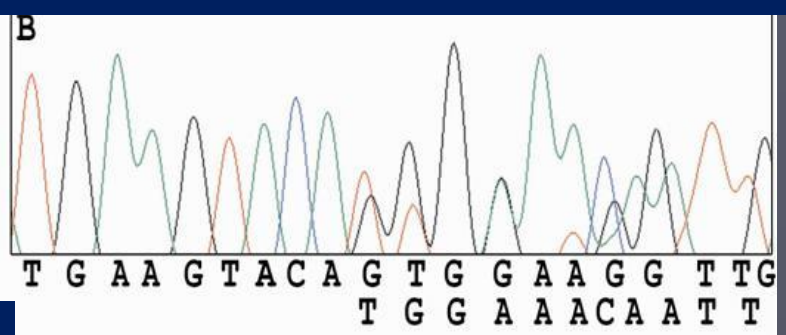
“Worrisome” KIT mutations in benign microGISTs that struggle to grow!

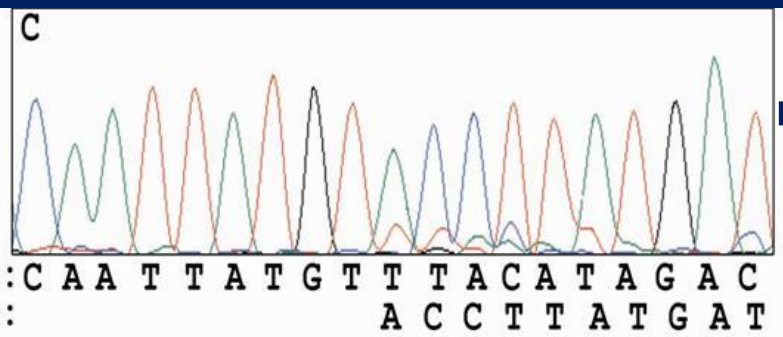
Exon 9 (4mm)

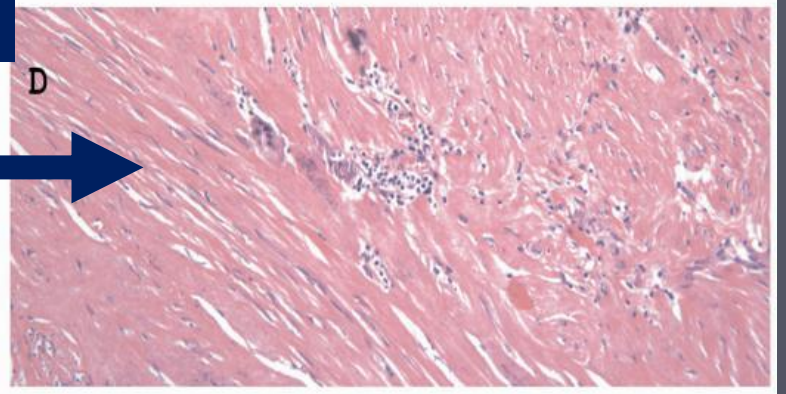


Ex 11 del557-558 (3mm)



Ex 11 homozygous (3mm)





