Evaluating cell lines as tumor models by comparison of genomic profiles

Domcke, S. et al. Nat. Commun 4:2126

Motivation

- Problem: Genomic differences between cancer cell lines and tissue samples
- TCGA and CCLE provide molecular profiles for tumor samples and cell lines
- Compared high-grade serous ovarian cancer (HGSOC) to genomic profiles to identify suitable cell lines for *in vitro* models

Ovarian Cancer

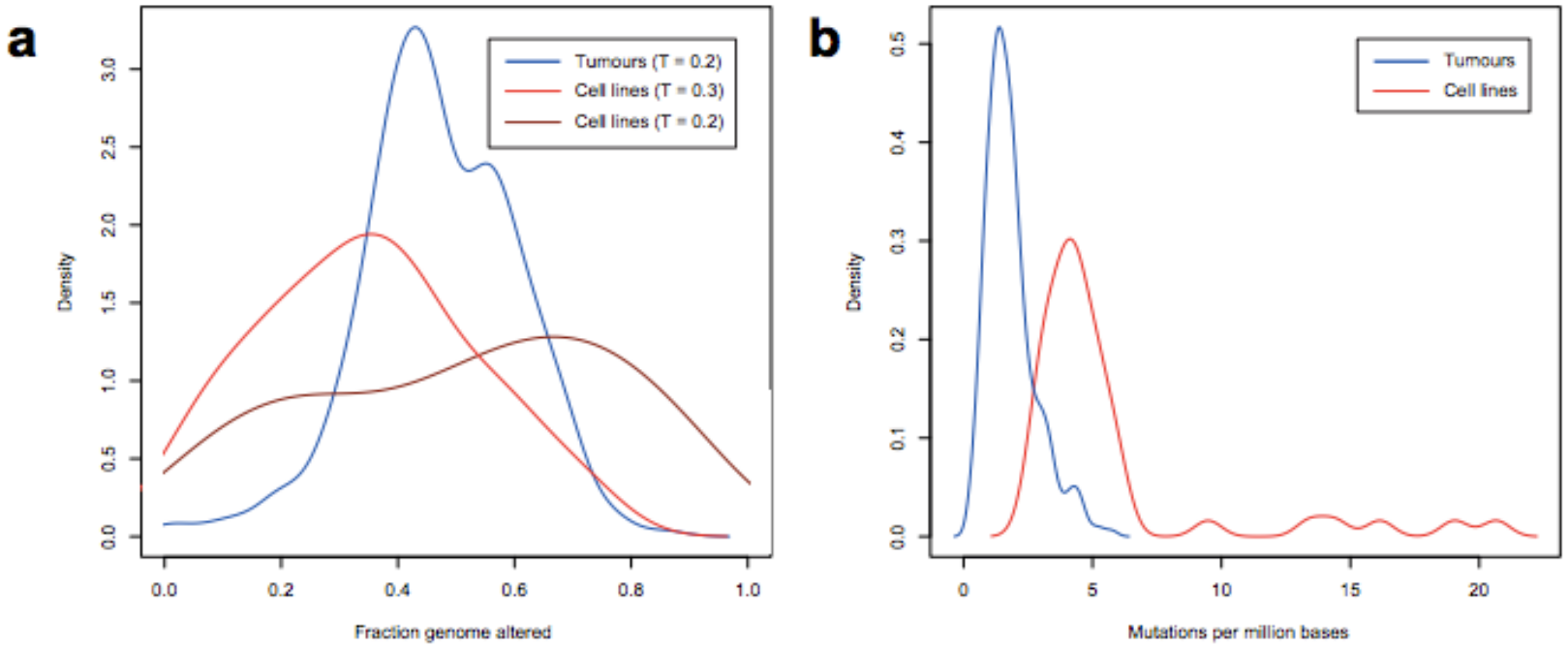
- Over 100,000 women die of ovarian cancer each year
- 5th leading cause of cancer death
- Divided into 4 major histological subtypes:
  - Serous (study's focus)
  - Endometrioid
  - Clear Cell
  - Mucinous carcinoma

- Common cell line models for ovarian cancer and HGSOC are: SK-OV-3, A2780, OVCAR-3, CAOV3 and IGROV1

