Novel Driver Genes and Prognostic Mutation Signatures Identified by Genomic Analyses of Gastric Cancer

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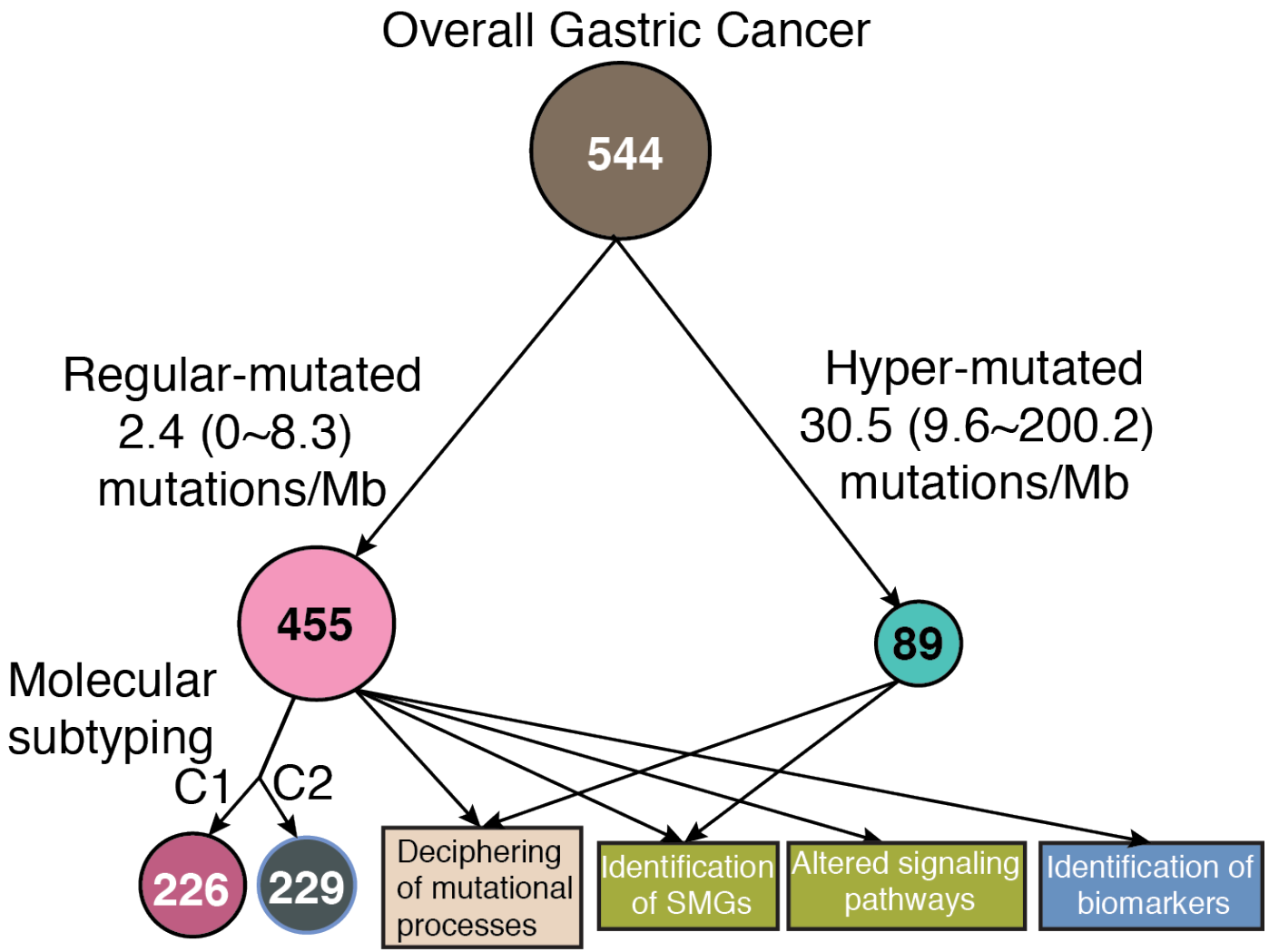
The authors declare no conflict of interest

