

# Somatic Copy Number Alterations and Aneuploidy Events in Uveal Melanoma

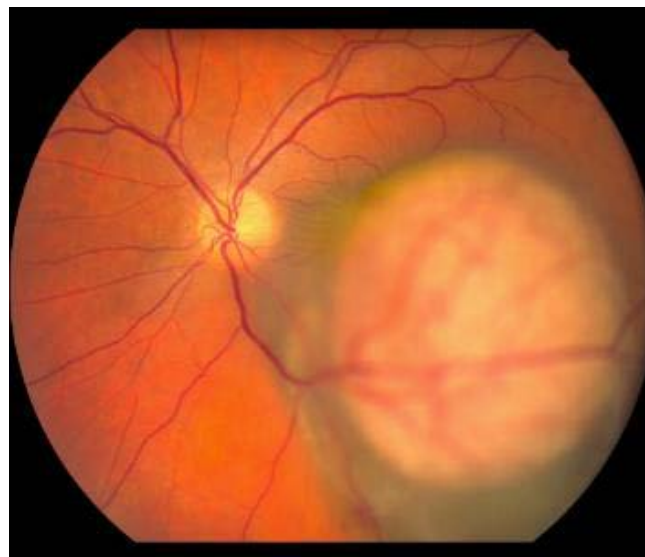
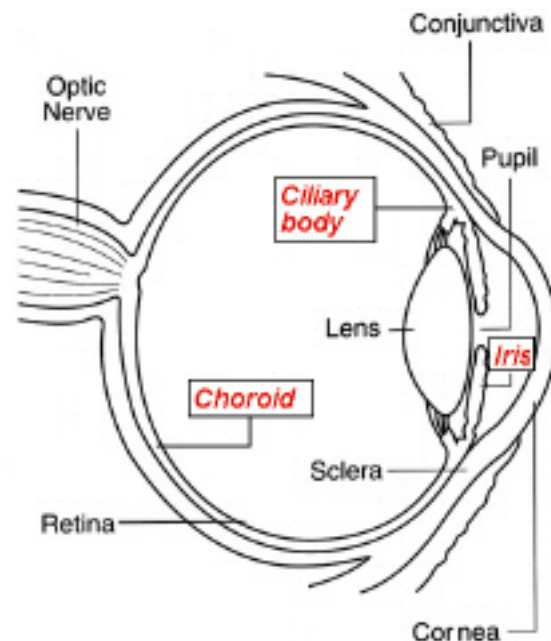
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UVM AWG

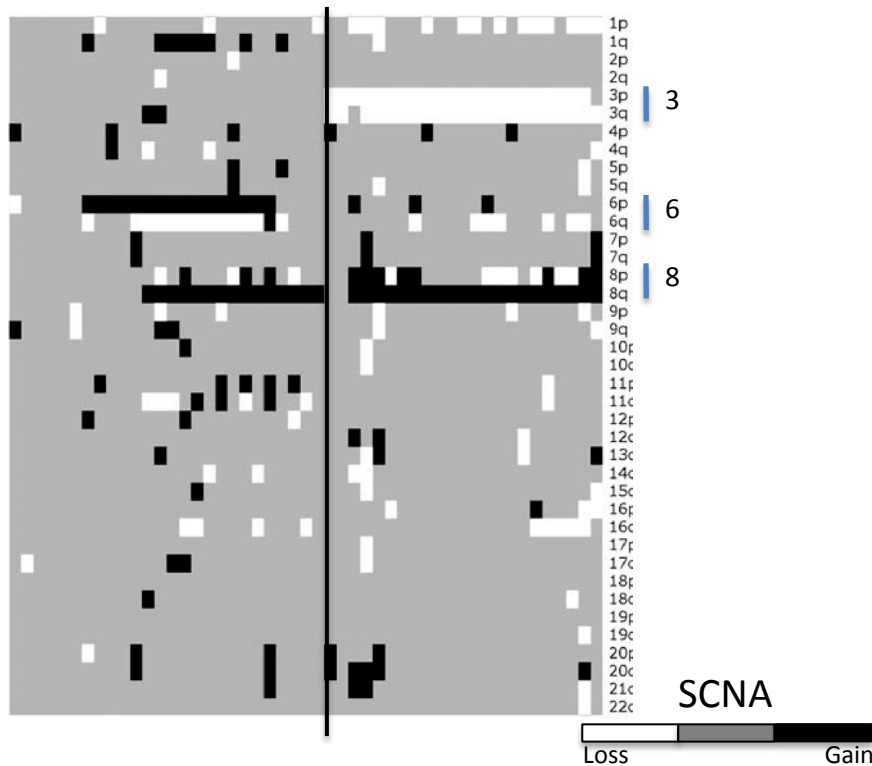
# Uveal Melanoma (UVM): An Introduction

- Occurs in the iris, ciliary body, or choroid
- Rare, but most common intraocular cancer (6 per million per year)
- Clinically distinct from cutaneous melanoma:
  - <2% have clinically detectable metastases at presentation
  - >70% develop liver metastasis as first and only site
  - 30-50% die of metastatic disease
- Molecularly distinct:
  - Lack of BRAF mutations (Spendlove et al. Melanoma Res. 2004)
  - 83% have GNAQ or GNA11 mutations (Van Raamsdonk et al. NEJM 2010)
  - 84% of metastasizing tumors have BAP1 inactivating mutations (Harbour et al. Science 2010)
  - 15-gene classifier (Castle Biosciences DecisionDx-UM) predicts metastatic risk