- Need for well-characterized cell line models for cell types

- Found differences between most common models and majority of HGSOC samples

Figure S1


a
Tumours (T = 0.2)
Cell lines (T = 0.3)
Cell lines (T = 0.2)
Density
0.0
0.5
1.0
1.5
2.0
2.5
3.0
0.0
0.2
0.4
0.6
0.8
1.0
Fraction genome altered
b
Tumours
Cell lines
Density
0.0
0.1
0.2
0.3
0.4
0.5
0
5
10
15
20
Mutations per million bases

- Analyzed 316 HGSOC tumor samples from TCGA and 47 ovarian cancer cell lines from CCLE
- DNA copy-number, mutation and mRNA expression data
- Fraction genome altered (FGA):

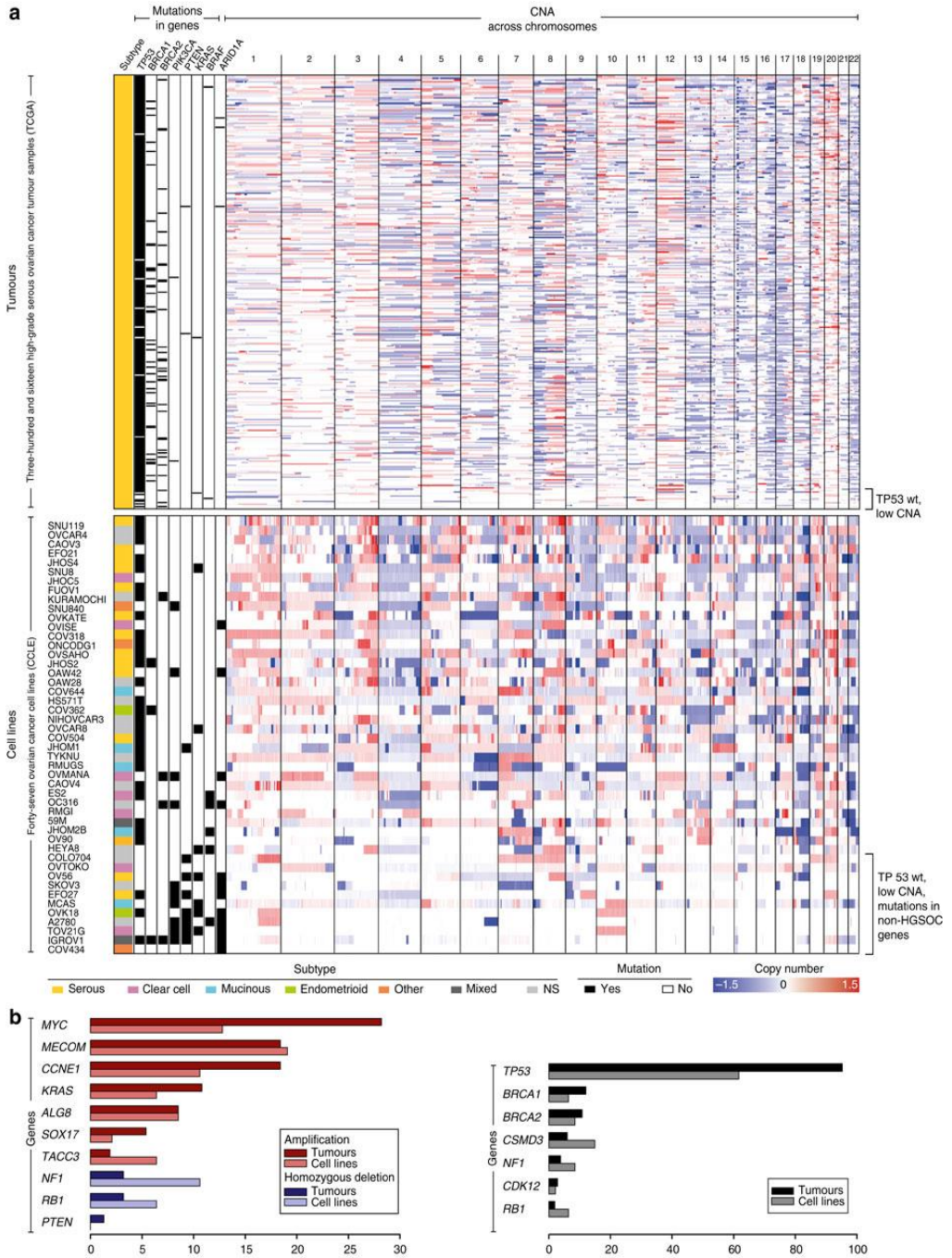
$$\mathrm{FGA} = \left(\sum_{CNi > T} L(i)\right) / \left(\sum L(i)\right)$$