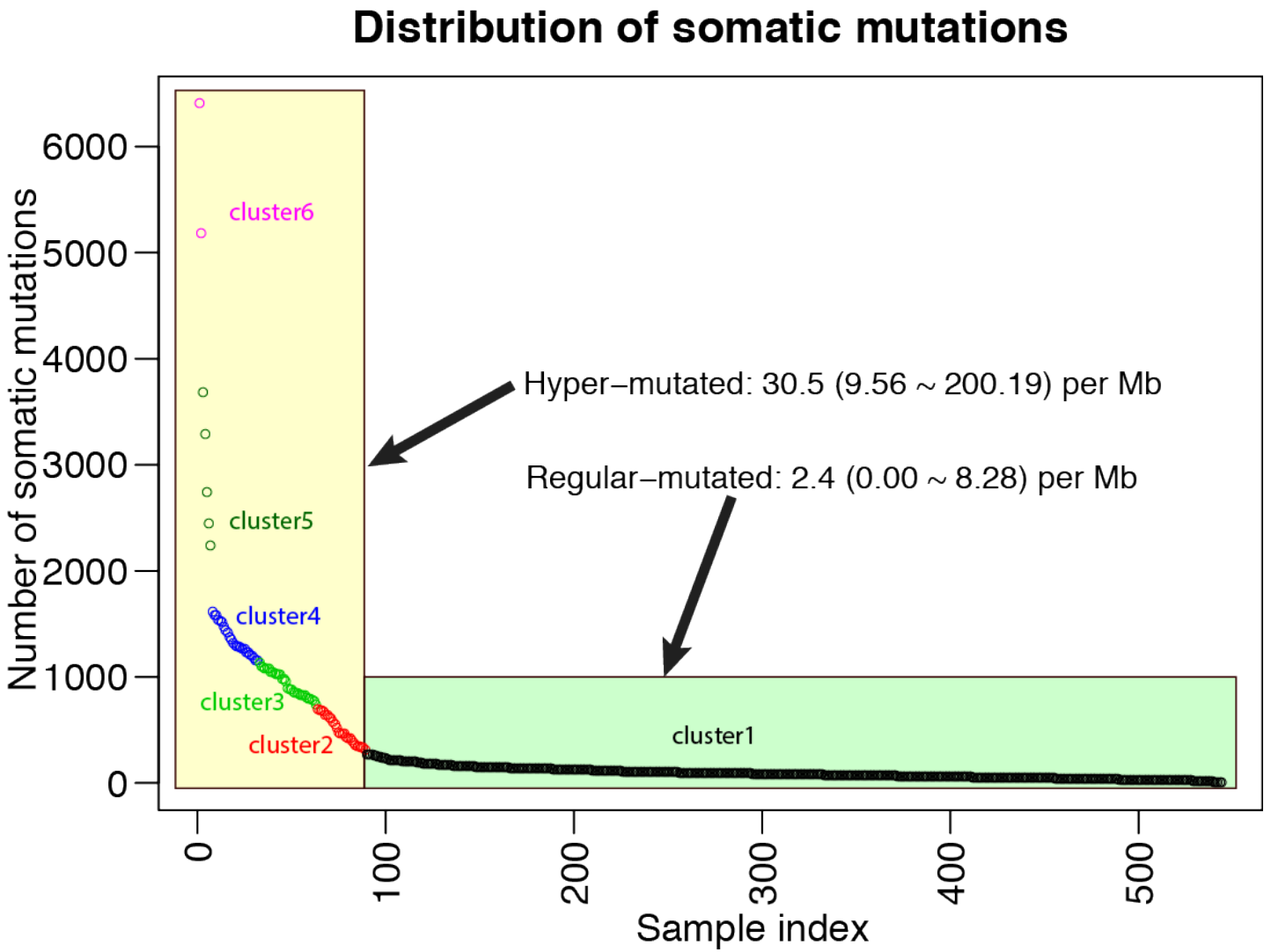
The analysis workflow



Source of genomic data

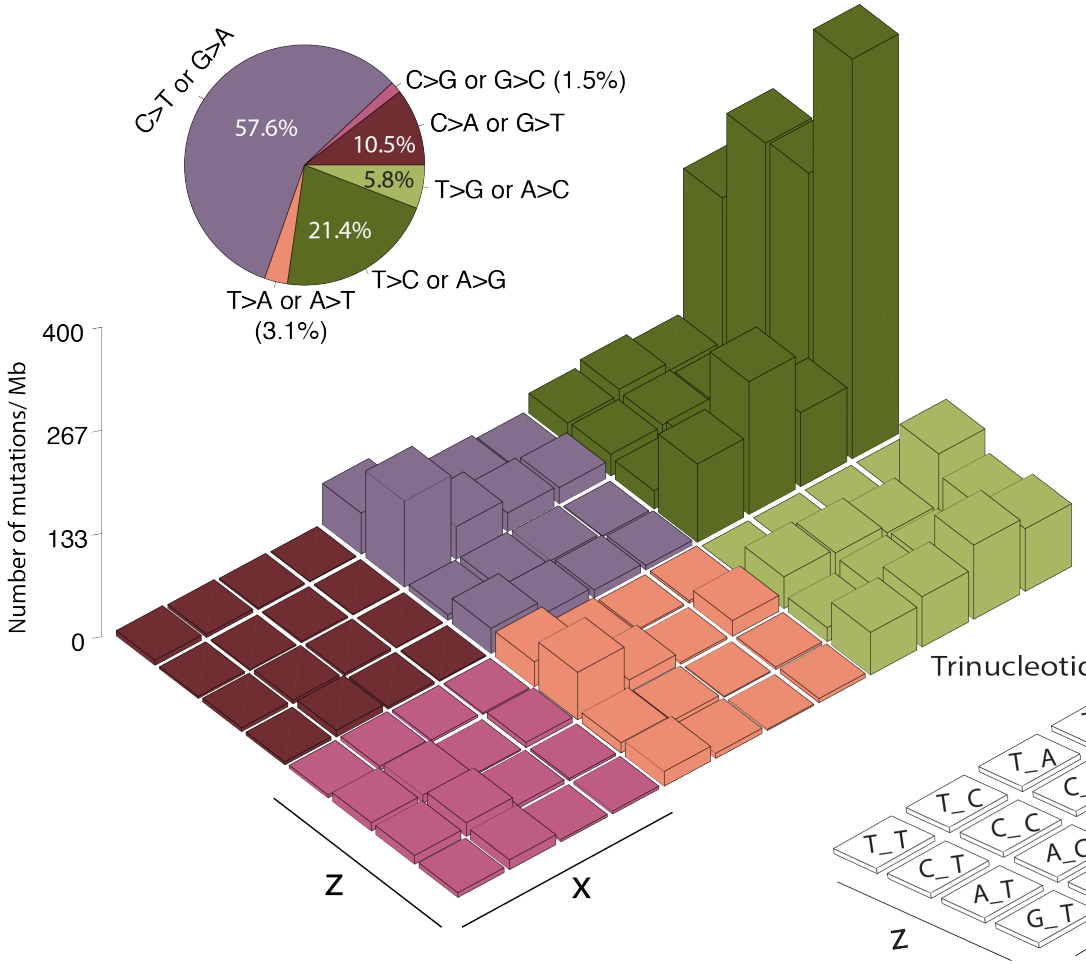
Published publications	Cohort
Chen K, Yang D, Li X, et al: Mutational landscape of gastric adenocarcinoma in Chinese : Implications for prognosis and therapy. Proc Natl Acad Sci 6:1–6, 2015	Tianjin China
Cancer T, Atlas G: Comprehensive molecular characterization of gastric adenocarcinoma. Nature , 2014	TCGA
Wang K, Yuen ST, Xu J, et al: Whole-genome sequencing and comprehensive molecular profiling identify new driver mutations in gastric cancer. Nat Genet 46:573–82, 2014	Hong Kong
Wong SS, Kim K-M, Ting JC, et al: Genomic landscape and genetic heterogeneity in gastric adenocarcinoma revealed by whole-genome sequencing. Nat Commun 5:5477, 2014	S. Korean
Kakiuchi M, Nishizawa T, Ueda H, et al: Recurrent gain-of-function mutations of RHOA in diffuse-type gastric carcinoma. Nat Genet 46:583–7, 2014	Japan

Stratification of GC according to mutation burdens

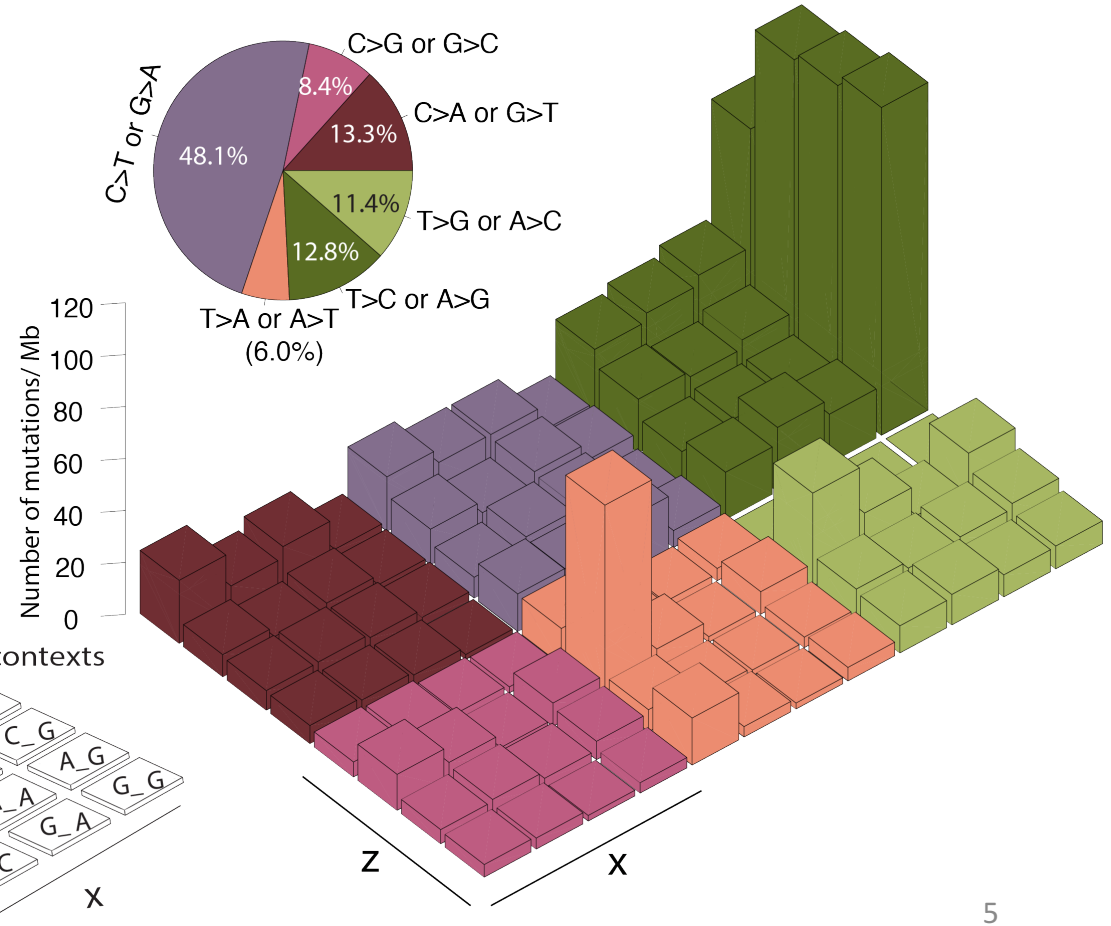


Mutation spectrum of GC with different mutation burdens

Hyper-mutated gastric cancer
(n=89)