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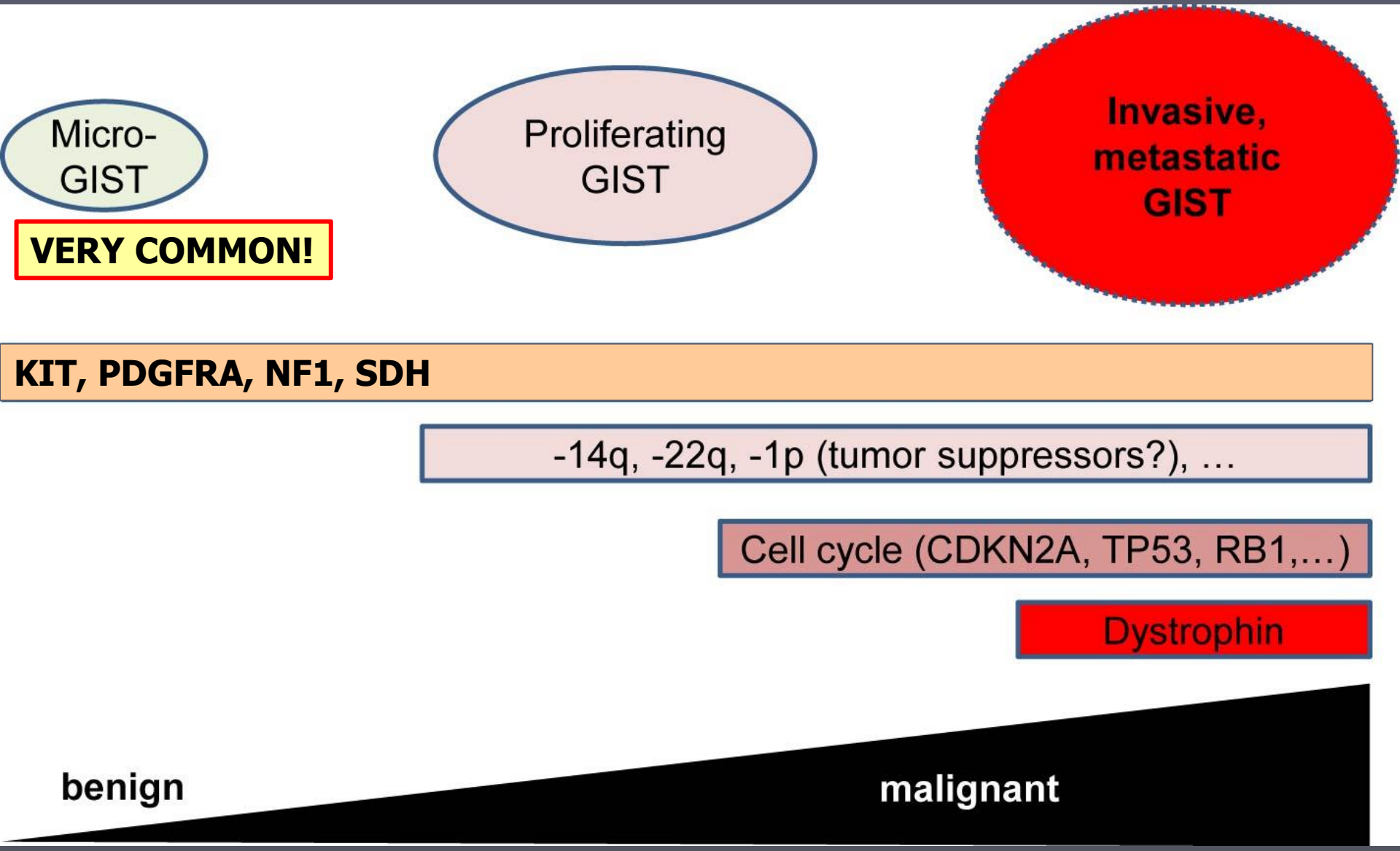