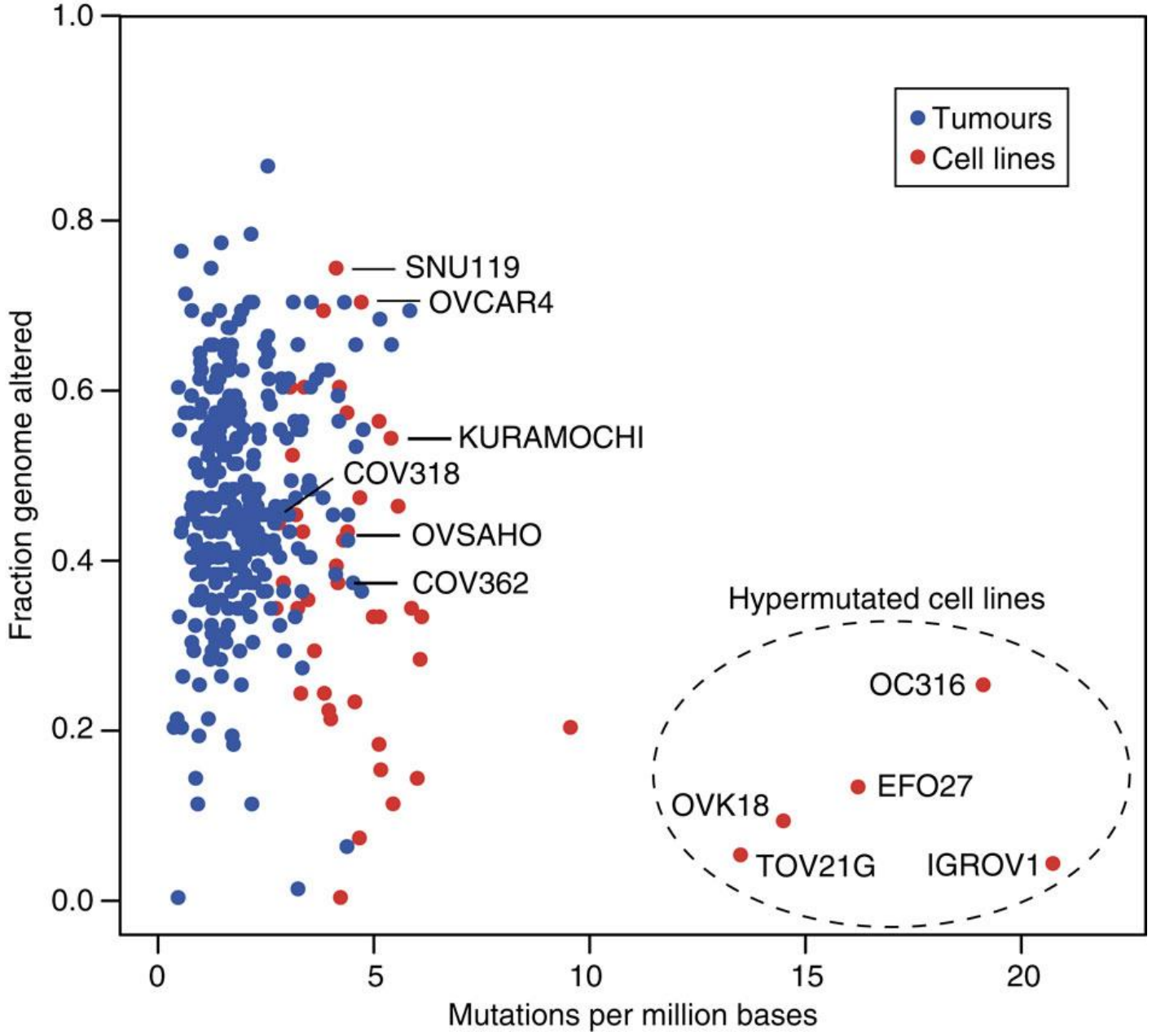
CN=log2(sample intensity/reference intensity)