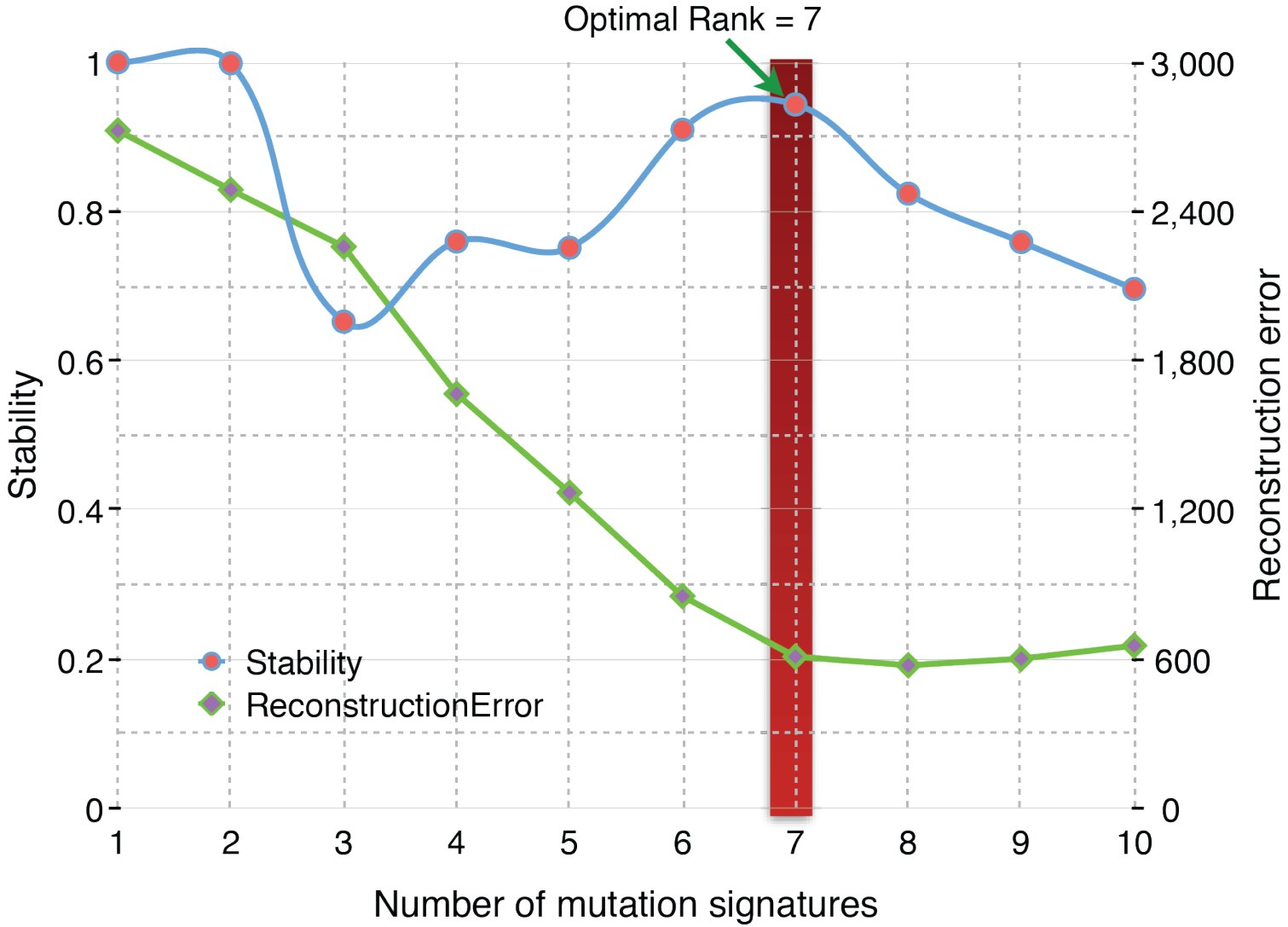


Regular-mutated gastric cancer
(n=455)

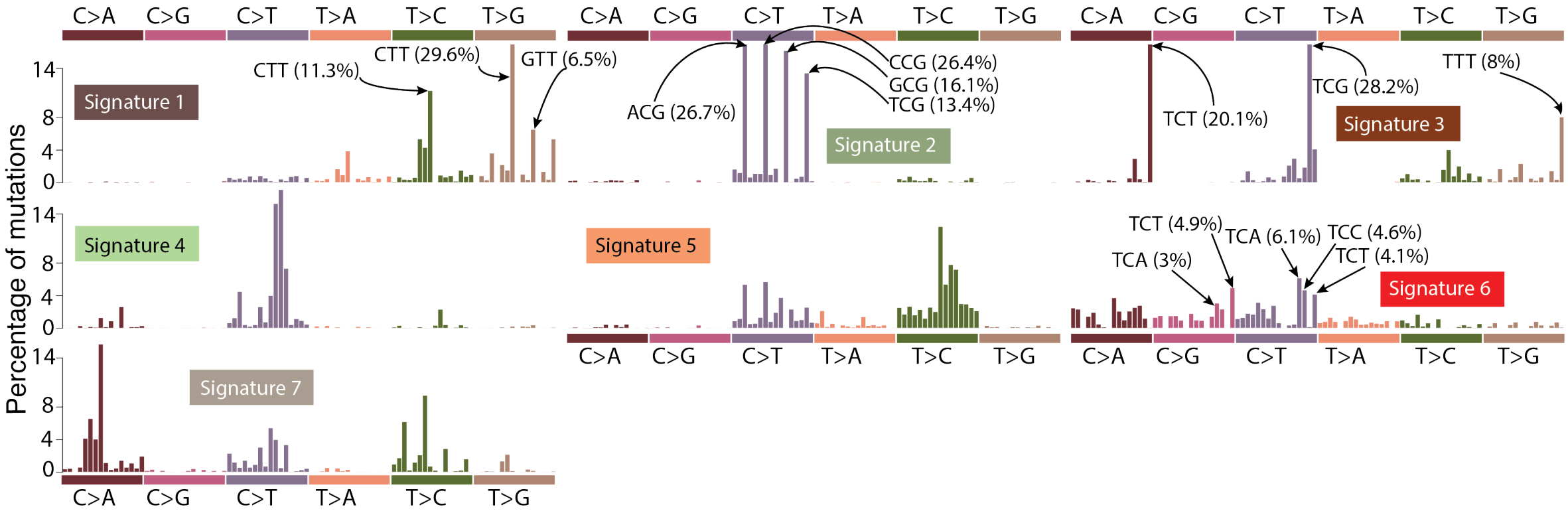


Trinucleotide contexts

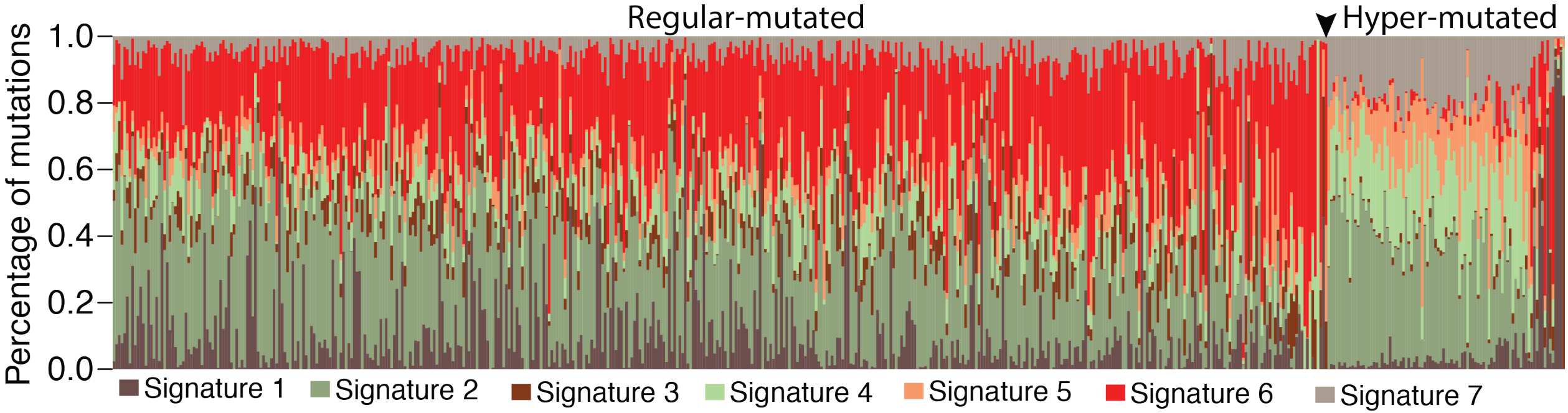
Mutational signature deciphering



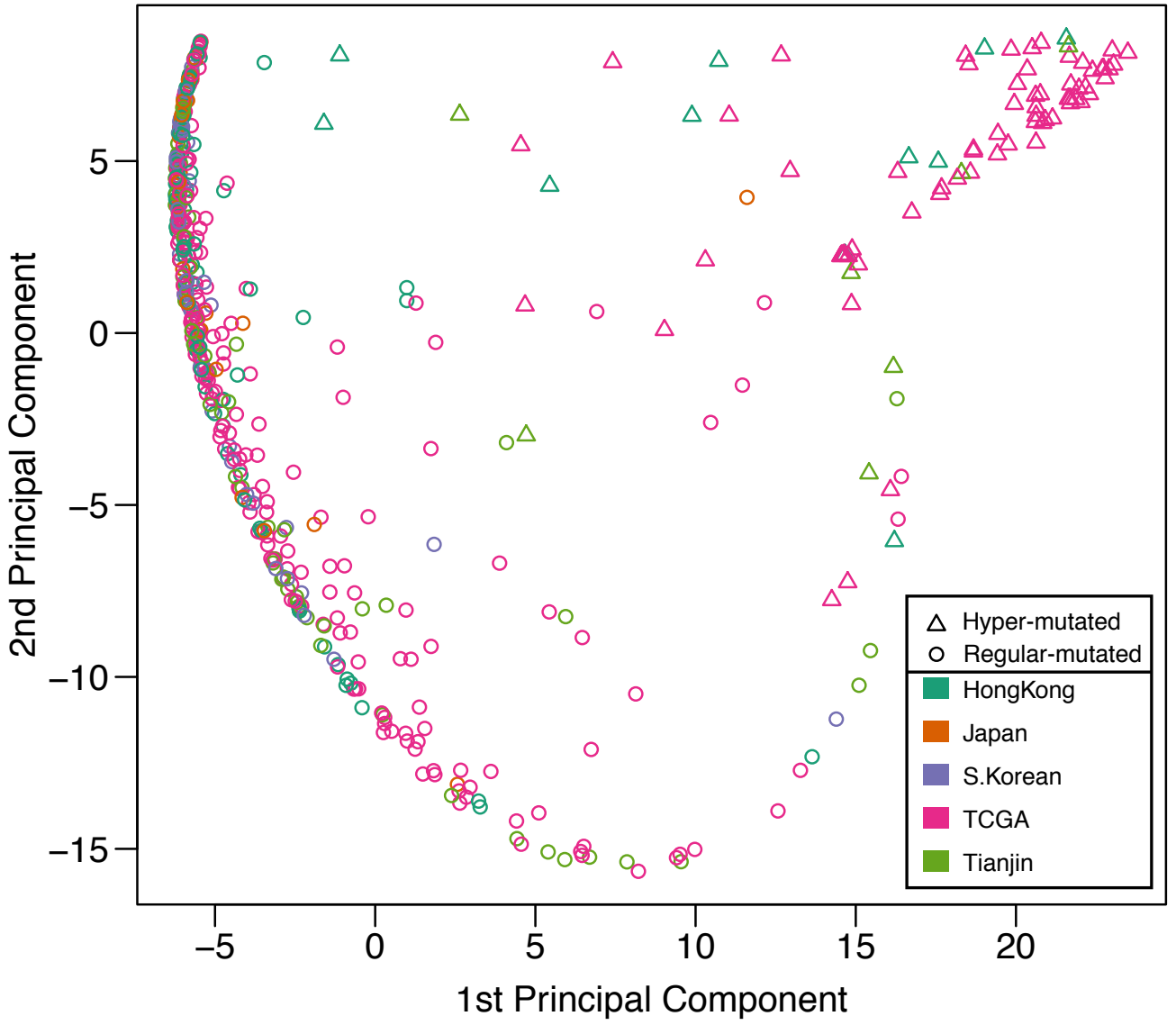
Mutational signatures operative in gastric cancer