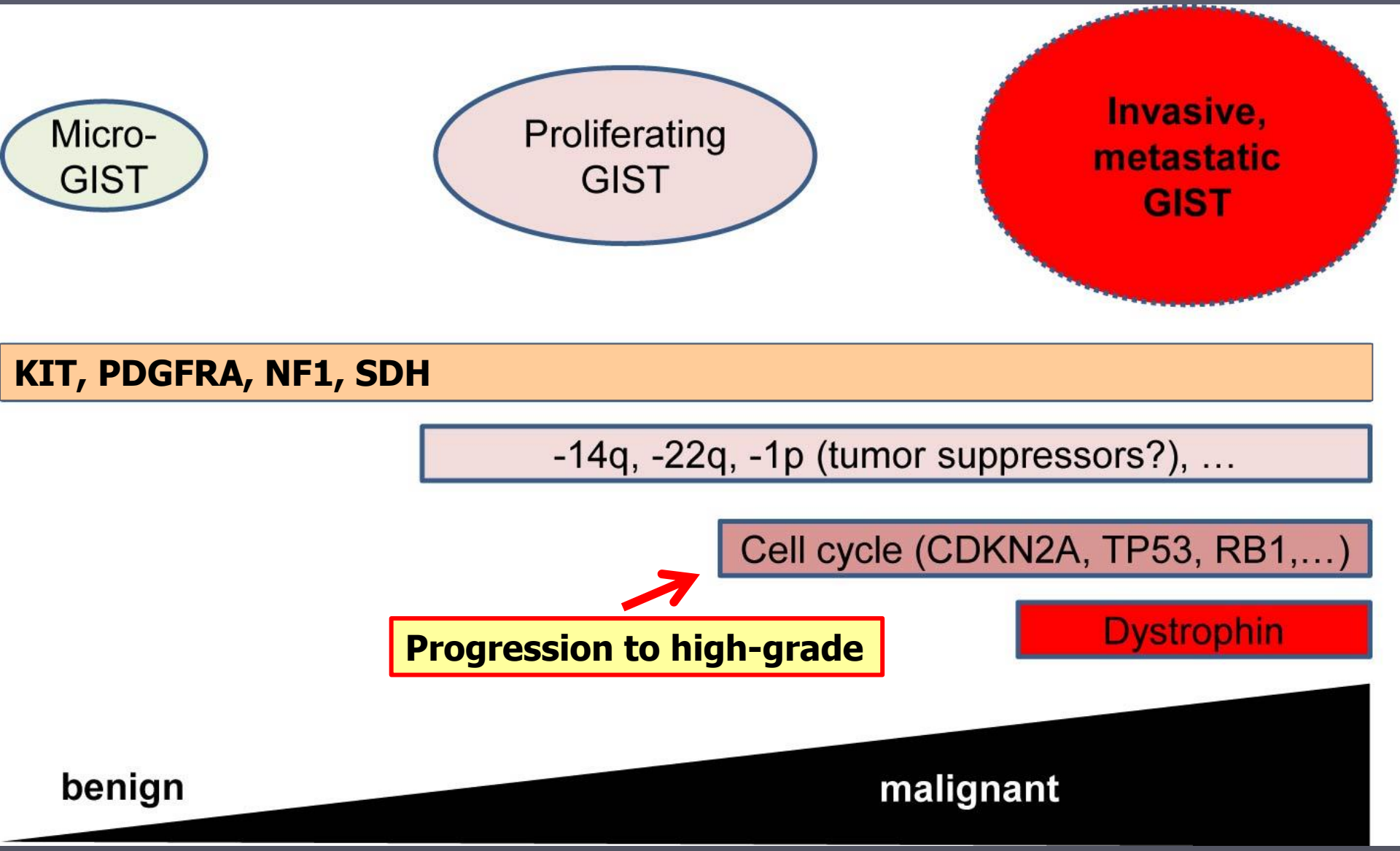
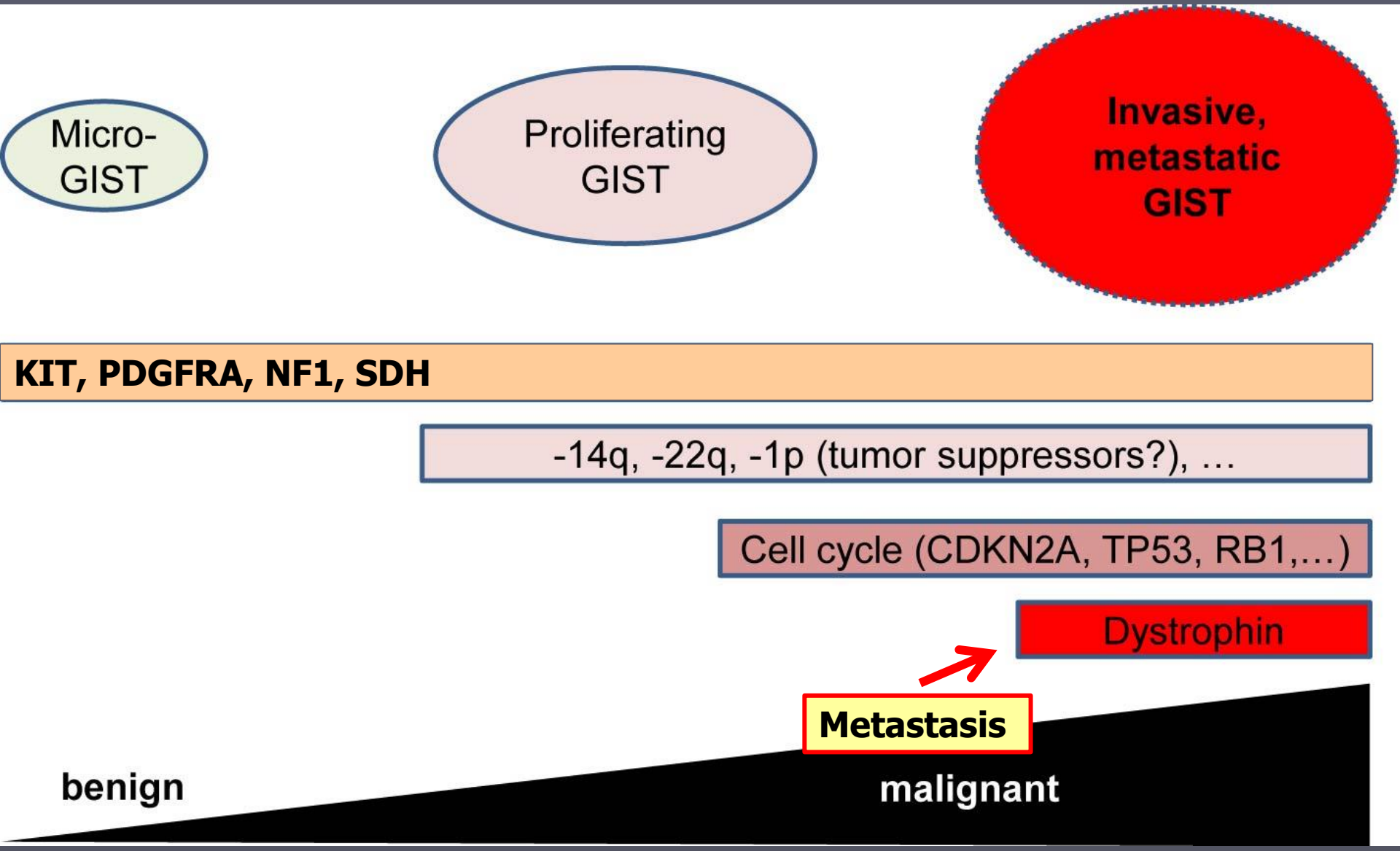
GIST Biologic Progression