L(i) is length of segment *i*

T is threshold value of Cn_i above which segments are altered

- T= 0.2 for TCGA samples
- T=0.3 for CCLE cell lines


a
Mutations in genes
CNA across chromosomes
Subtype
TP53
BRCA1
BRCA2
PIK3CA
PTEN
KRAS
BRAF
ARID1A
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Tumours
Three-hundred and sixteen high-grade serous ovarian cancer tumour samples (TCGA)
TP53 wt, low CNA
Cell lines
Forty-seven ovarian cancer cell lines (CCLE)
SNU119
OVCAR4
CAOV3
EFO21
JHOS4
SNU8
JHOC5
FUOV1
KURAMOCHI
SNU840
OVKATE
OVISE
COV318
ONCODG1
OVSAHO
JHOS2
OAW42
OAW28
COV644
HS571T
COV362
NIHOVCAR3
OVCAR8
COV504
JHOM1
TYKNU
RMUGS
OVMANA
CAOV4
ES2
OC316
RMGI
59M
JHOM2B
OV90
HEYA8
COLO704
OVTOKO
OV56
SKOV3
EFO27
MCAS
OVK18
A2780
TOV21G
IGROV1
COV434
TP 53 wt, low CNA, mutations in non-HGSOC genes
Subtype
Serous
Clear cell
Mucinous
Endometrioid
Other
Mixed
NS
Mutation
Yes
No
Copy number
−1.5
0
1.5
b
Genes
MYC
MECOM
CCNE1
KRAS
ALG8
SOX17
TACC3
NF1
RB1
PTEN
Amplification
Tumours
Cell lines
Homozygous deletion
Tumours
Cell lines
0 5 10 15 20 25 30
Percentage of samples with copy-number alteration
Genes
TP53
BRCA1
BRCA2
CSMD3
NF1
CDK12
RB1
Tumours
Cell lines
0 20 40 60 80 100
Percentage of samples with mutation


1.0
0.8
0.6
0.4
0.2
0.0
Fraction genome altered
0
5
10
15
20
Mutations per million bases
Tumours
Cell lines
SNU119
OVCAR4
KURAMOCHI
COV318
OVSAHO
COV362
Hypermutated cell lines
OC316
EFO27
OVK18
TOV21G
IGROV1