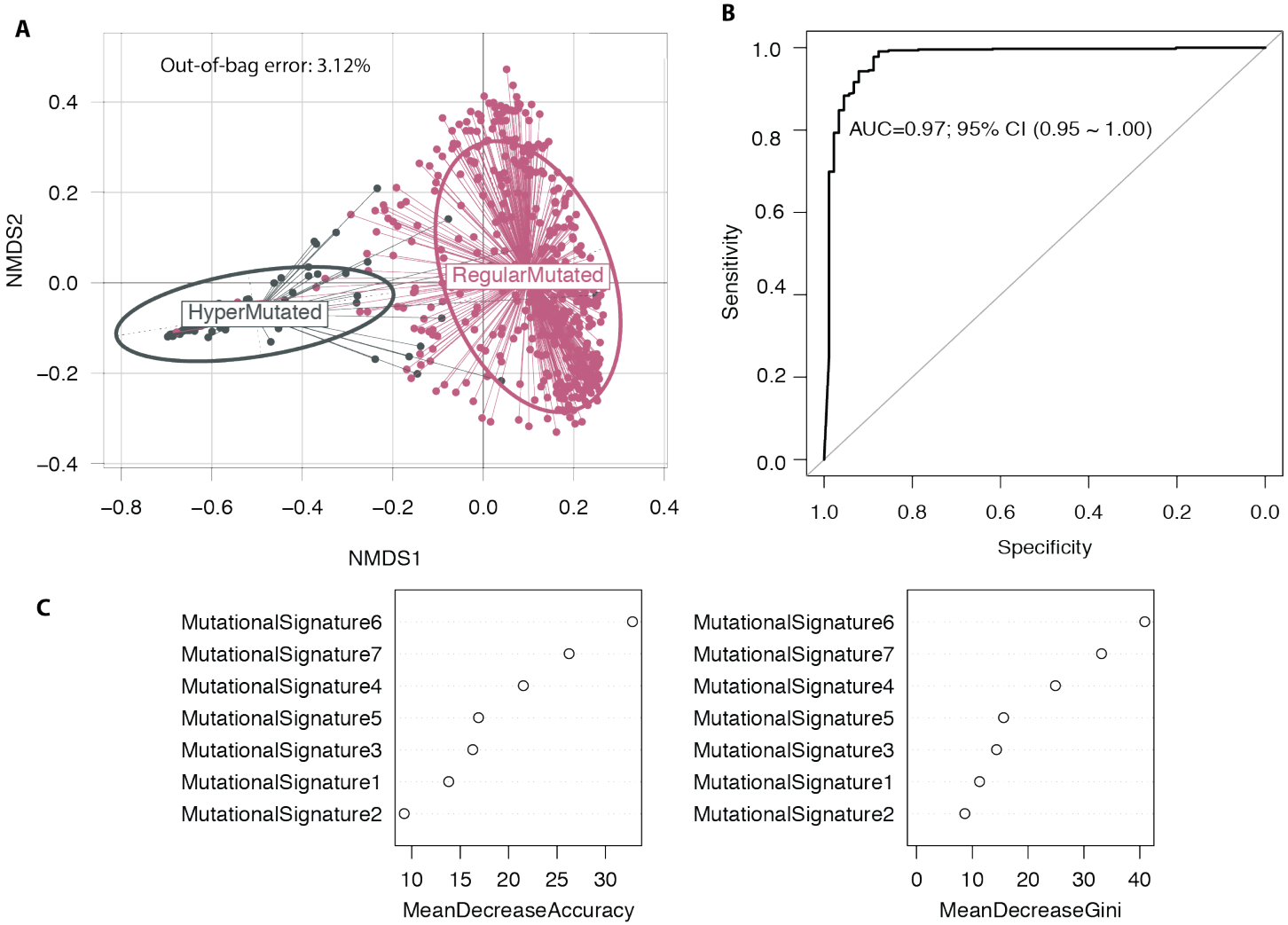
Mutational signatures operative in gastric cancer



Kernal PCA of mutational signatures



The importance of mutational signature in distinguishing between RGC and HGC

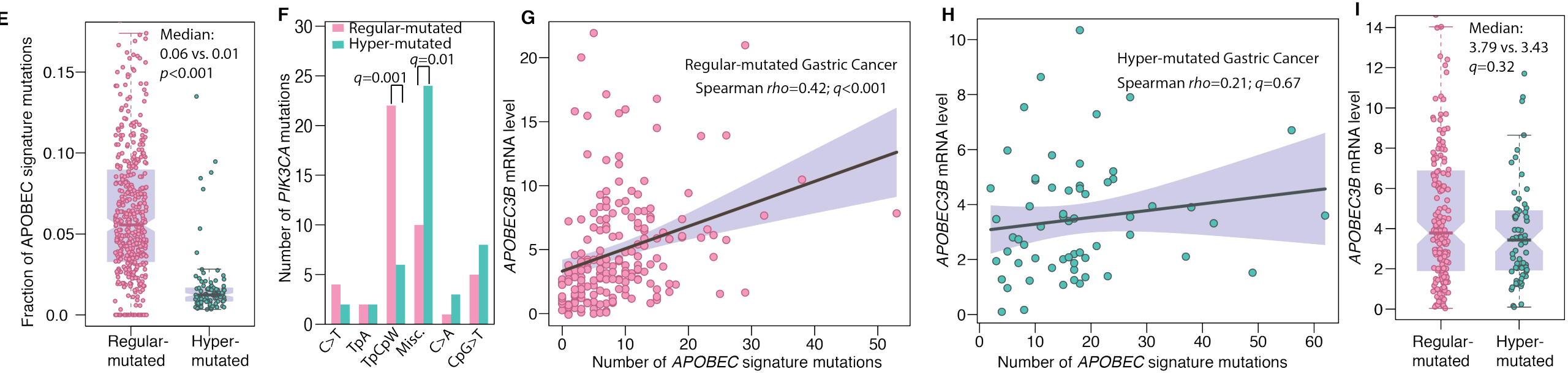


The presence of mutational signatures

Mutational signature	Operativ in RGC	Operativ in HGC	Mutation in RGC	Mutation in HGC	Association in RGC	Association in HGC
Signature 1	11.9%	10.1%	15.5%	5.7%		
Signature 2	59.3%	82.0%	26.6%	26.3%	Age	
Signature 3	0.7%	3.4%	5.9%	6.1%		
Signature 4	2.0%	80.9%	8.6%	22.2%		
Signature 5	1.1%	51.7%	4.8%	20.2%		
Signature 6	70.8%	10.1%	32.5%	3.2%	APOBEC	APOBEC
Signature 7	0.4%	80.9%	6.2%	16.2%		

