Update on IBC project

July 29,2015

Background

- Inflammatory Breast Cancer (IBC)[1]
  - Rare (1%~4%) & Aggressive
  - Affects young patients population
  - Standard breast cancer risk factors NOT applicable
  - NO known risk factors specified to IBC
  - Recurrence and/or metastases
  - 5-year survival rate: limited to 40%[2]
- Whole genome sequencing on 20 IBC samples
  - Matched tumor-normal pairs
  - Coverage: tumor sample: 60X; normal sample: 60X(the first two) /40X
  - Currently two pairs of samples have been finished

[1] Kerger, Amy L., and Mary C. Mahoney. "Inflammatory Breast Carcinoma." Contemporary Diagnostic Radiology 38.17 (2015): 1-5.
[2] Bertucci, Francois, et al. "Gene expression profiling for molecular characterization of inflammatory breast cancer and prediction of response to chemotherapy." *Cancer research* 64.23 (2004): 8558-8565.

Somatic SNVs for IBC Samples

Sample Id	IBC_228	IBC_298
Somatic	4041 (novel*:3578 | standard*: 463)	5475 (novel:5000 | standard: 475)
Coding	38 (novel: 32 | standard: 6) (syn:16; non-syn:20; stopgain:2)	54 (novel: 47 | standard: 7) (syn:10; non-syn:43; stopgain:1)
Intronic	1447 (novel:1277 | standard: 170)	1942 (novel:1752 | standard: 190)
Intergenic	2264 (novel:2008 | standard: 256)	3034 (novel:2792 | standard: 242)
Splicing	0	1

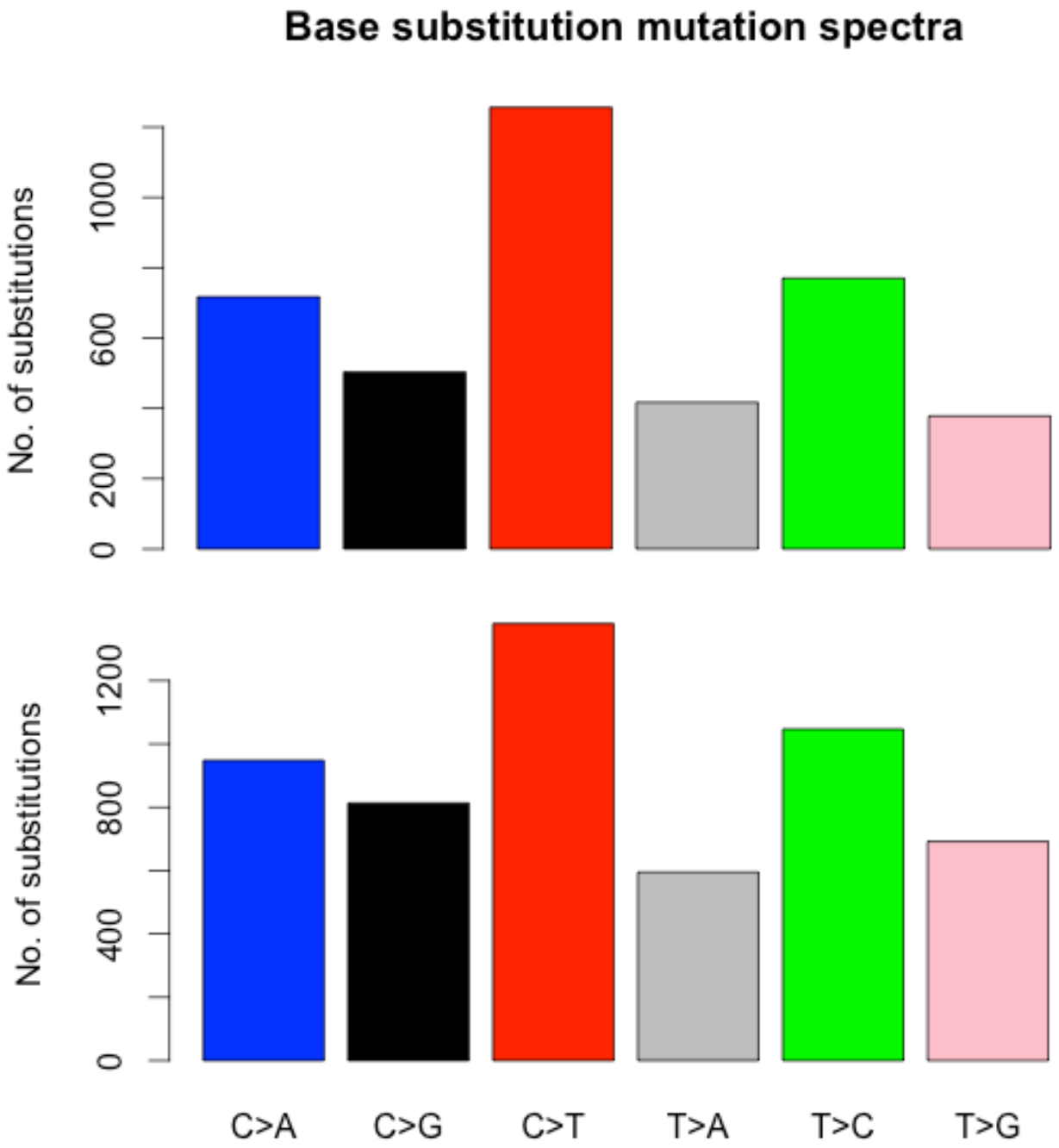
* Absent in dbSNP database; * Present in dbSNP database