Suitability of HGSOC Models

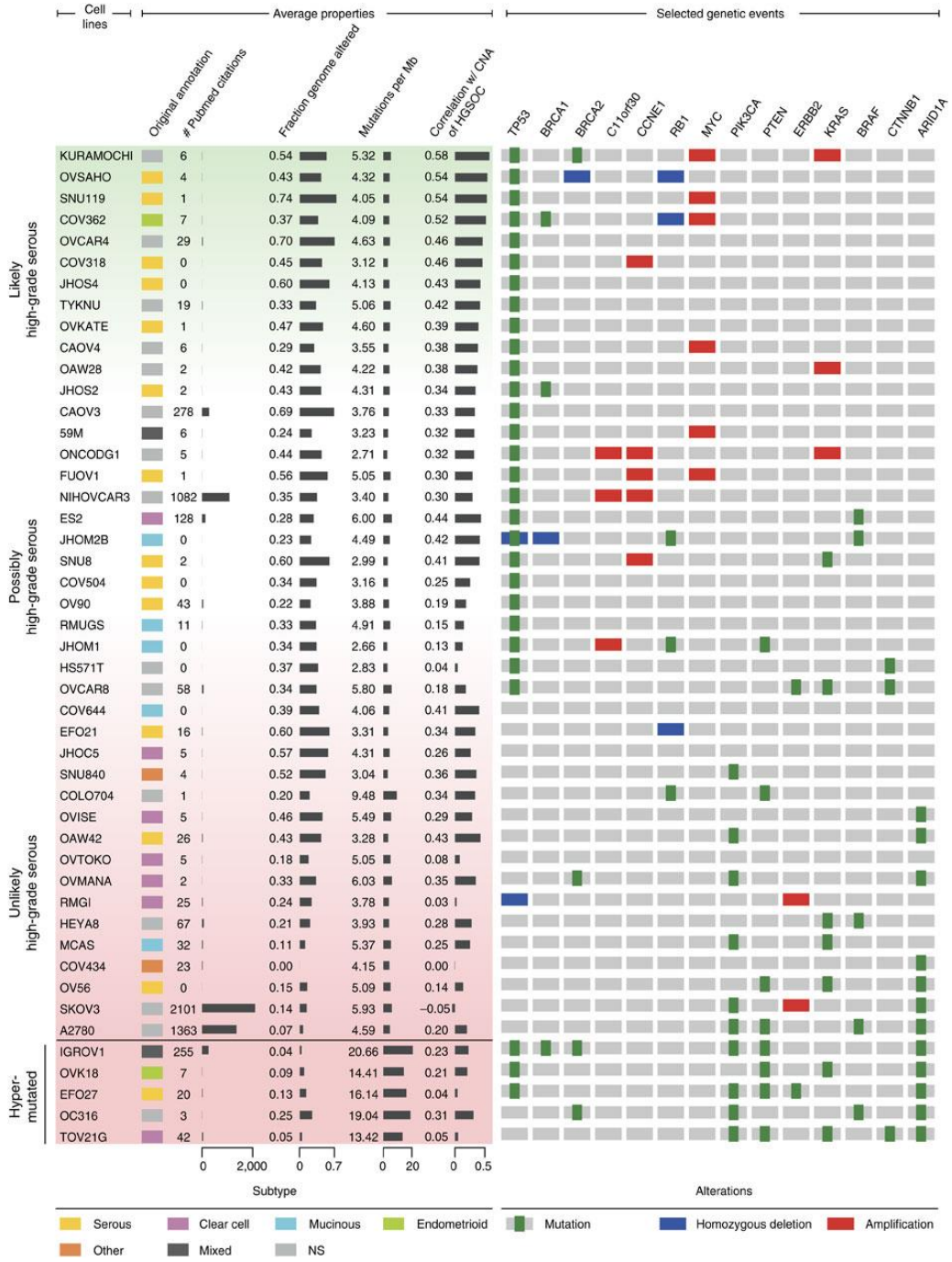
$S = A + B - 2 \times C - D/7$