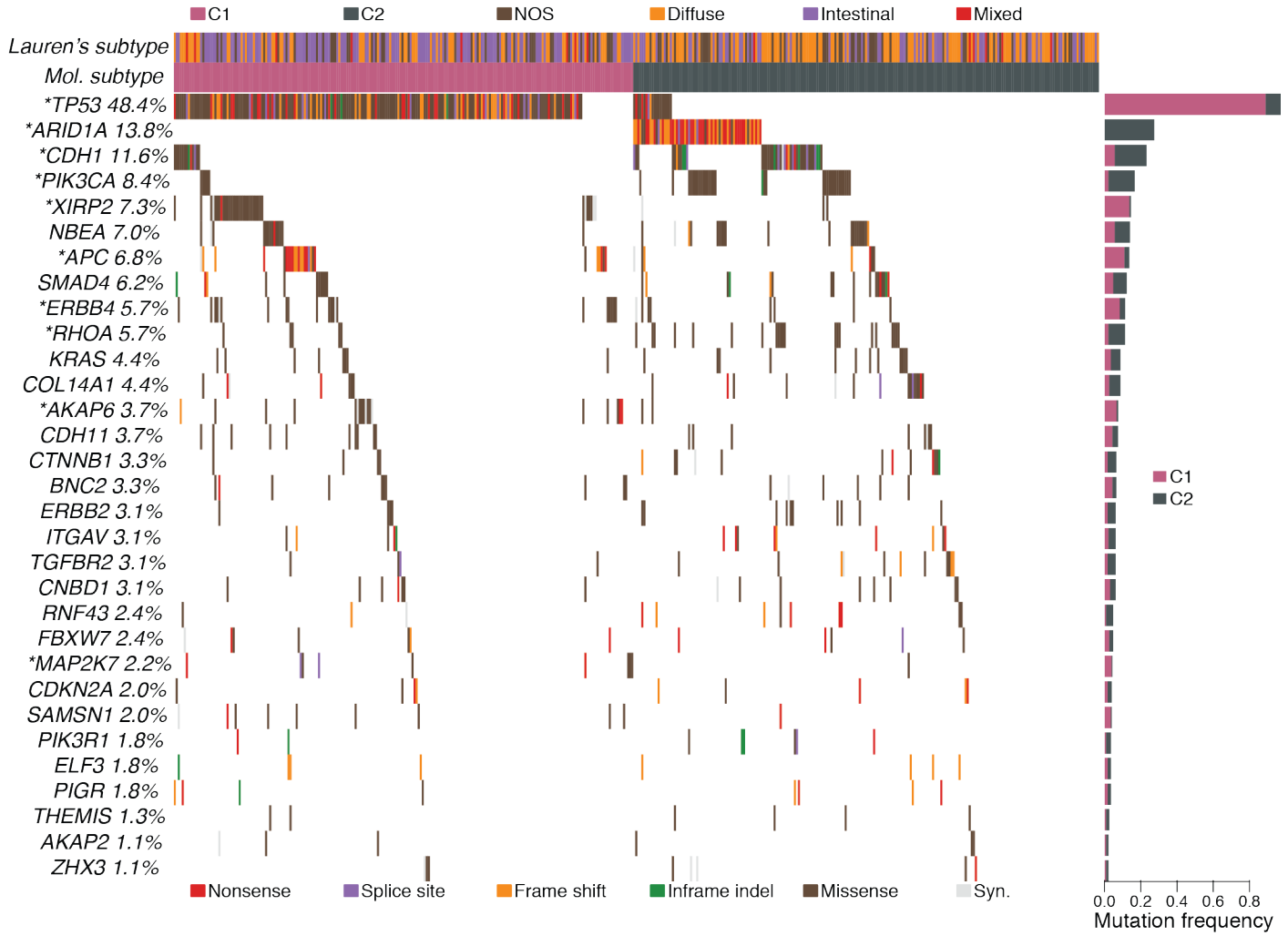
APOBEC signature mutation: **TCW** (where W = A or T)

The APOBEC signature mutation

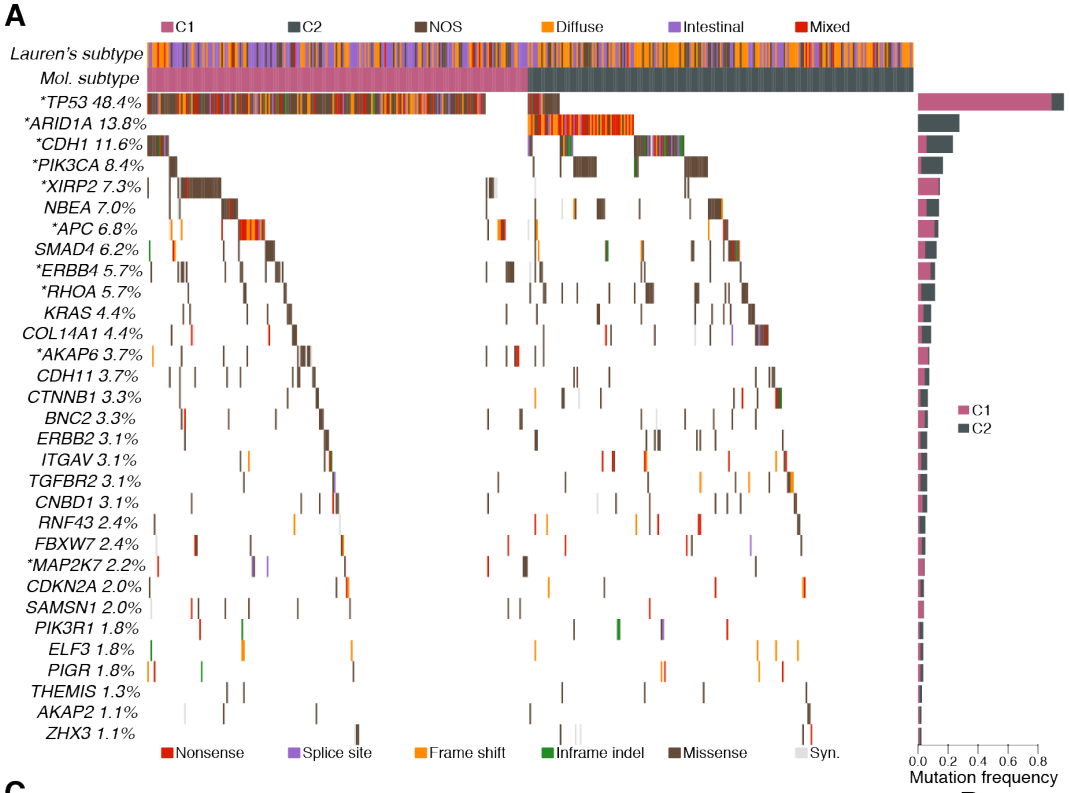


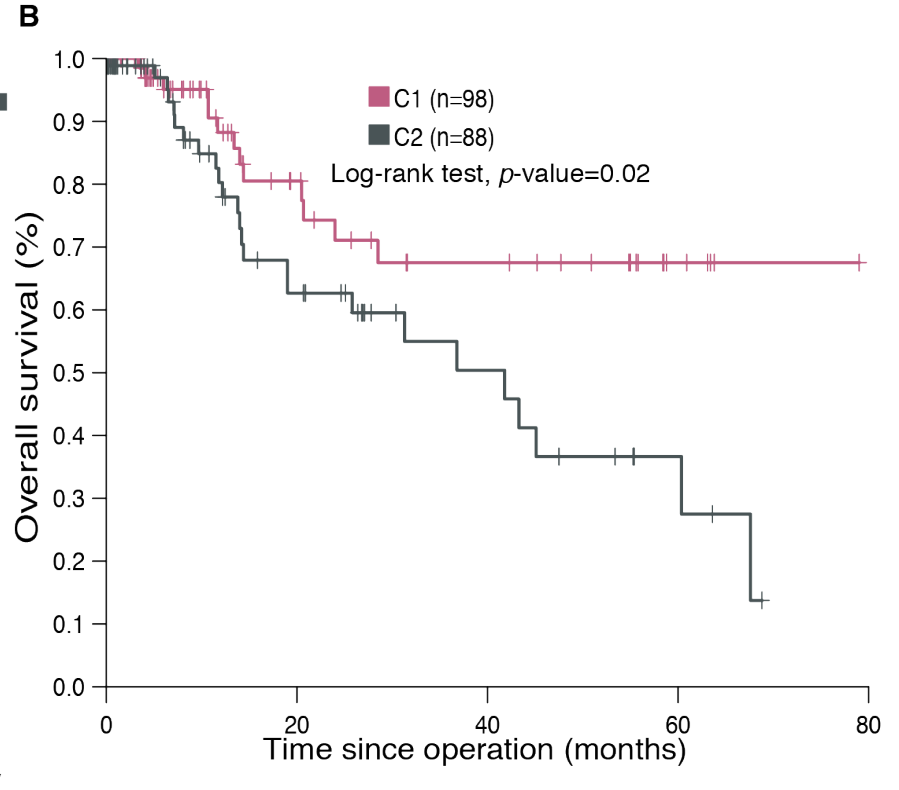
APOBEC signature mutation: **TCW** (where W = A or T)

Mutational landscape in regular-mutated GC



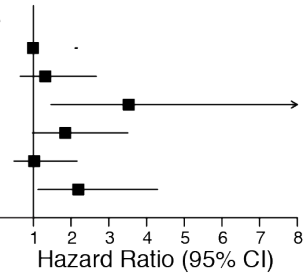
Prognostic significance of C1/2 in RGC





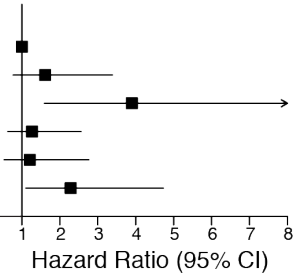
C

Variable	HR (95% CI)	P–value
Age	0.99 (0.96 ~ 1.02)	0.45
Sex (Male vs. Female)	1.32 (0.65 ~ 2.67)	0.45
Stage (III,IV vs. I,II)	3.53 (1.47 ~ 8.5)	0.005
Subtype (Diffuse vs. Intestinal)	1.85 (0.97 ~ 3.51)	0.06
Cohort (TCGA vs. Asian)	1.02 (0.48 ~ 2.16)	0.96
Mol. Subtype (C2 vs. C1)	2.19 (1.12 ~ 4.3)	0.02