GIST Biologic Progression

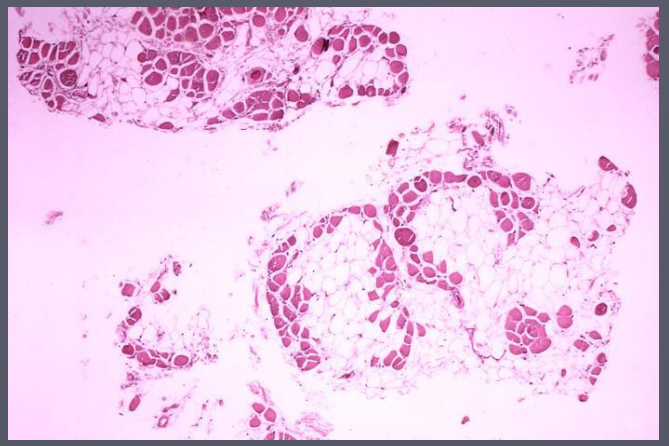


GIST Biologic Progression



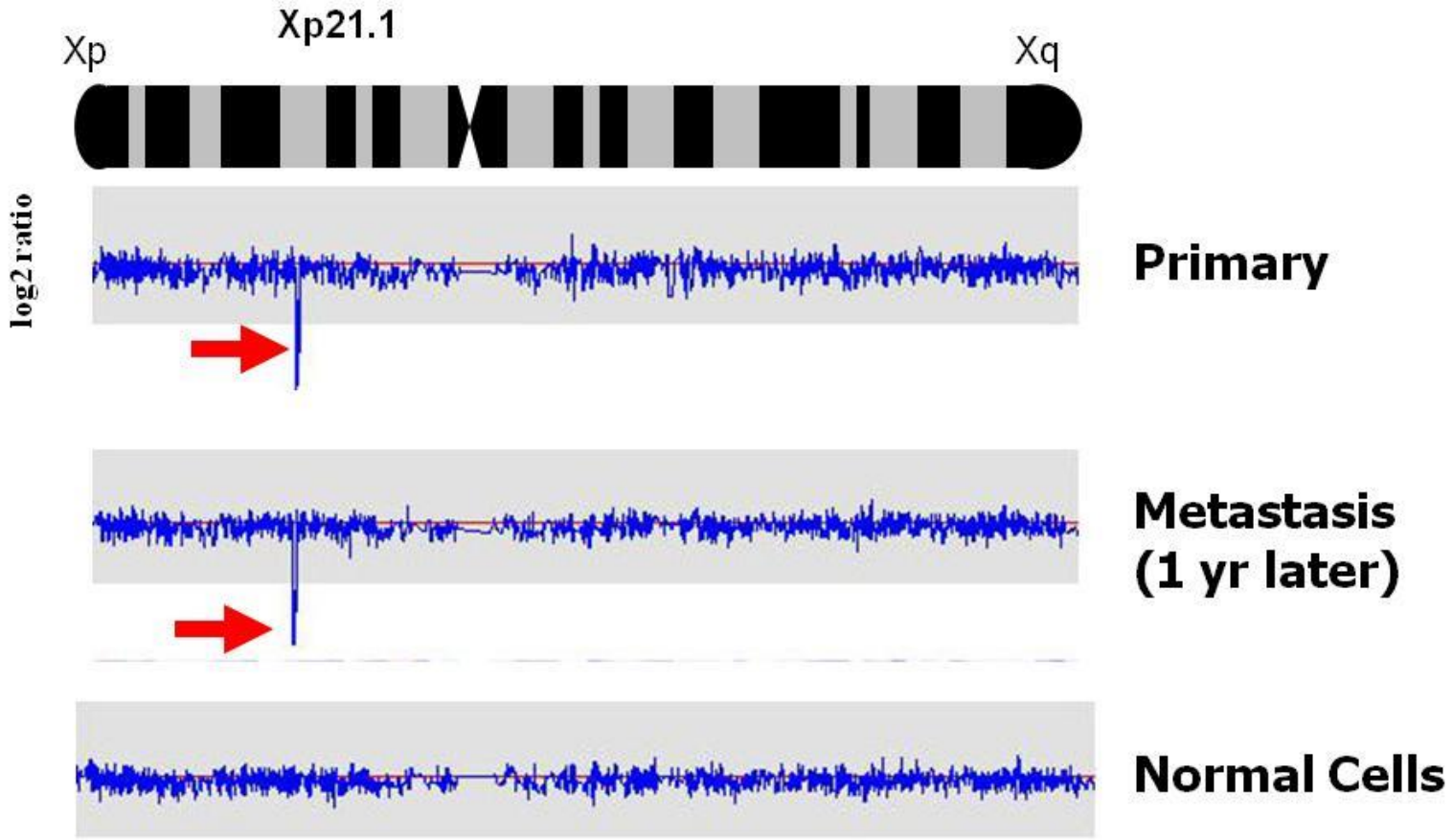
DMD (dystrophin)