A = Correlation with mean CNA of tumors

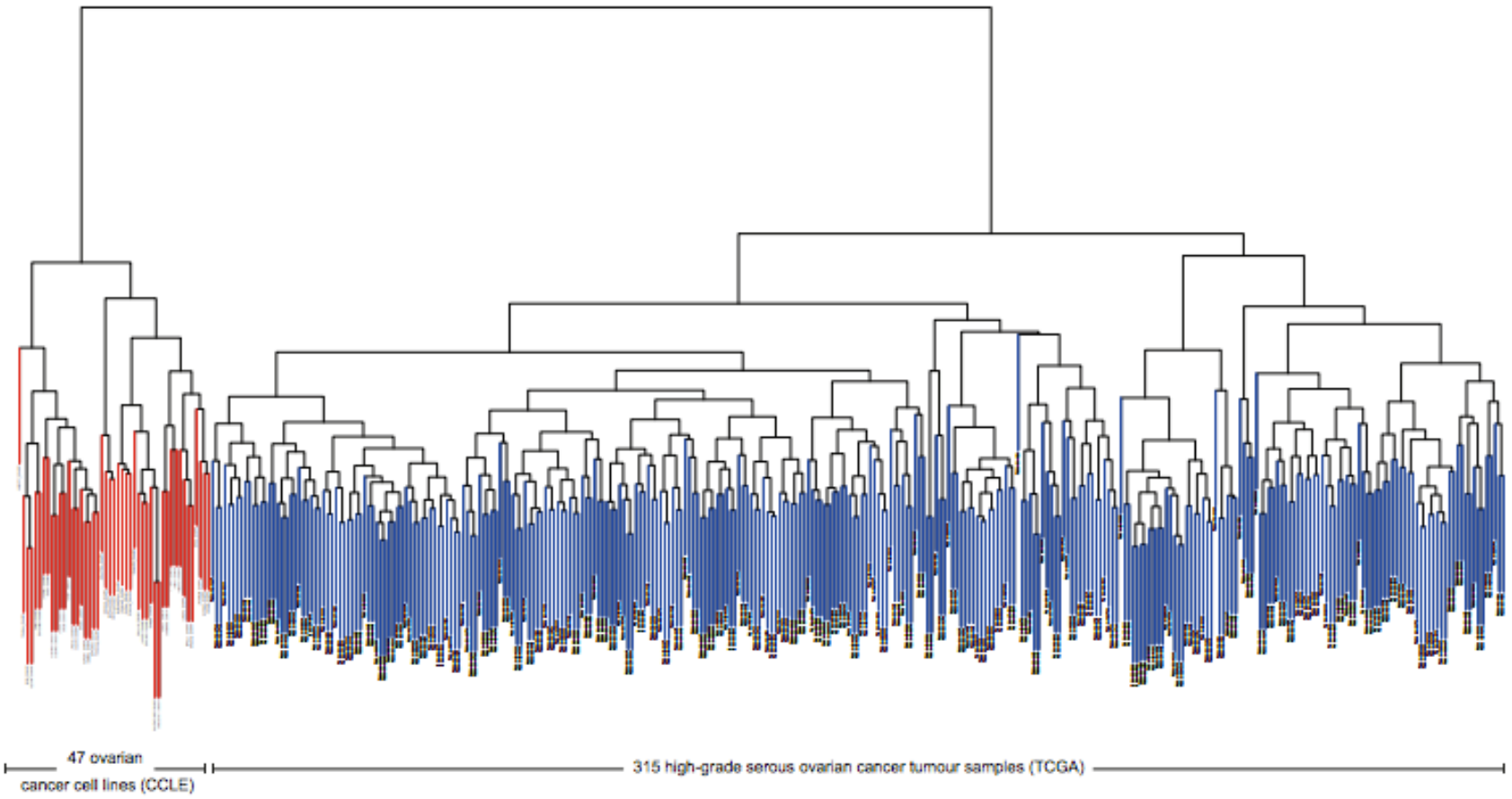
B = 1 for cell lines with *TP53* mutation or else 0