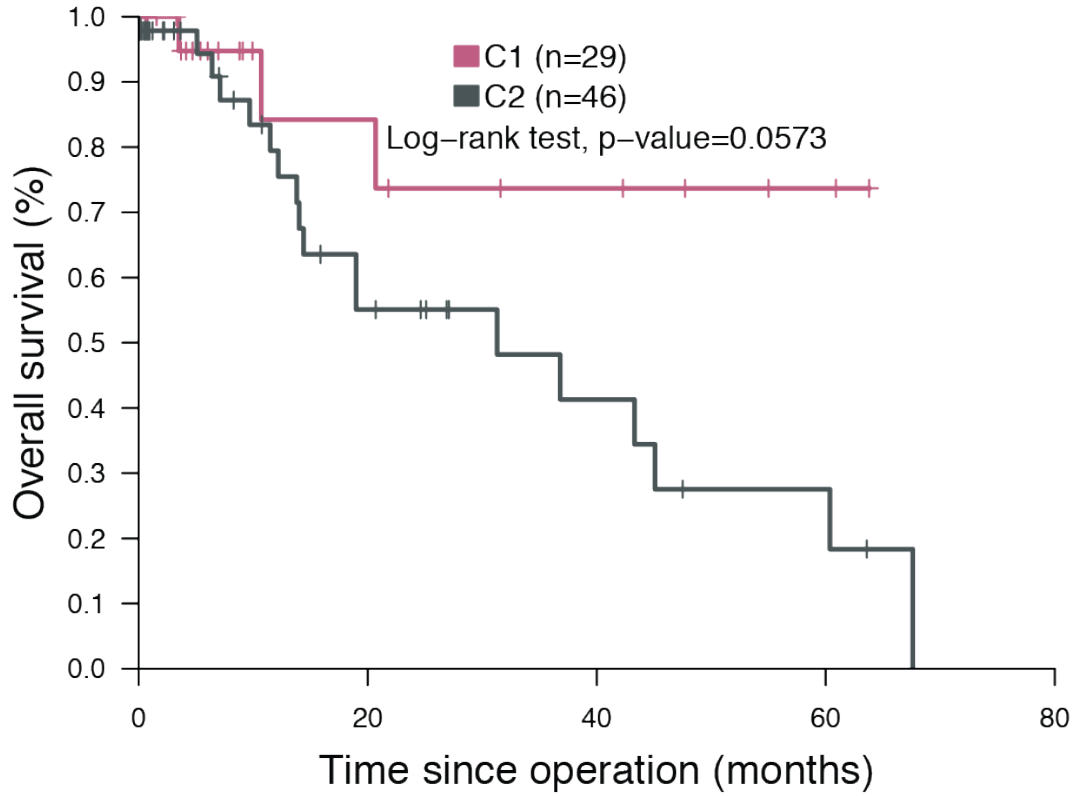


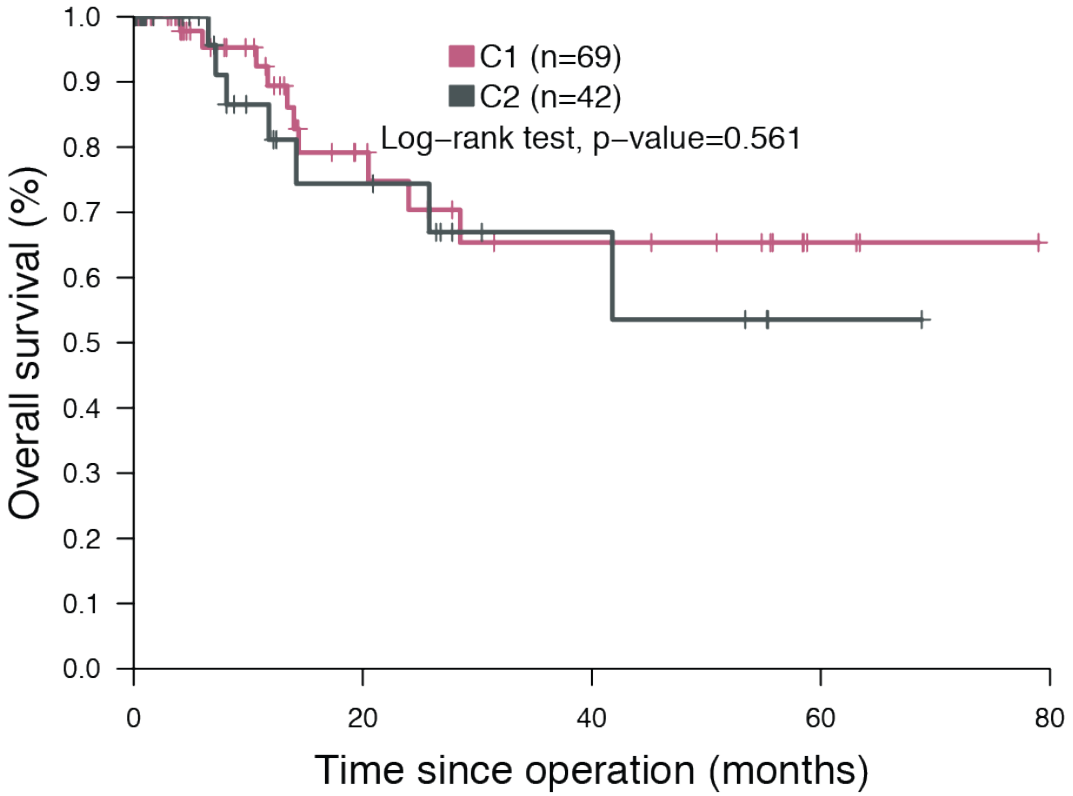
D

Variable	HR (95% CI)	P–value
Age	1.0 (0.97 ~ 1.03)	0.94
Sex (Male vs. Female)	1.61 (0.77 ~ 3.39)	0.21
Stage (III,IV vs. I,II)	3.9 (1.59 ~ 9.56)	0.003
Subtype (Diffuse vs. Intestinal)	1.27 (0.63 ~ 2.56)	0.51
Cohort (TCGA vs. Asian)	1.21 (0.53 ~ 2.76)	0.66
Mol. Subtype (C2 vs. C1)	2.28 (1.1 ~ 4.73)	0.026