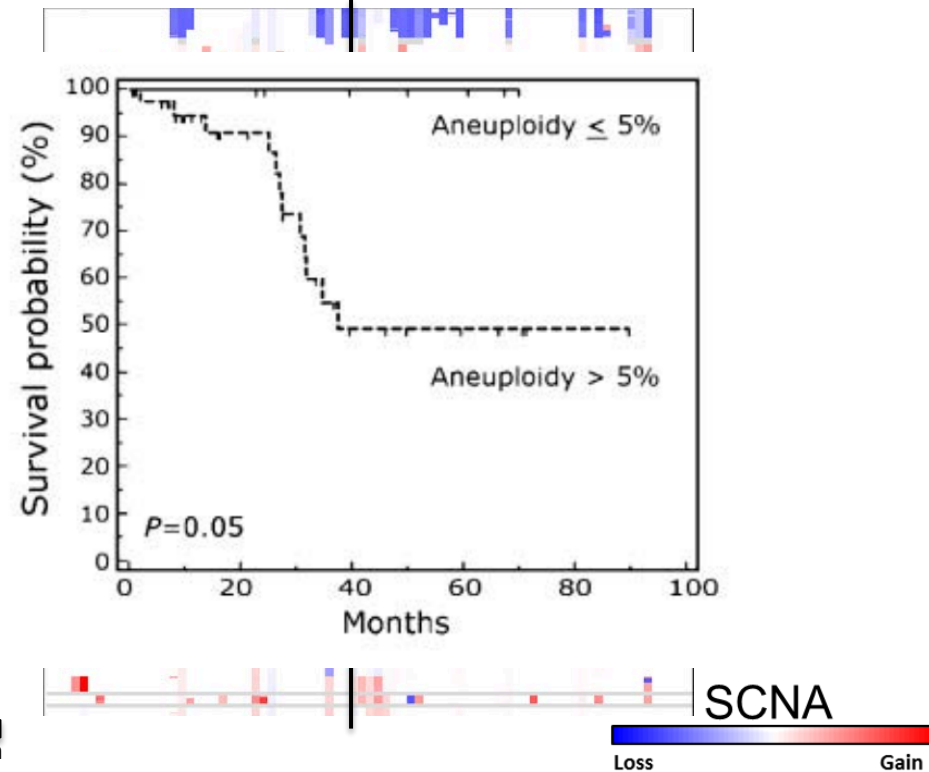


# Previous Work in Aneuploidy

Ehlers et al.  
Clin. Cancer Res. 2008  
n=49, aCGH



TCGA UVM  
n=79, Affymetrix SNP 6.0



Ehlers et al. findings:

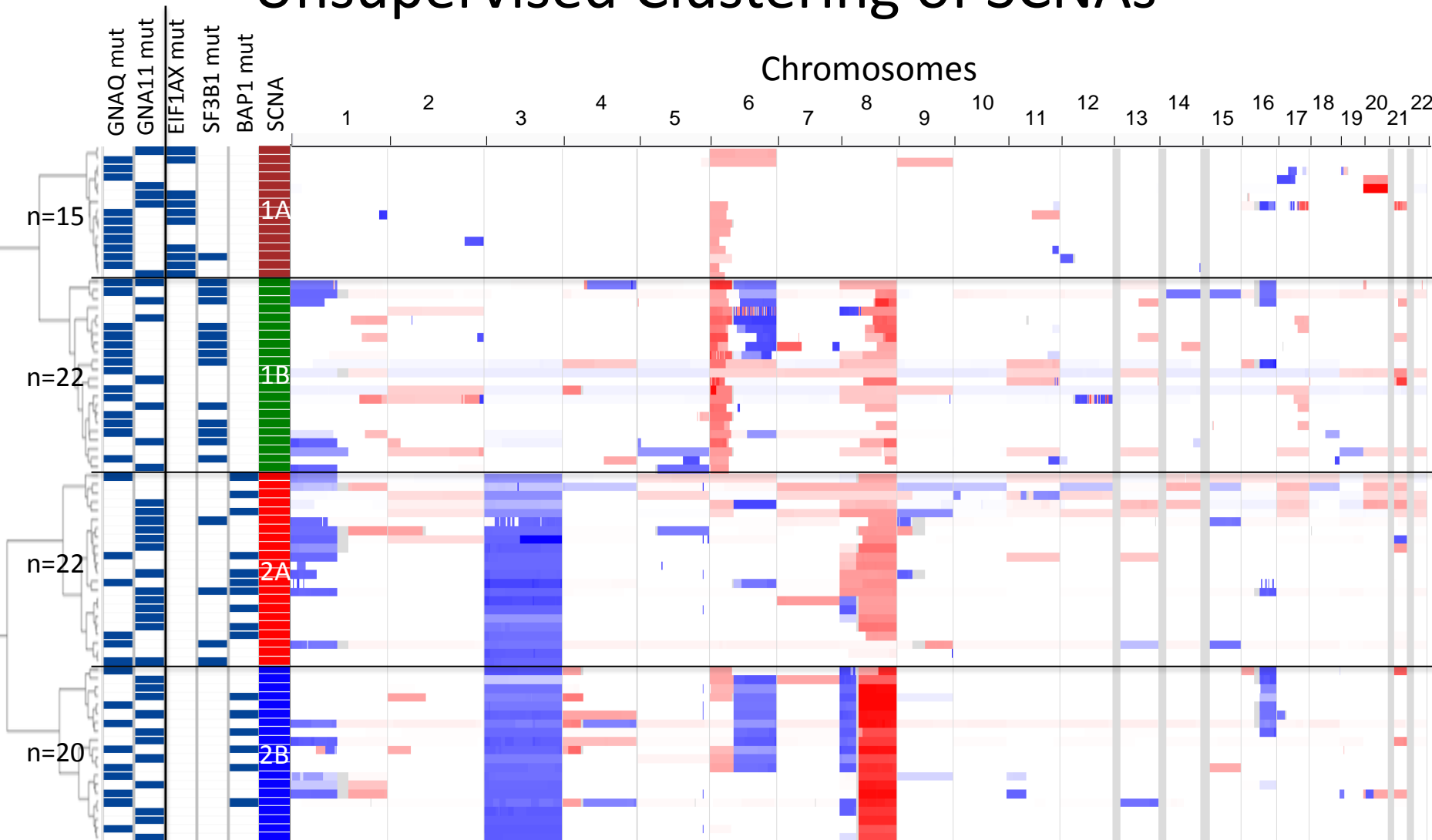
- Around 50% have chromosome 3 loss (marker for metastasis and poor prognosis)
- Higher aneuploidy tumors have worse survival

# Significantly Mutated Genes in TCGA UVM

	gene	p	q	pCV	pCL	pFN
<b>n=39</b>	GNAQ	$1.00 \times 10^{-16}$	$4.59 \times 10^{-13}$	$1.04 \times 10^{-16}$	$1.00 \times 10^{-5}$	$1.43 \times 10^{-3}$
<b>n=36</b>	GNA11	$1.00 \times 10^{-16}$	$4.59 \times 10^{-13}$	$2.22 \times 10^{-16}$	$1.00 \times 10^{-5}$	$2.57 \times 10^{-3}$
<b>n=18</b>	SF3B1	$1.00 \times 10^{-16}$	$4.59 \times 10^{-13}$	$1.42 \times 10^{-14}$	$1.00 \times 10^{-5}$	$9.25 \times 10^{-1}$
<b>n=10</b>	EIF1AX	$1.00 \times 10^{-16}$	$4.59 \times 10^{-13}$	$2.47 \times 10^{-16}$	$1.00 \times 10^{-5}$	$1.03 \times 10^{-2}$
<b>n=16</b>	BAP1	$3.33 \times 10^{-16}$	$1.22 \times 10^{-12}$	$1.00 \times 10^{-16}$	1	$3.40 \times 10^{-2}$
<b>n=3</b>	CYSLTR2	$5.85 \times 10^{-8}$	$1.79 \times 10^{-4}$	$2.82 \times 10^{-6}$	$1.00 \times 10^{-3}$	$4.59 \times 10^{-3}$
<b>n=3</b>	SFRS2	$6.95 \times 10^{-6}$	$1.82 \times 10^{-2}$	$4.45 \times 10^{-7}$	1	$3.34 \times 10^{-1}$
<b>n=2</b>	MAPKAPK5*	$6.58 \times 10^{-5}$	$1.51 \times 10^{-1}$	$6.64 \times 10^{-5}$	1	$2.20 \times 10^{-2}$
<b>n=2</b>	SELE*	$1.83 \times 10^{-4}$	$3.73 \times 10^{-1}$	$4.73 \times 10^{-4}$	1	$2.60 \times 10^{-2}$

\*near significance (threshold of  $q \leq 0.1$ )

# Unsupervised Clustering of SCNAs



**EIF1AX:** mutated in 10 Subtype 1A Tumors ( $p < 0.0001$ )

**SF3B1:** mutated in 1 Subtype 1A, 13 Subtype 1B, and 4 Subtype 2A Tumors ( $p < 0.0001$ )

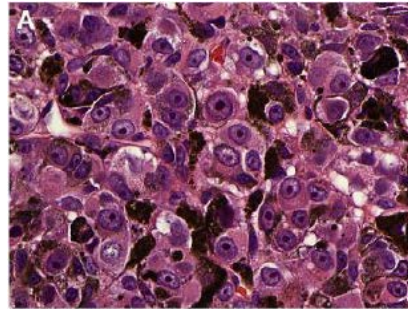
**BAP1:** mutated in 16 Subtype 2 Tumors ( $p < 0.0001$ )