C = 1 for hypermutated cell line or else 0

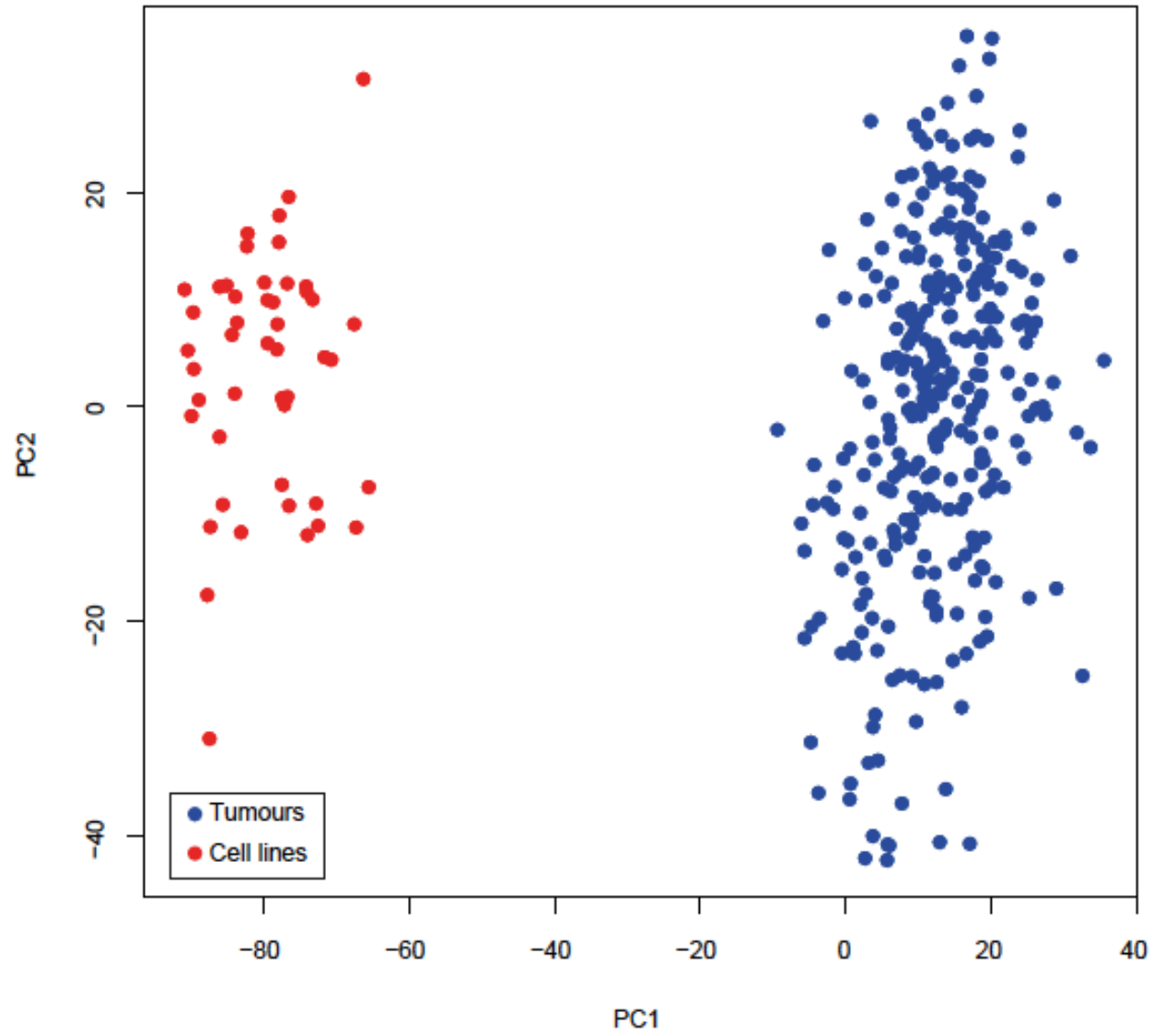
D = # of genes mutated in 7 “non-HGSOC” genes