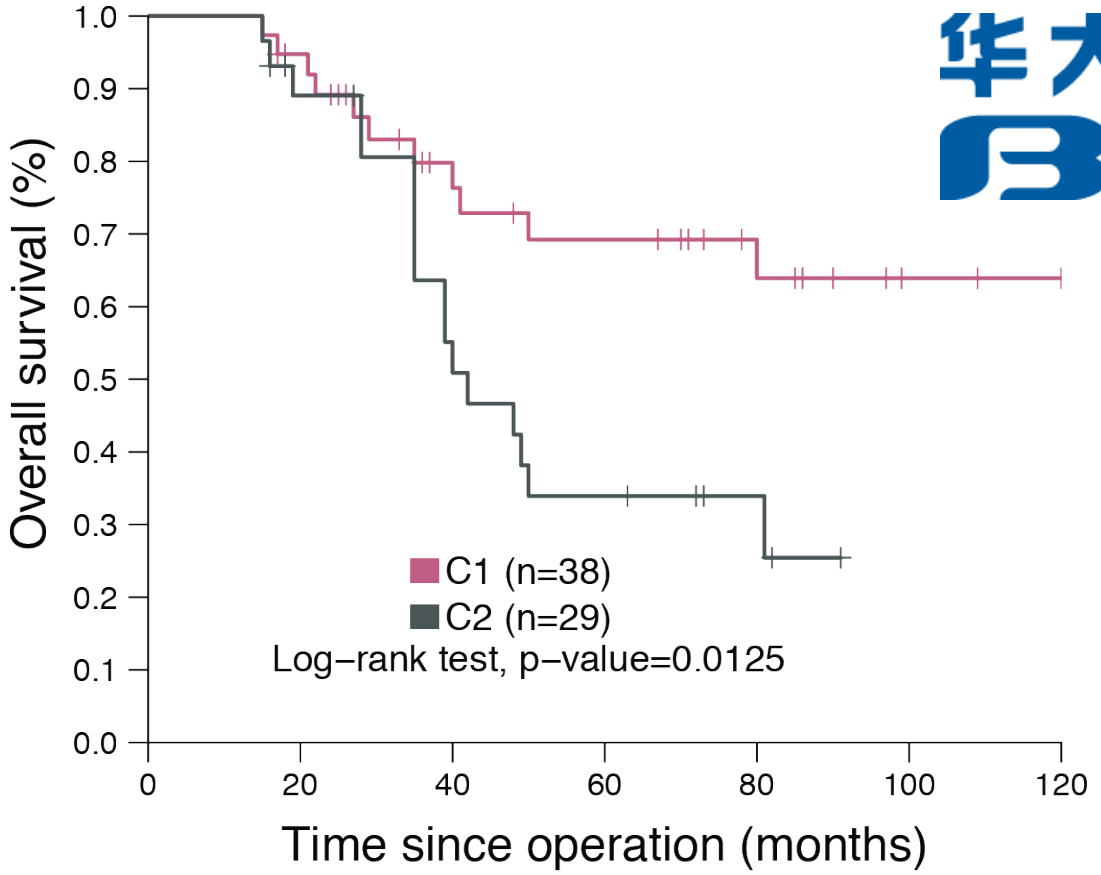


Prognosis of C1/2 stratified by Lauren's classification

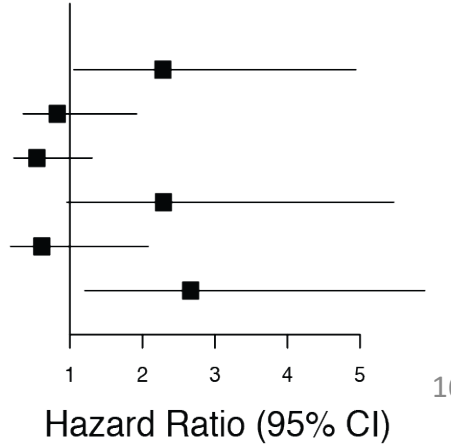




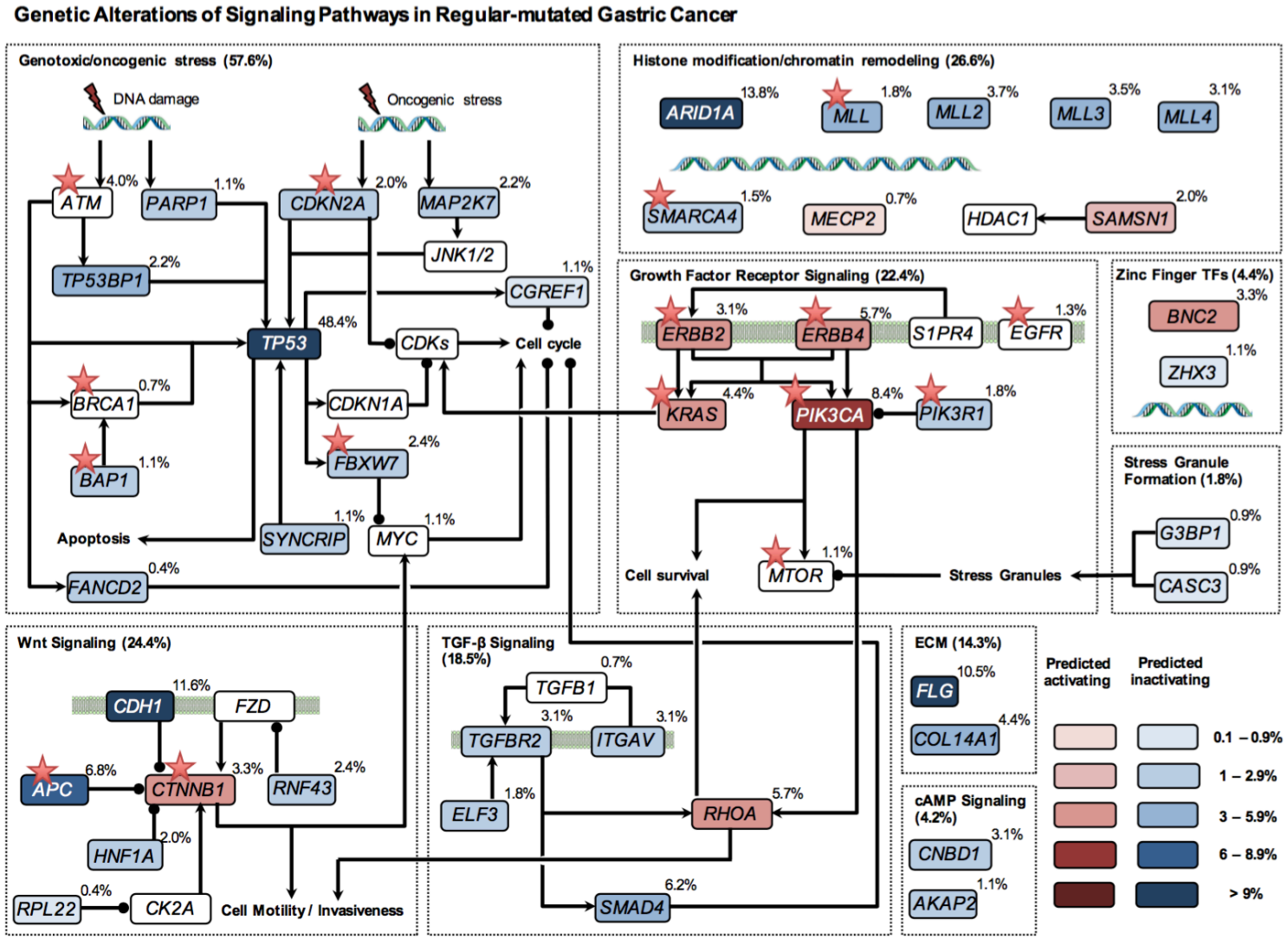
Prognostic significance of C1/2 in the 2nd cohort



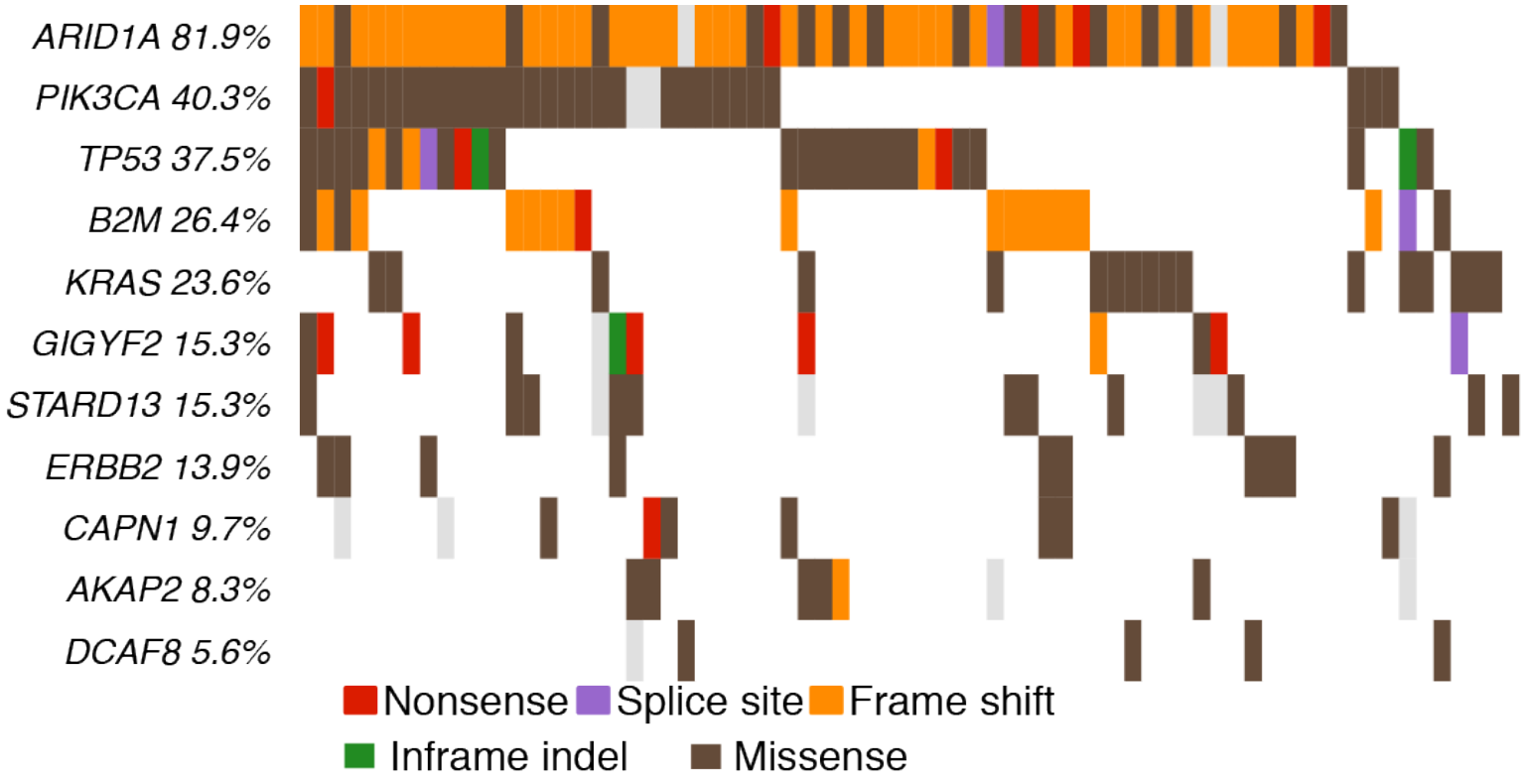
Variable	HR (95% CI)	P−value
Age	2.28 (1.05 ~ 4.94)	0.0363
Lauren	0.826 (0.356 ~ 1.92)	0.657
Gender	0.545 (0.227 ~ 1.31)	0.173
Stage	2.29 (0.959 ~ 5.47)	0.0622
MSI	0.612 (0.18 ~ 2.08)	0.431
C2 vs. C1	2.66 (1.2 ~ 5.89)	0.0155