# Clinical Correlations

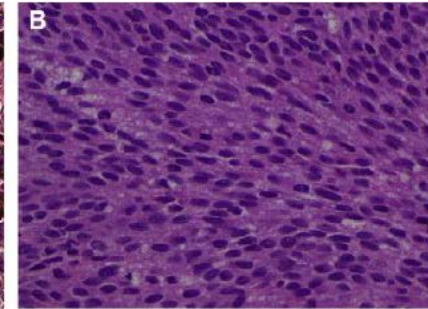
## Histologic Diagnosis – k4

Subtype	Epithelioid	Spindle
1A	7	<b>8</b>
1B	7	<b>15</b>
2A	<b>14</b>	8
2B	<b>19</b>	1
Total	47	32

p=0.0003



Epithelioid



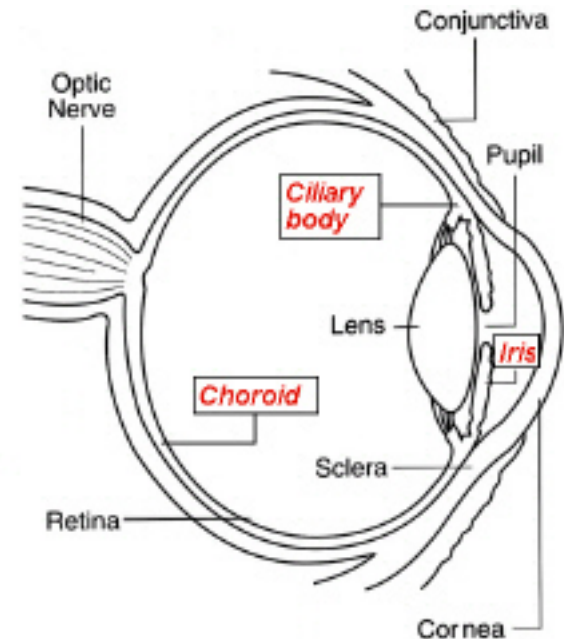
Spindle

Fig 1, Damato 2011

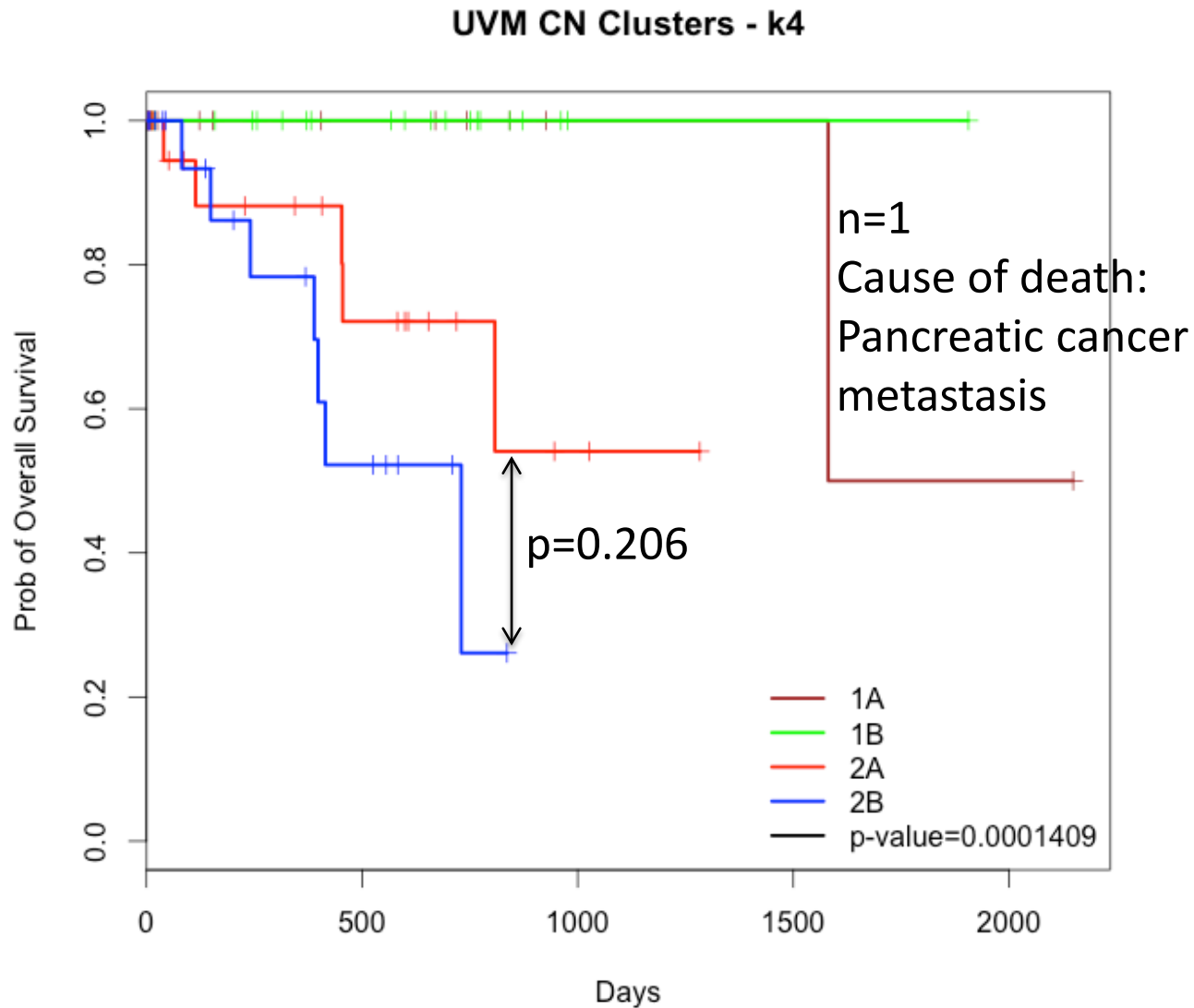
Vonn Walter

## Tumor Site – k4

Subtype	Choroid	Choroid   Ciliary body	Ciliary body   Iris
1A	13	1	1
1B	17	4	1
2A	10	<b>12</b>	0
2B	15	<b>5</b>	0
Total	55	22	2