- X-linked
  - Duchenne muscular dystrophy
  - Becker's muscular dystrophy



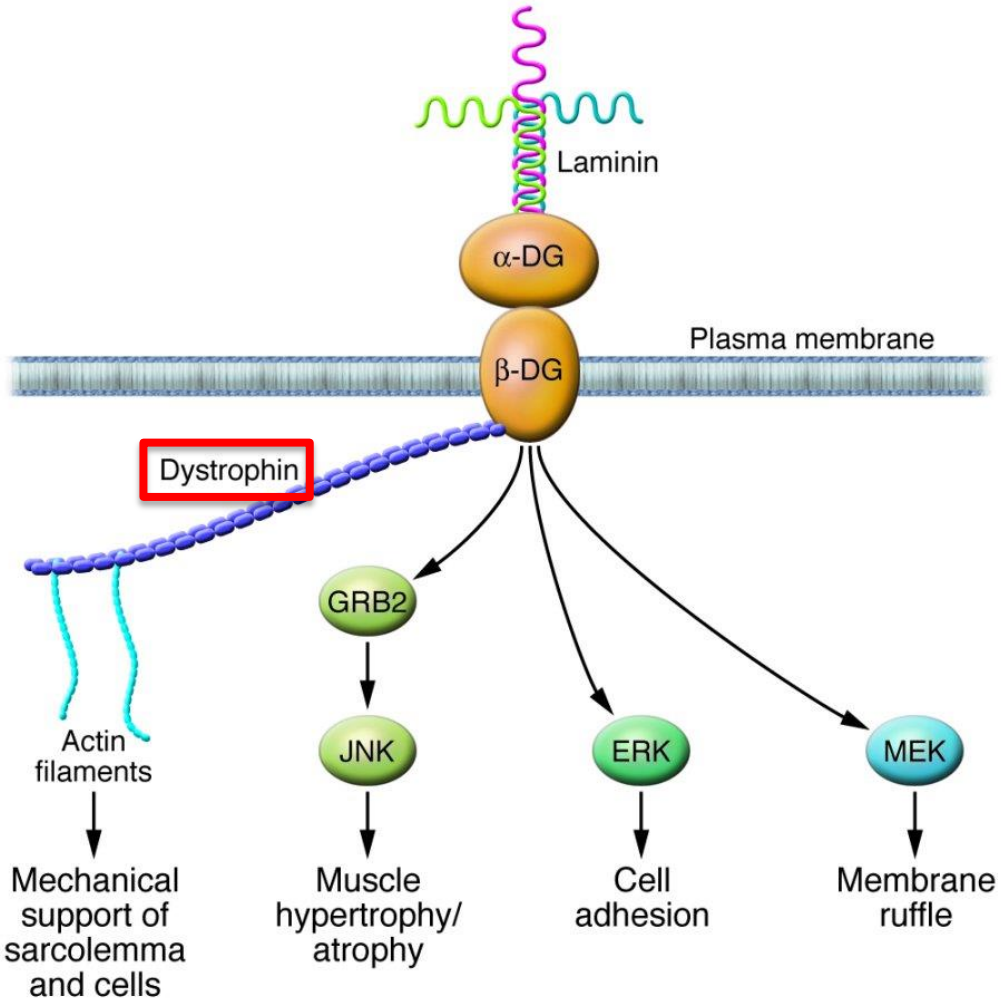
- *DMD* expressed strongly in:
  - Skeletal muscle
  - Smooth muscle
  - Cardiac muscle
  - Schwann cells
  - Interstitial cells of Cajal

Background – Dystrophin genomic inactivation: 0% of low-risk GIST; 94% of GIST mets