Altered signalling pathways in regular-mutated GC

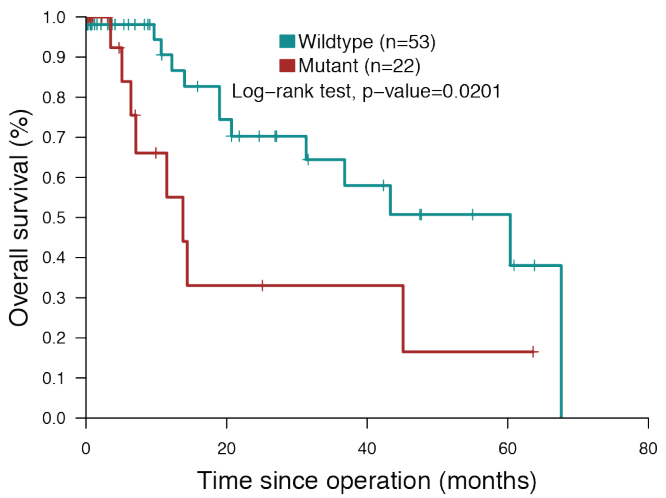


Mutational landscape in hyper-mutated GC



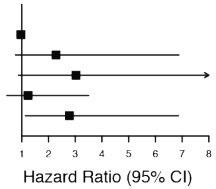
Prognosis of *CDH1* mutation in diffuse-/intestinal-type GC

A



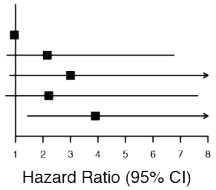
B

Variable	HR (95% CI)	P−value
Age	0.969 (0.932 ~ 1.01)	0.111
Sex (Male vs. Female)	2.29 (0.76 ~ 6.88)	0.141
Stage (III,IV vs. I,II)	3.03 (0.872 ~ 10.5)	0.081
Cohort (TCGA vs. Asian)	1.24 (0.436 ~ 3.51)	0.69
CDH1(Mutant vs. Wildtype)	2.78 (1.13 ~ 6.87)	0.0264

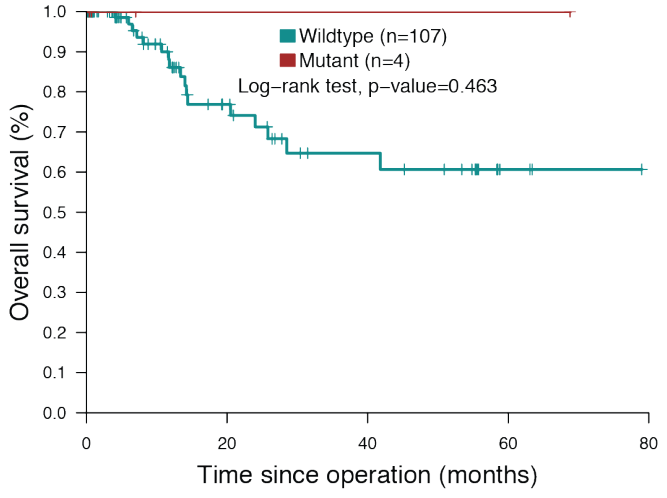


C

Variable	HR (95% CI)	P−value
Age	0.958 (0.921 ~ 0.997)	0.0347
Sex (Male vs. Female)	2.15 (0.686 ~ 6.77)	0.189
Stage (III,IV vs. I,II)	3 (0.794 ~ 11.3)	0.105
Cohort (TCGA vs. Asian)	2.21 (0.642 ~ 7.64)	0.208
CDH1(Mutant vs. Wildtype)	3.91 (1.43 ~ 10.6)	0.00773

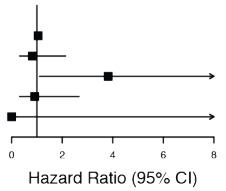


D



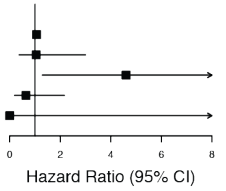
E

Variable	HR (95% CI)	P−value
Age	1.04 (0.986 ~ 1.1)	0.149
Sex (Male vs. Female)	0.812 (0.309 ~ 2.14)	0.674
Stage (III,IV vs. I,II)	3.81 (1.09 ~ 13.3)	0.0359
Cohort (TCGA vs. Asian)	0.911 (0.311 ~ 2.67)	0.865
CDH1(Mutant vs. Wildtype)	3.92e−08 (0 ~ Inf)	0.998



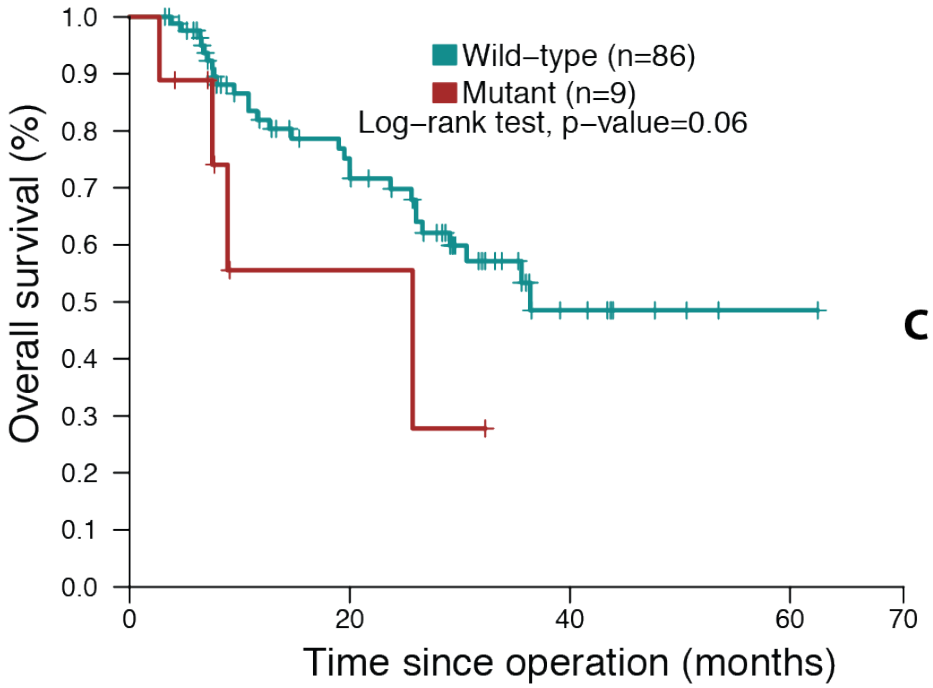
F

Variable	HR (95% CI)	P−value
Age	1.06 (1 ~ 1.13)	0.0417
Sex (Male vs. Female)	1.05 (0.367 ~ 3)	0.927
Stage (III,IV vs. I,II)	4.6 (1.29 ~ 16.5)	0.0189
Cohort (TCGA vs. Asian)	0.645 (0.192 ~ 2.17)	0.478
CDH1(Mutant vs. Wildtype)	1.2e−07 (0 ~ Inf)	0.998



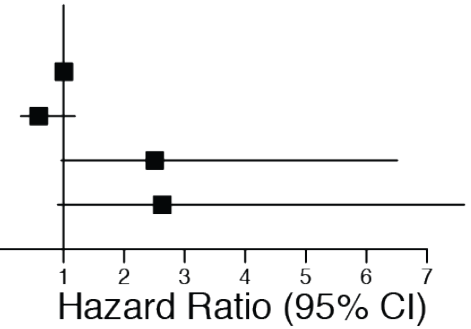
Prognosis of *CDH1* mutation in the 2nd diffuse-type GC cohort

A



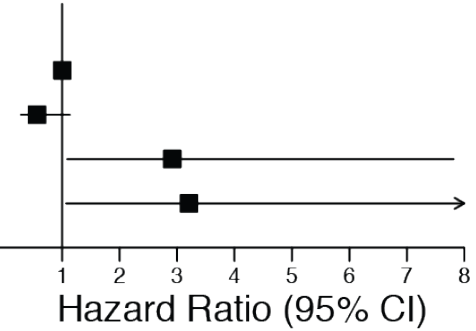
B

Variable	HR (95% CI)	P–value
Age	1.01 (0.98 ~ 1.03)	0.66
Sex (Male vs. Female)	0.59 (0.29 ~ 1.19)	0.14
Stage (III,IV vs. I,II)	2.51 (0.97 ~ 6.51)	0.06
CDH1 (mutant vs. wildtype)	2.63 (0.91 ~ 7.62)	0.07



C

Variable	HR (95% CI)	P–value
Age	1 (0.98 ~ 1.03)	0.88
Sex (Male vs. Female)	0.56 (0.28 ~ 1.13)	0.11
Stage (III,IV vs. I,II)	2.92 (1.09 ~ 7.81)	0.03
CDH1 (mutant vs. wildtype)	3.21 (1.07 ~ 9.63)	0.04



Conclusions

- There are ubiquitous and specific mutational processes underlying the pathogenesis of different subtypes of GC with varying mutation burdens.
- Several novel SMGs that are mutated at intermediate or low prevalence were identified.
- Regular-mutated GC can be further stratified into two subtypes (i.e. C1/2) with distinct clinical outcomes.
- *CDH1* mutation is an independent prognostic factor for poorer survival in patients with diffuse-type GC.

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State Key Laboratory of Digestive Disease