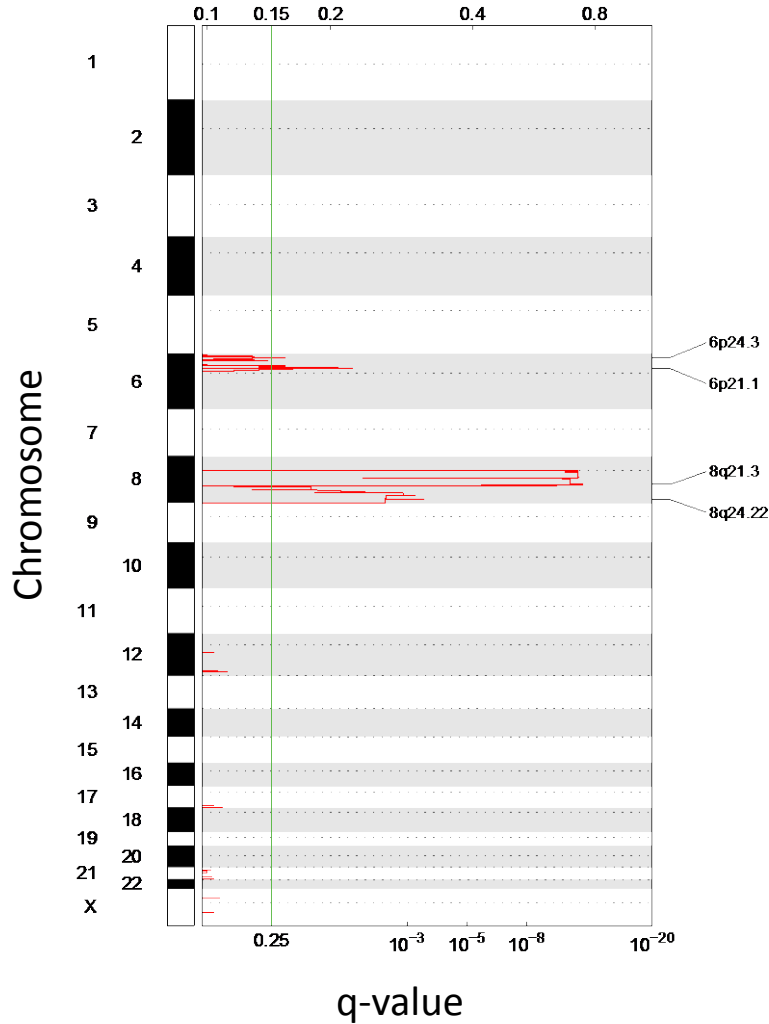


# Survival by SCNA Subtypes

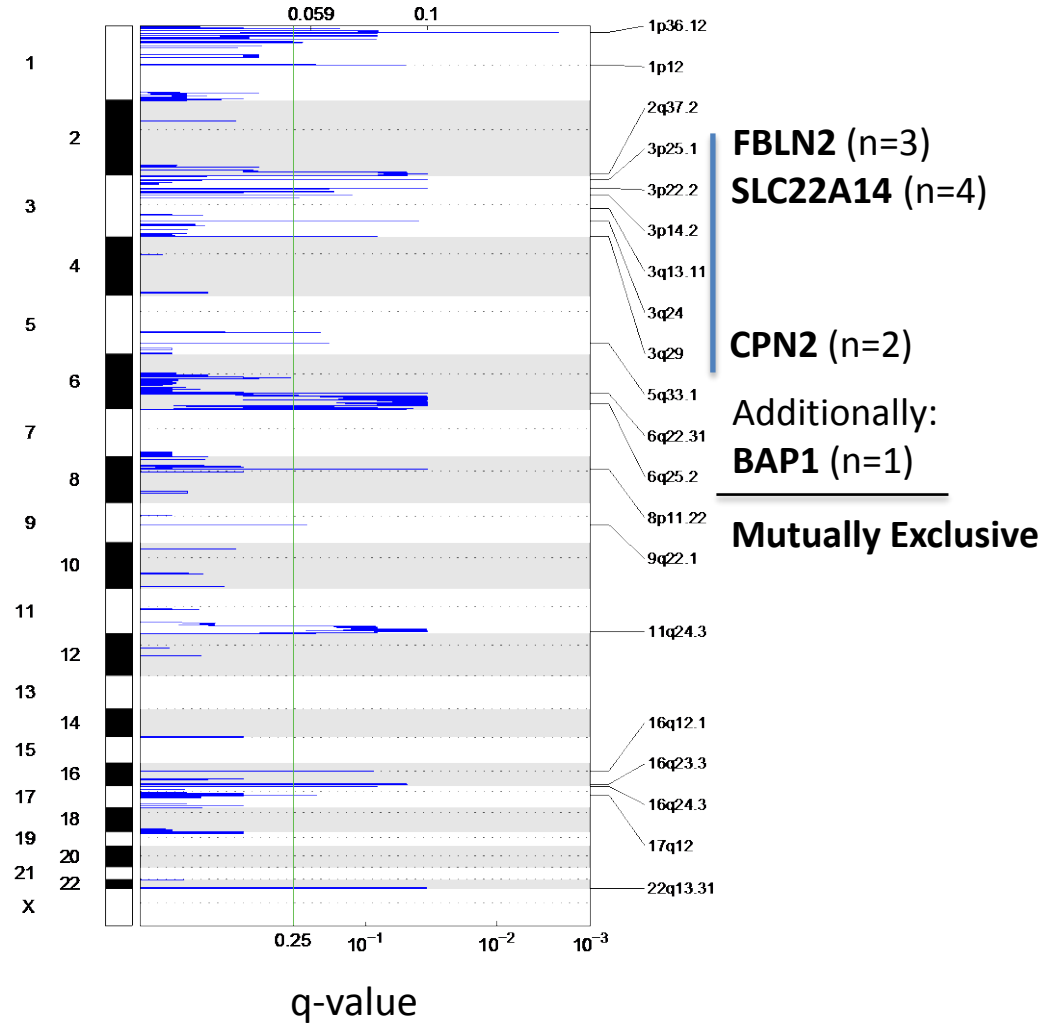