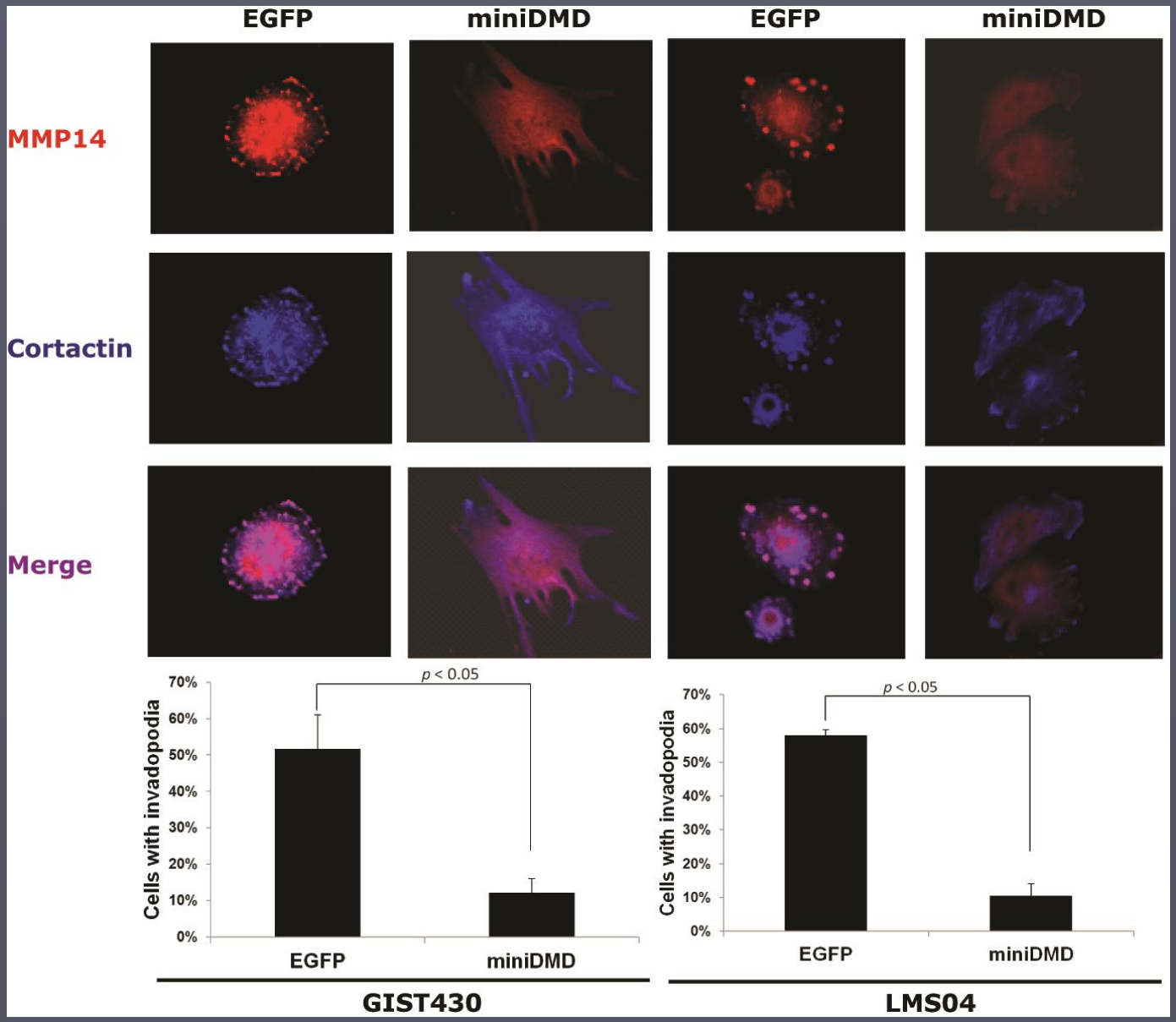


Yuexiang Wang et al. Nature Genetics, 2014; 46:601-6.