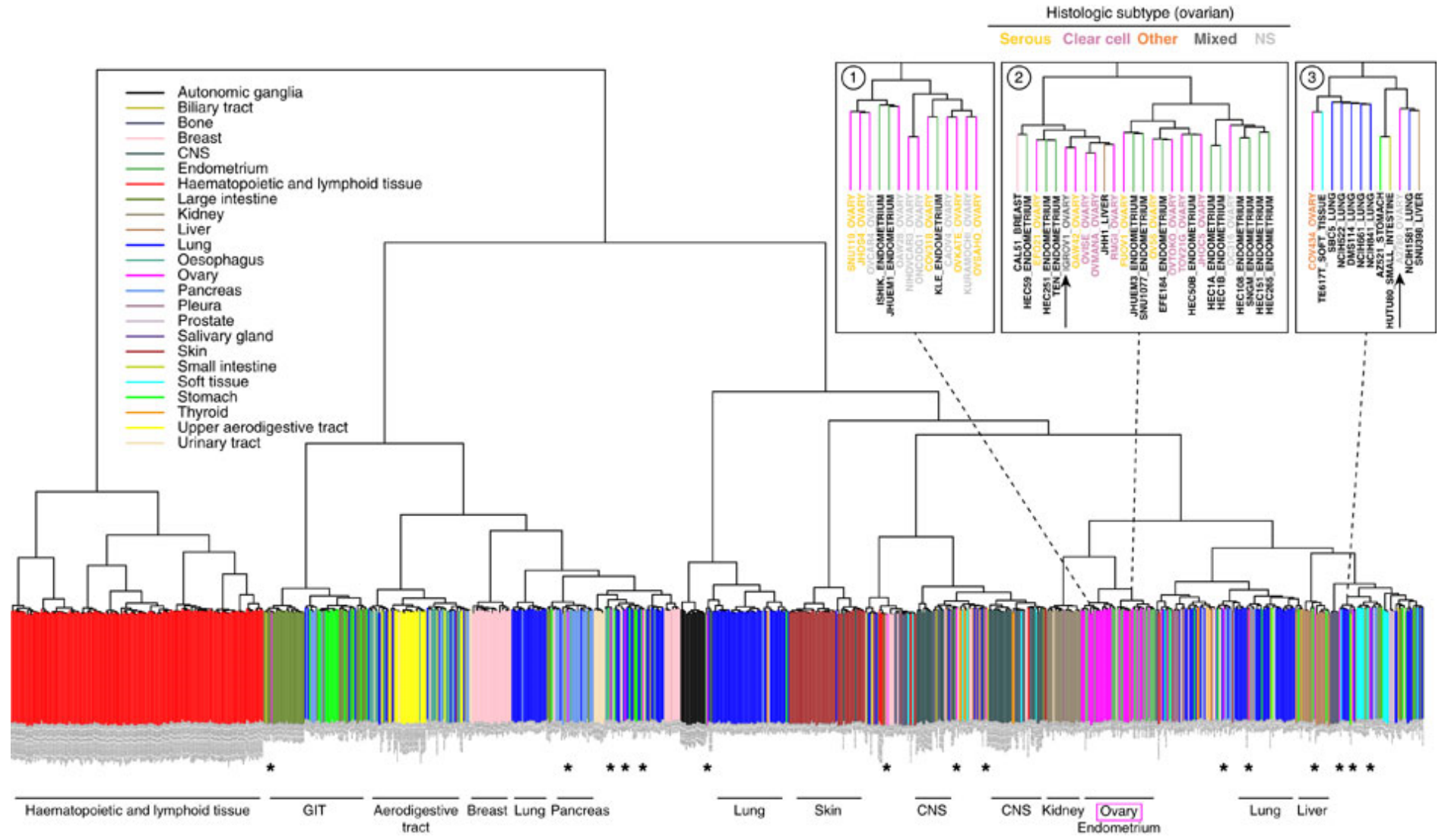

Cell lines
Average properties
Selected genetic events
Original annotation
Pubmed citations
Fraction genome altered
Mutations per Mb
Correlation w/ CNA of HGSOC
TP53
BRCA1
BRCA2
C11orf30
CCNE1
RB1
MYC
PIK3CA
PTEN
ERBB2
KRAS
BRAF
CTNNB1
ARID1A
Likely high-grade serous
Possibly high-grade serous
Unlikely high-grade serous
Hyper-mutated
KURAMOCHI 6 0.54 5.32 0.58
OVSAHO 4 0.43 4.32 0.54
SNU119 1 0.74 4.05 0.54
COV362 7 0.37 4.09 0.52
OVCAR4 29 0.70 4.63 0.46
COV318 0 0.45 3.12 0.46
JHOS4 0 0.60 4.13 0.43
TYKNU 19 0.33 5.06 0.42
OVKATE 1 0.47 4.60 0.39
CAOV4 6 0.29 3.55 0.38
OAW28 2 0.42 4.22 0.38
JHOS2 2 0.43 4.31 0.34
CAOV3 278 0.69 3.76 0.33
59M 6 0.24 3.23 0.32
ONCODG1 5 0.44 2.71 0.32
FUOV1 1 0.56 5.05 0.30
NIHOVCAR3 1082 0.35 3.40 0.30
ES2 128 0.28 6.00 0.44
JHOM2B 0 0.23 4.49 0.42
SNU8 2 0.60 2.99 0.41
COV504 0 0.34 3.16 0.25
OV90 43 0.22 3.88 0.19
RMUGS 11 0.33 4.91 0.15
JHOM1 0 0.34 2.66 0.13
HS571T 0 0.37 2.83 0.04
OVCAR8 58 0.34 5.80 0.18
COV644 0 0.39 4.06 0.41
EFO21 16 0.60 3.31 0.34
JHOC5 5 0.57 4.31 0.26
SNU840 4 0.52 3.04 0.36
COLO704 1 0.20 9.48 0.34
OVISE 5 0.46 5.49 0.29
OAW42 26 0.43 3.28 0.43
OVTOKO 5 0.18 5.05 0.08
OVMANA 2 0.33 6.03 0.35
RMGI 25 0.24 3.78 0.03
HEYA8 67 0.21 3.93 0.28
MCAS 32 0.11 5.37 0.25
COV434 23 0.00 4.15 0.00
OV56 0 0.15 5.09 0.14
SKOV3 2101 0.14 5.93 −0.05
A2780 1363 0.07 4.59 0.20
IGROV1 255 0.04 20.66 0.23
OVK18 7 0.09 14.41 0.21
EFO27 20 0.13 16.14 0.04
OC316 3 0.25 19.04 0.31
TOV21G 42 0.05 13.42 0.05
0 2,000
0 0.7
0 20
0 0.5
Subtype
Alterations
Serous
Clear cell
Mucinous
Endometrioid
Other
Mixed
NS
Mutation
Homozygous deletion
Amplification

a


47 ovarian
cancer cell lines (CCLE)
315 high-grade serous ovarian cancer tumour samples (TCGA)

b




Histologic subtype (ovarian)
Serous
Clear cell
Other
Mixed
NS
Autonomic ganglia
Biliary tract
Bone
Breast
CNS
Endometrium
Haematopoietic and lymphoid tissue
Large intestine
Kidney
Liver
Lung
Oesophagus
Ovary
Pancreas
Pleura
Prostate
Salivary gland
Skin
Small intestine
Soft tissue
Stomach
Thyroid
Upper aerodigestive tract
Urinary tract
1
2
3
Haematopoietic and lymphoid tissue
GIT
Aerodigestive tract
Breast
Lung
Pancreas
Lung
Skin
CNS
CNS
Kidney
Ovary
Endometrium
Lung
Liver

Future Directions

- Drug response profiles using accurate cell line models with known alterations for patient selection in clinical trials
- Perform preclinical drug screens for more-informed patient therapy
- Any others?