# GISTIC 2.0: Focal SCNAs

## Amplifications



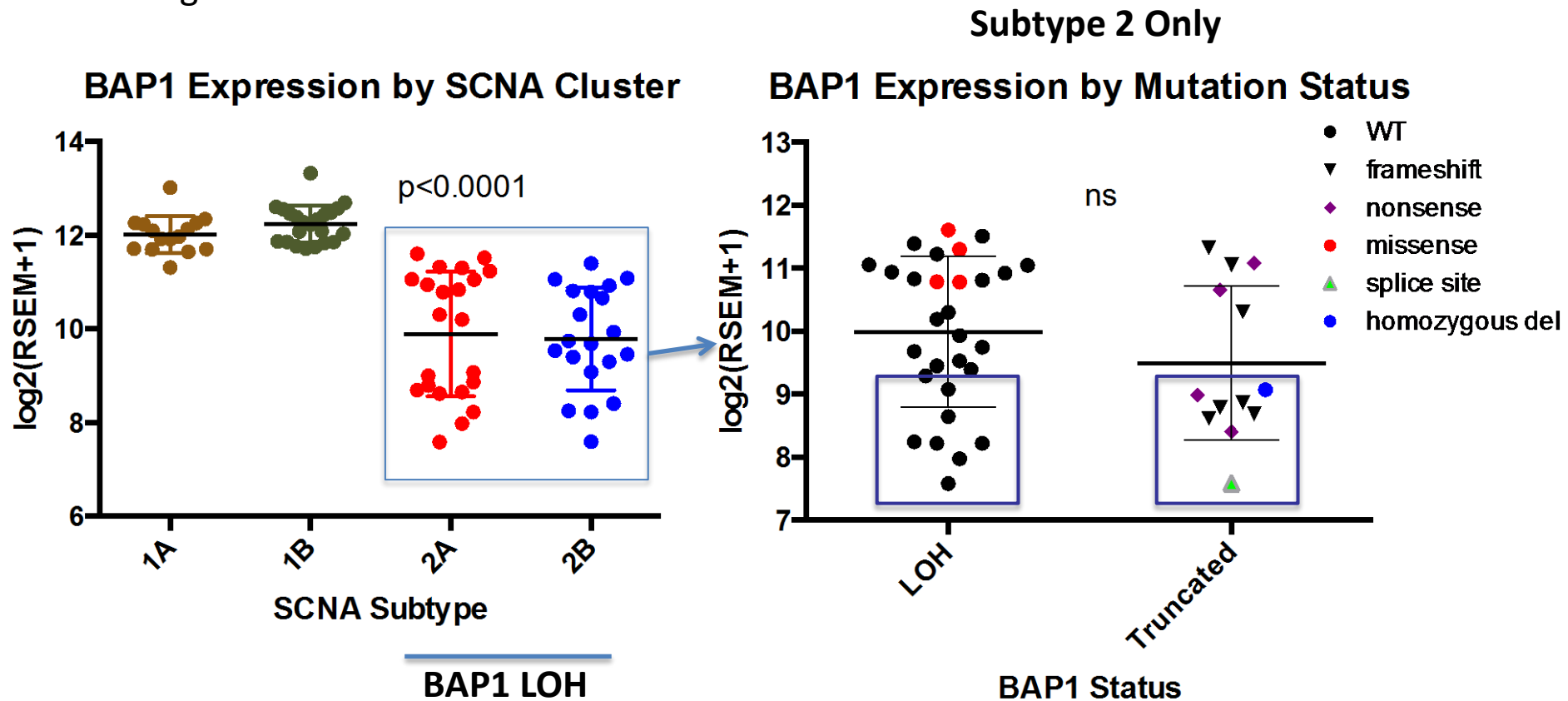
## Deletions





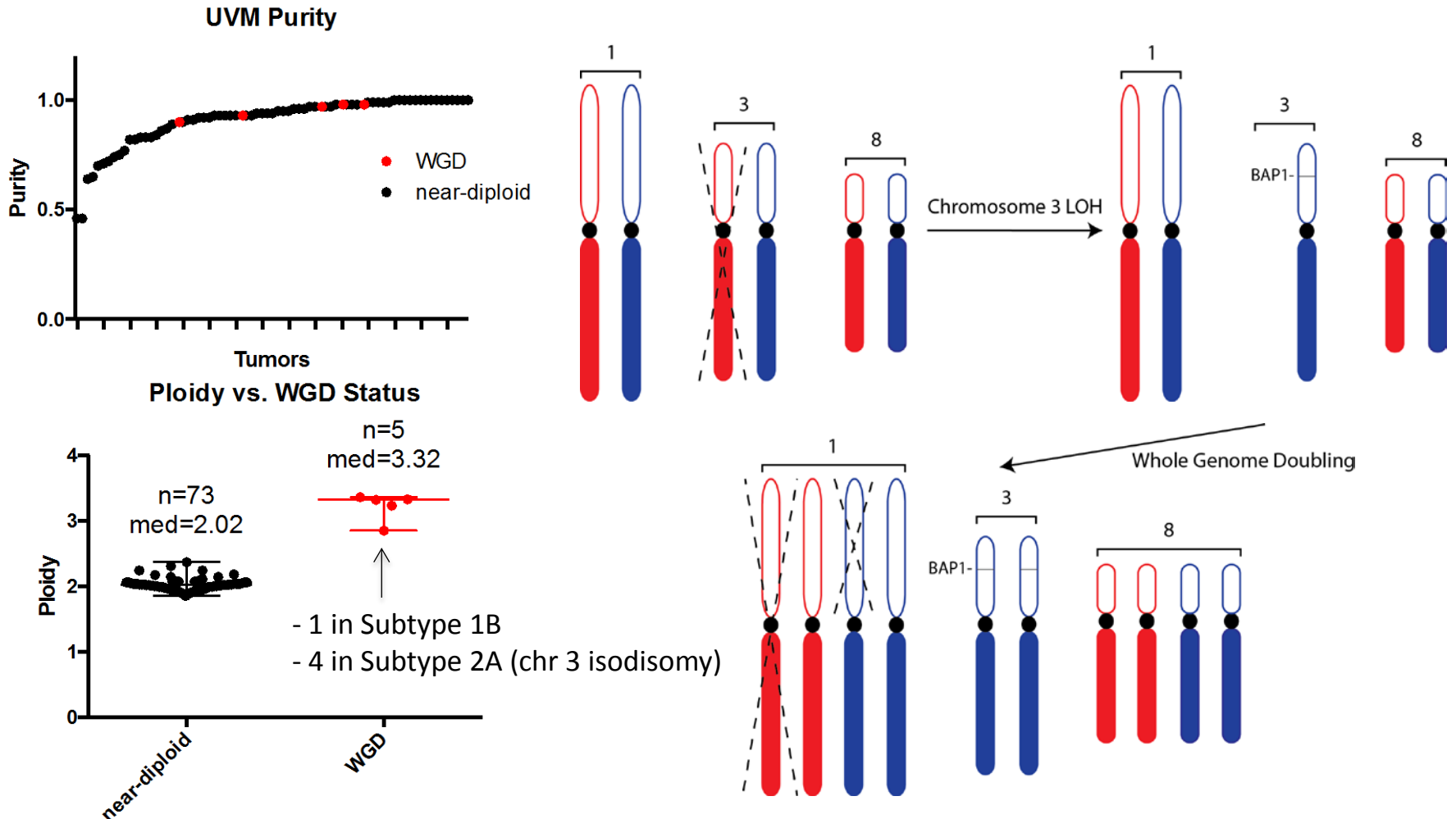
# BAP1 Expression in UVM

- BAP1 is on chromosome 3
- 12/16 BAP1 mutations are truncating
- No germline BAP1 mutations found

