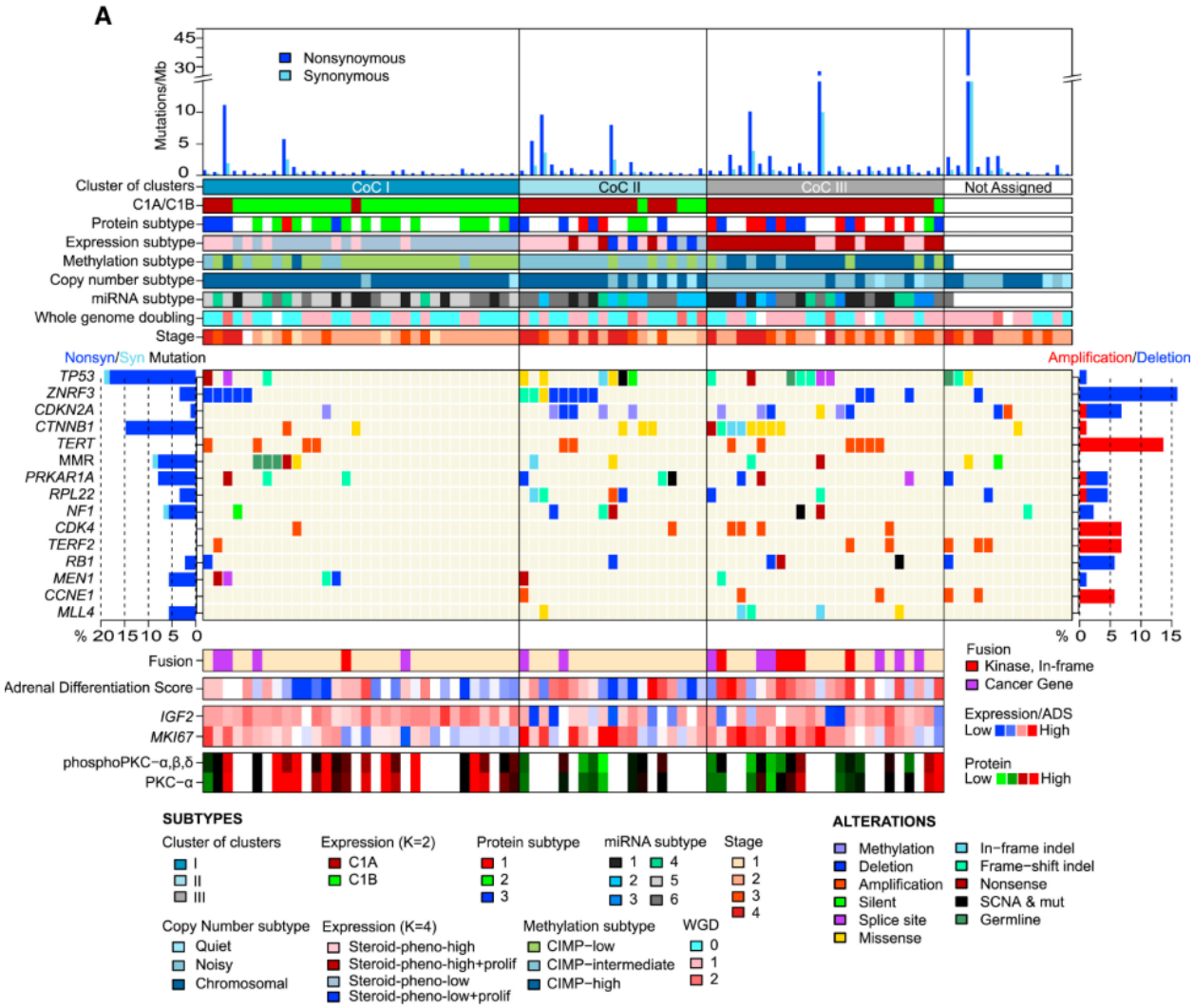
ACC - Adrenocortical Carcinoma

Subtype	Proliferation	Prognosis	Therapy (Typical / Investigational)	Common Driver Alterations
C1A	High (strong cell-cycle gene upregulation: MKI67, PLK1, CDK1)	Poor (median OS ≈2–3 years; 5-year ~40%)	Surgery + mitotane; EDP chemo (etoposide, doxo, cisplatin); IGF1R inhibitors; mTOR inhibitors; Wnt-pathway agents; immune checkpoint inhibitors in trials	TP53 mutations; CDKN2A deletions; TERT promoter mutations; PRKAR1A, RPL22 alterations; universal IGF2 overexpression
C1B	Low (minimal proliferation signature)	Favorable (median OS >10 years; 5-year ~80%)	Surgery ± mitotane; less benefit from cytotoxic chemo; potential Wnt-pathway targeting in CTNNB1-mutant tumors	CTNNB1 (β-catenin) mutations; ZNRF3 inactivation; MEN1 mutations; IGF2 overexpression; generally fewer TP53 events


A
Nonsynoymous
Synonymous
Mutations/Mb
45
30
10
5
0
Cluster of clusters
CoC I
CoC II
CoC III
Not Assigned
C1A/C1B
Protein subtype
Expression subtype
Methylation subtype
Copy number subtype
miRNA subtype
Whole genome doubling
Stage
Nonsyn/Syn Mutation
Amplification/Deletion
TP53
ZNRF3
CDKN2A
CTNNB1
TERT
MMR
PRKAR1A
RPL22
NF1
CDK4
TERF2
RB1
MEN1
CCNE1
MLL4
% 20 15 10 5 0
% 0 5 10 15
Fusion
Adrenal Differentiation Score
IGF2
MKI67
phosphoPKC−α,β,δ
PKC−α
Fusion
Kinase, In-frame
Cancer Gene
Expression/ADS
Low High
Protein
Low High
SUBTYPES
Cluster of clusters
I
II
III
Expression (K=2)
C1A
C1B
Protein subtype
1
2
3
miRNA subtype
1 4
2 5
3 6
Stage
1
2
3
4
Copy Number subtype
Quiet
Noisy
Chromosomal
Expression (K=4)
Steroid-pheno-high
Steroid-pheno-high+prolif
Steroid-pheno-low
Steroid-pheno-low+prolif
Methylation subtype
CIMP−low
CIMP−intermediate
CIMP−high
WGD
0
1
2
ALTERATIONS
Methylation
Deletion
Amplification
Silent
Splice site
Missense
In−frame indel
Frame−shift indel
Nonsense
SCNA & mut
Germline