Compare Somatic SNVs across Breast Cancers

Sample Id	IBC	ER+,HER2-	Er+,HER2+	ER-,HER2+	TNBC	BRCA1	BRCA2
Somatic	4758	12643	2273	4256	3752	5658	8474
Exonic	46	157	18	48	38	43	51
Intronic	1674	4737	777	1609	1322	1849	2247
Intergenic	2649	6745	1316	2263	2127	3340	3963
Splicing	1	11	0	1	2	2	4

IBC_228

IBC_298

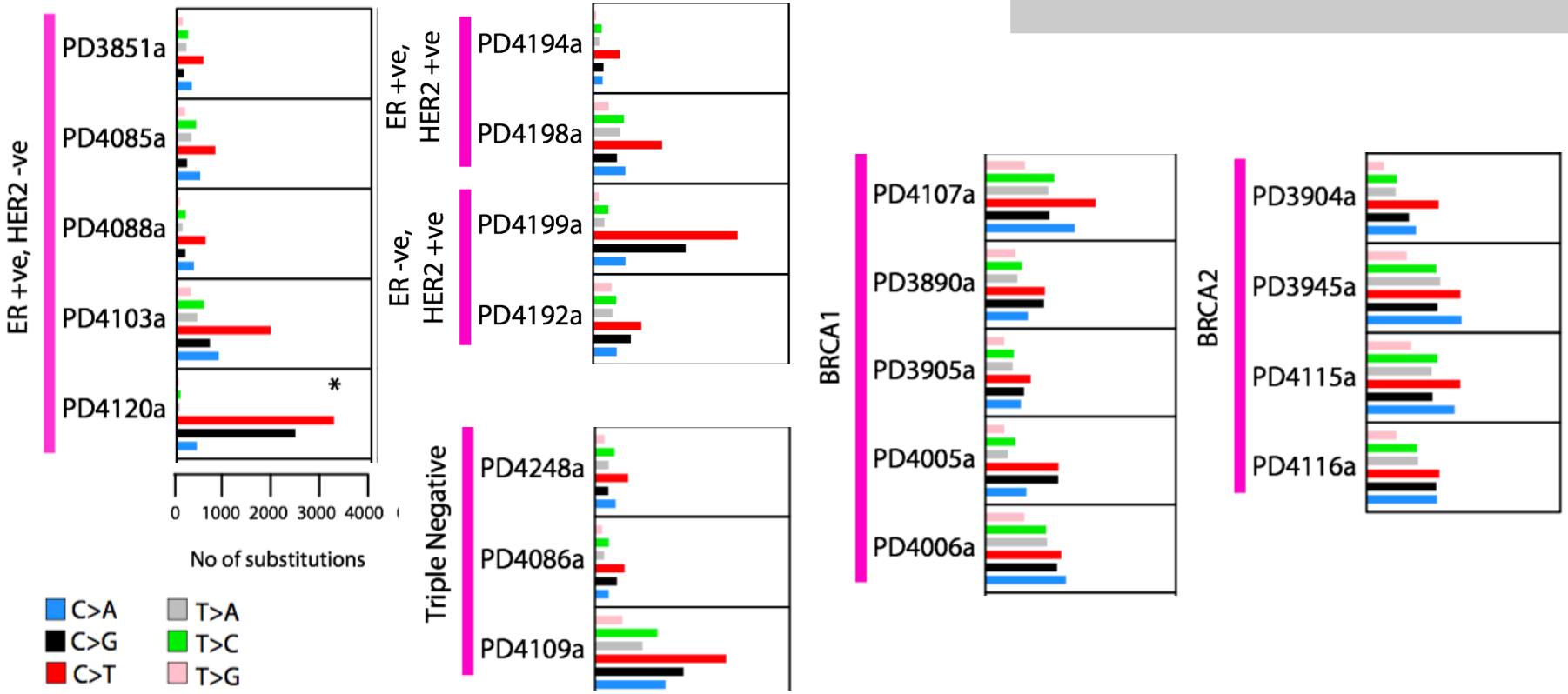


Cell

Mutational Processes Molding the Genomes of 21 Breast Cancers

Serena Nik-Zainal,[1] Ludmil B. Alexandrov,[1] David C. Wedge,[1] Peter Van Loo,[1,2,3] Christopher D. Greenman,[1,4,5]