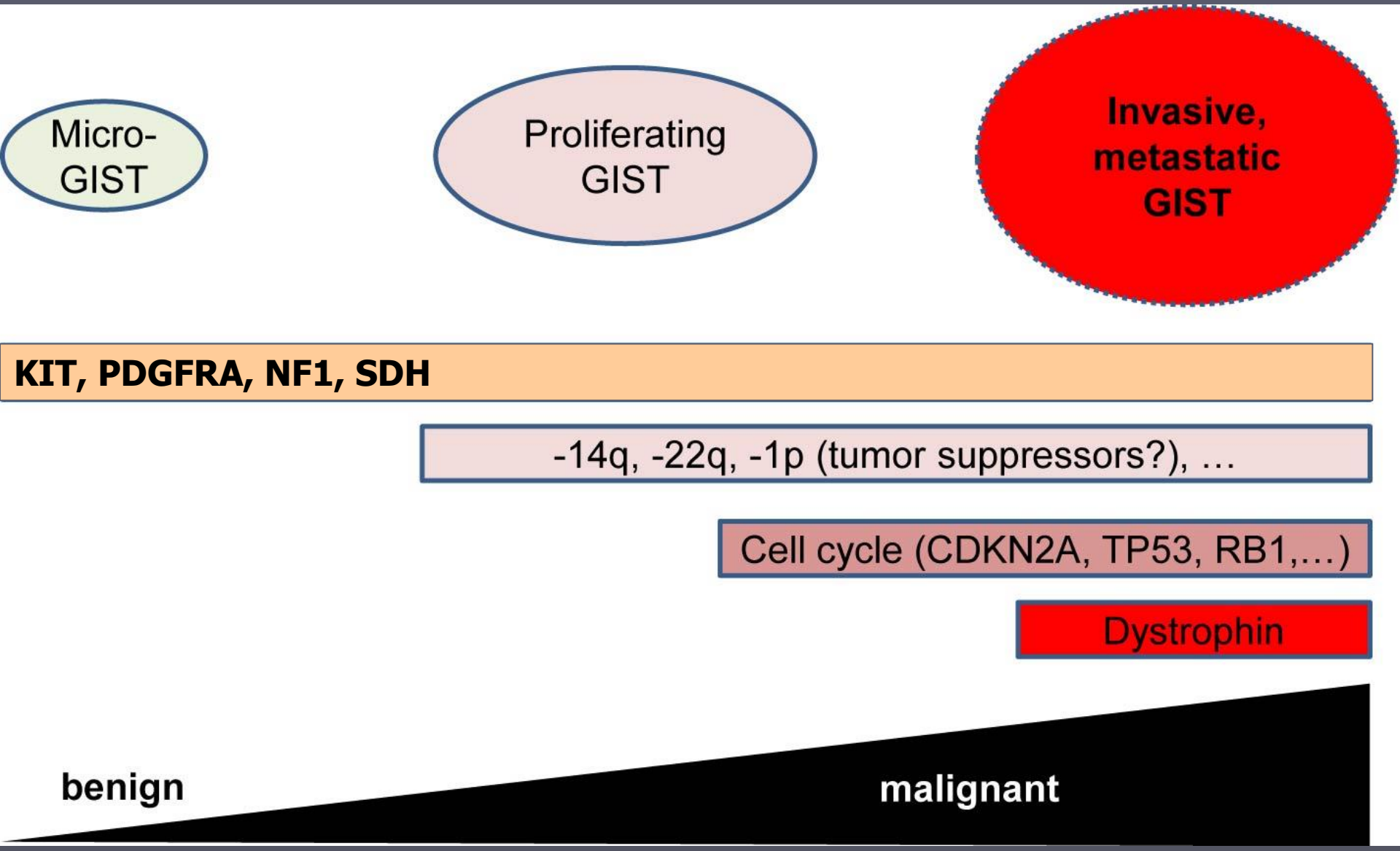
Dystrophin function // invasion



Dystrophin restoration inhibits filopodia formation

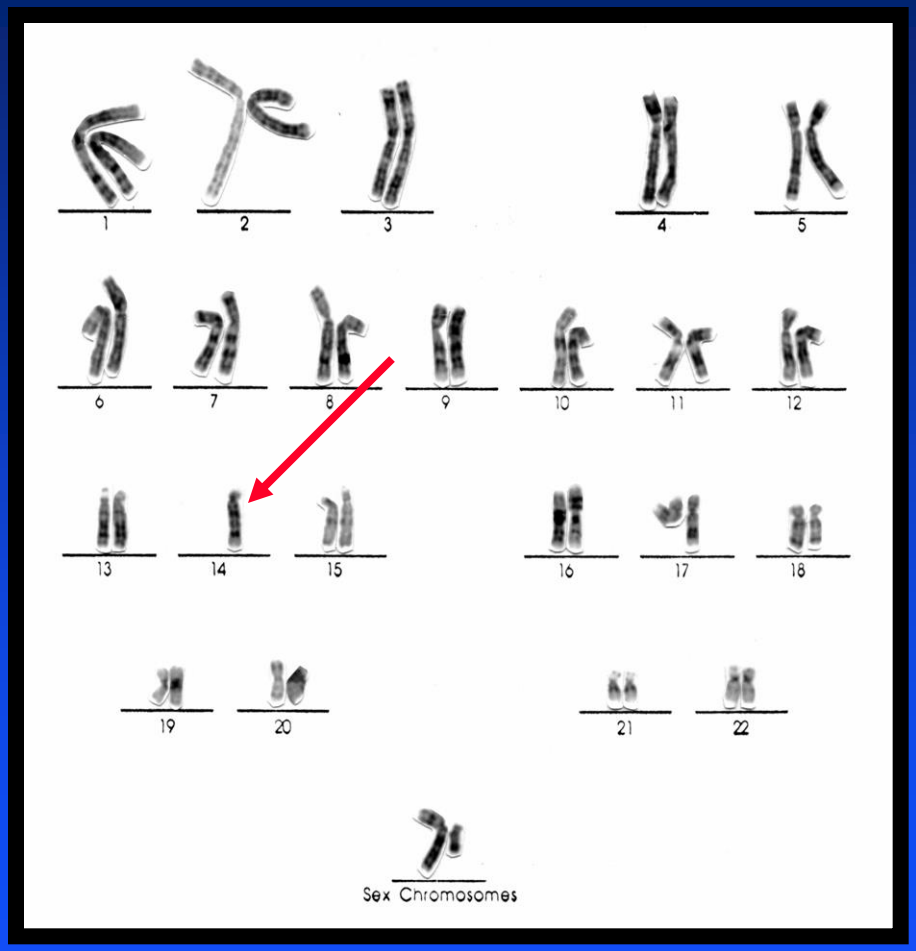


GIST Biologic Progression

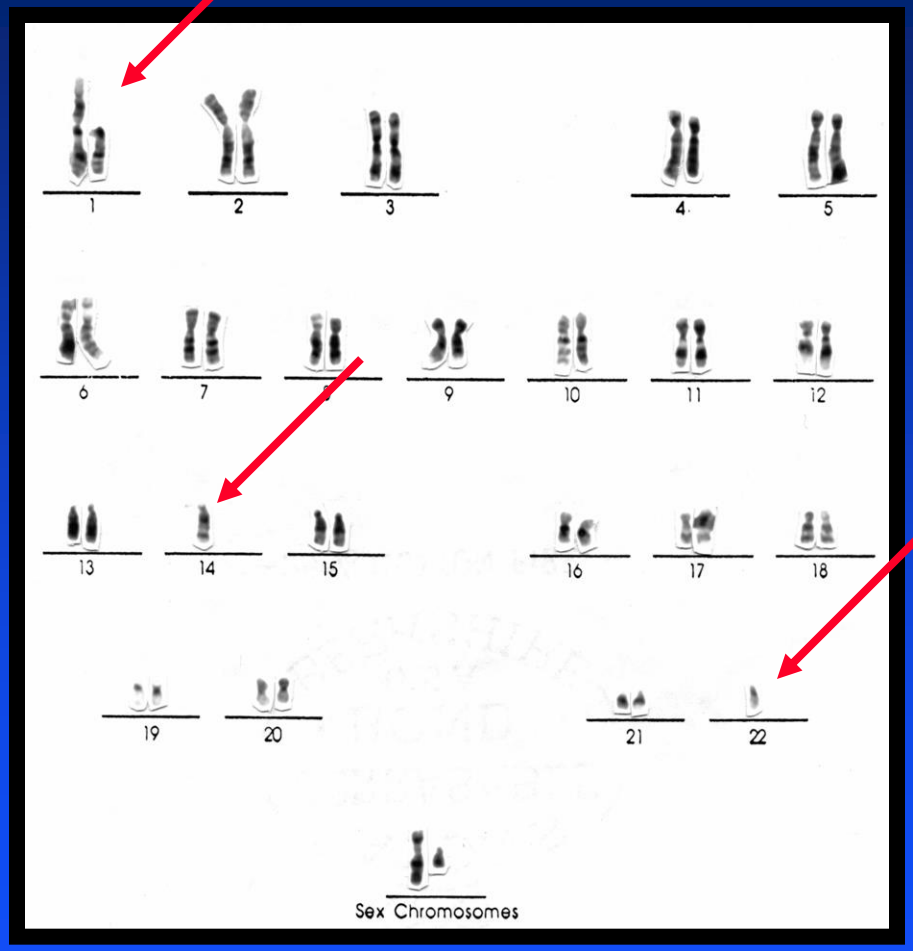


GIST: Genetic Progression

A

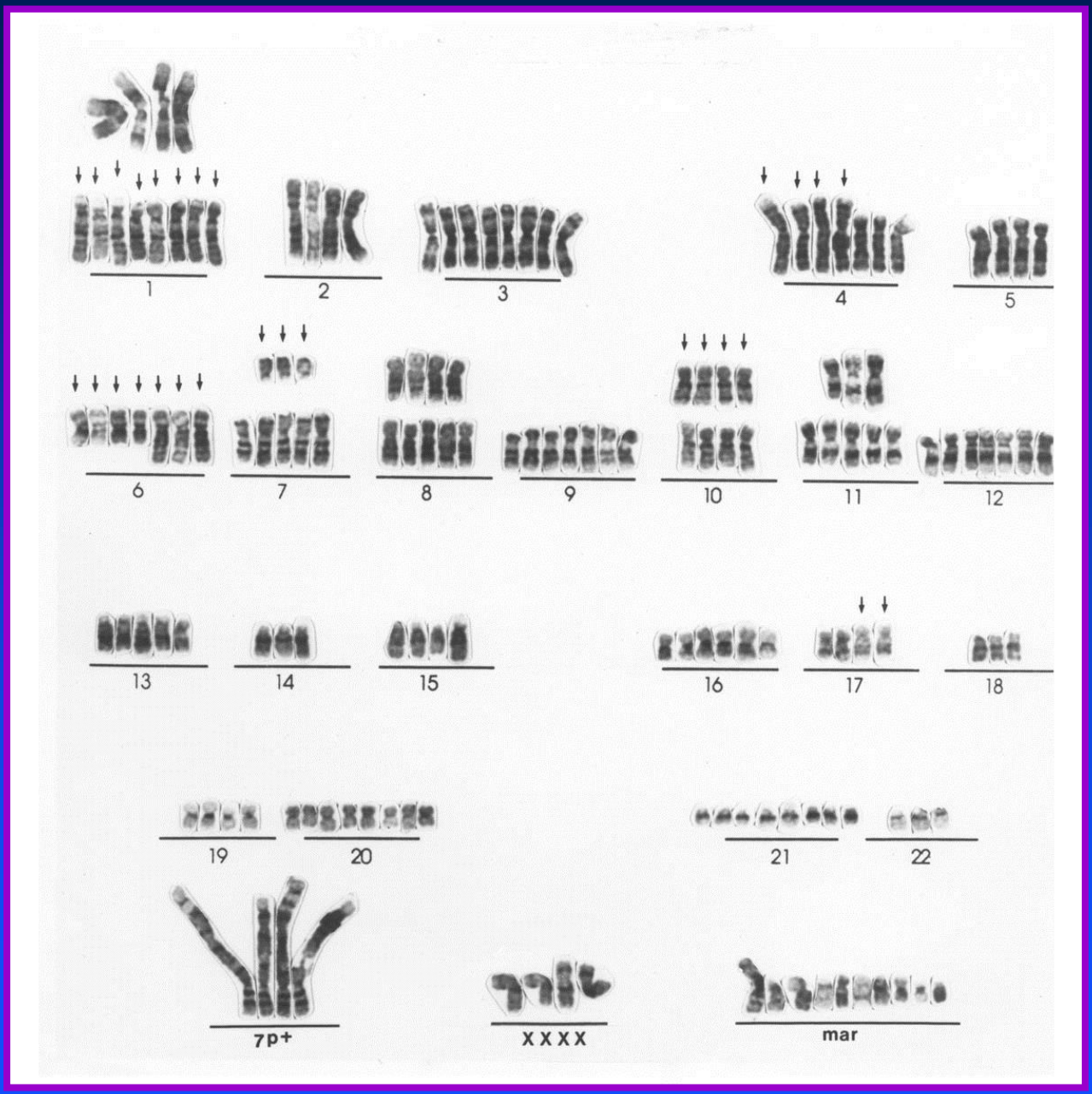


B



KIT → 14q- → 22q- → 1p- → cell cycle dysreg → 15q-

Leiomyosarcoma – genomic instability



Progression from microGIST to metastatic GIST constrained by:

1) Ligand-dependence (SCF needed, from smooth muscle)
2) Multiple genetic perturbations needed, after KIT/PDGFRA mutational activation
3) Genomic stability

Coauthors / Acknowledgements

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