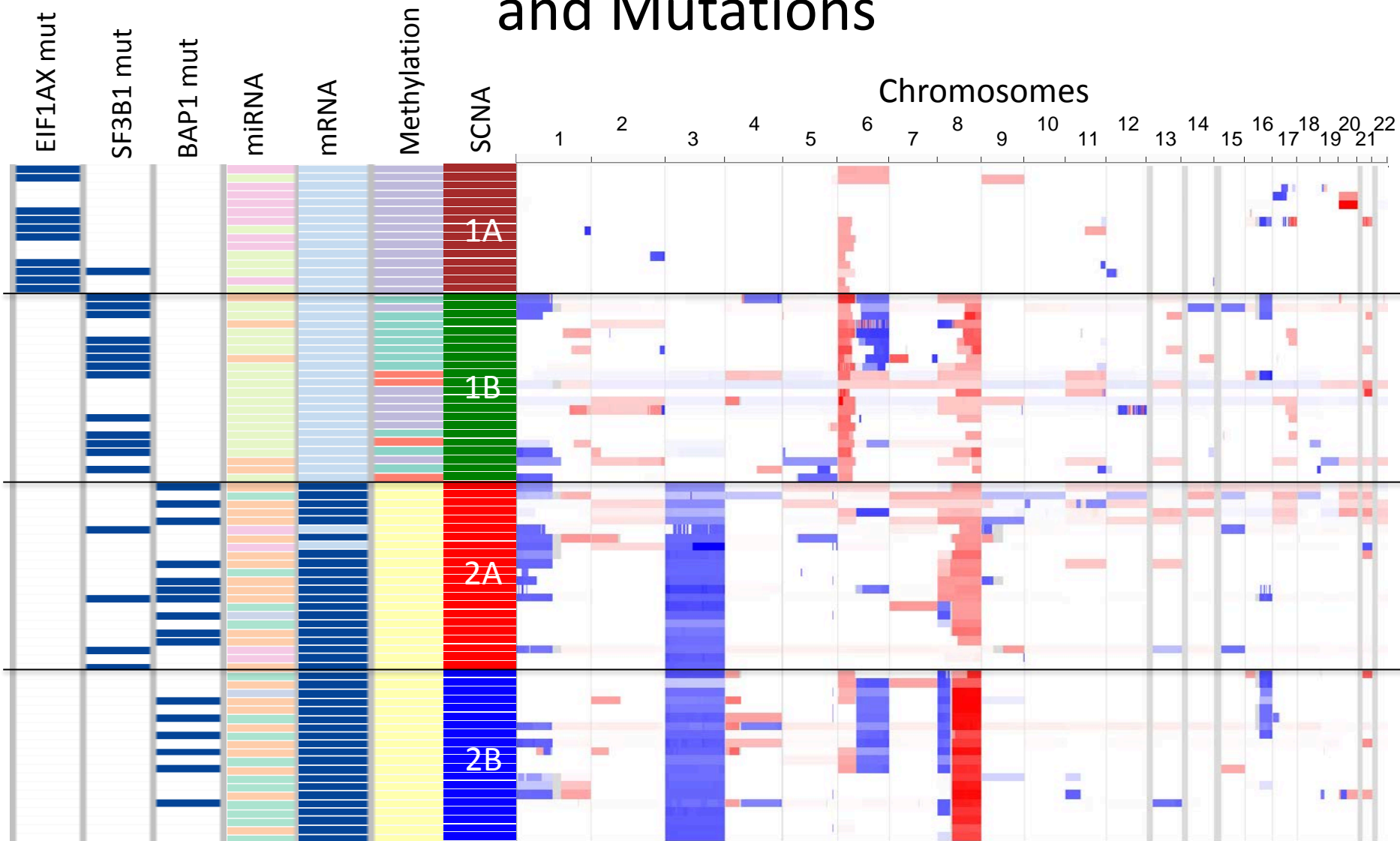


# ABSOLUTE Overview

- Infers tumor purity, ploidy, subclonality, and whole genome doubling (WGD) status (Carter et al. Nature Biotechnology 2012)
- Generates absolute copy number for homologous chromosomes (alleles)



# SCNA Subtypes Correlate with Methylation, mRNA, and Mutations



# Summary

- SCNA clusters are consistent with methylation and mRNA clusters
- Each defined by particular somatic mutations
- 1A: quiet; better survival; EIF1AX-mutated
- 1B: 6p, 8q gain; better survival; SF3B1-mutated
- 2A: chr 3 LOH; worse survival; BAP1-mutated
- 2B: chr 3 LOH; high 8q gain; worst survival; BAP1-mutated

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# Questions?