- Estrogen Receptors (**ER**)
- Progesterone Receptors (**PR**)
- Human Epidermal growth factor Receptor 2 (**HER2**)
- Germline mutations in **BRCA1**, **BRCA2**



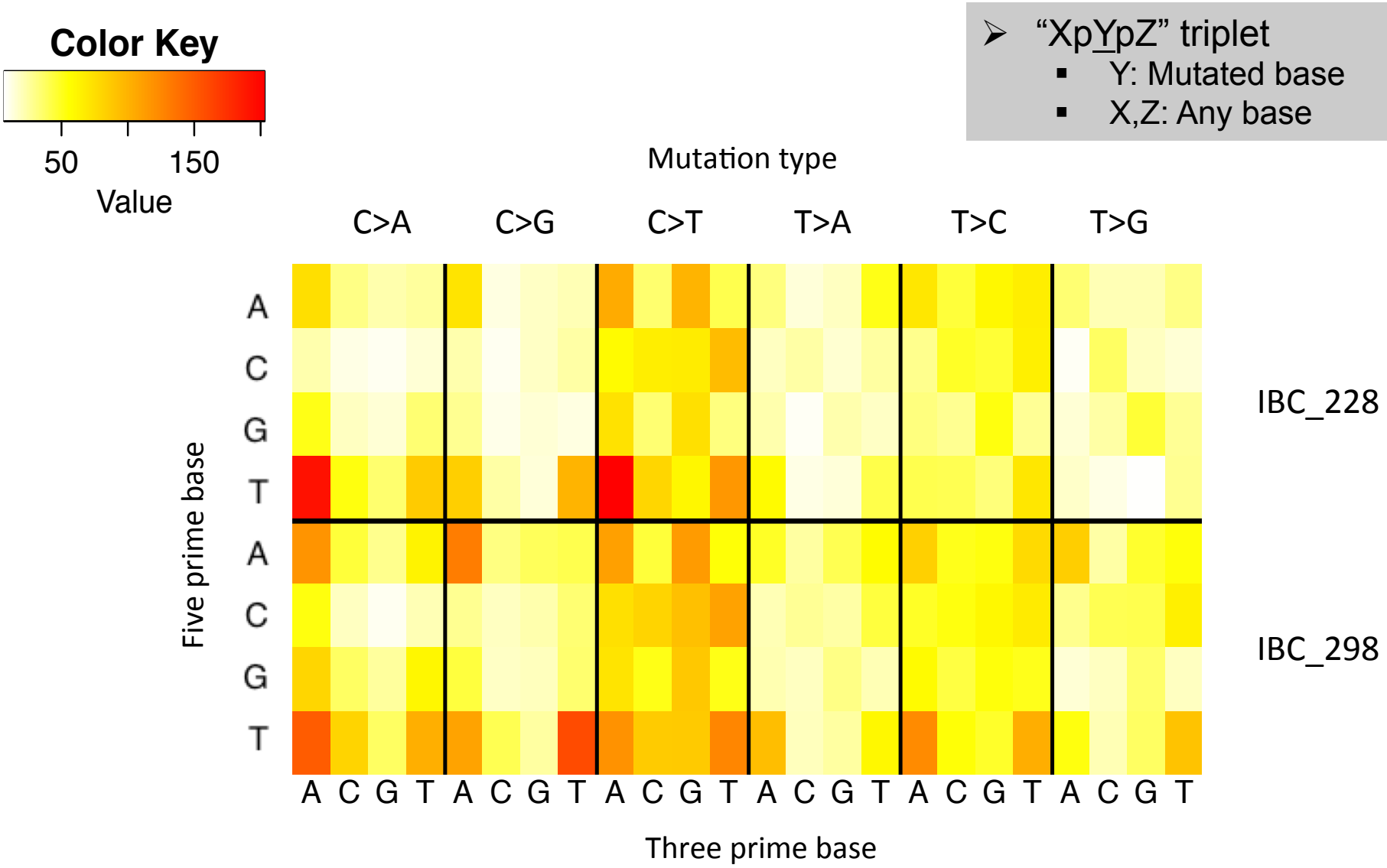
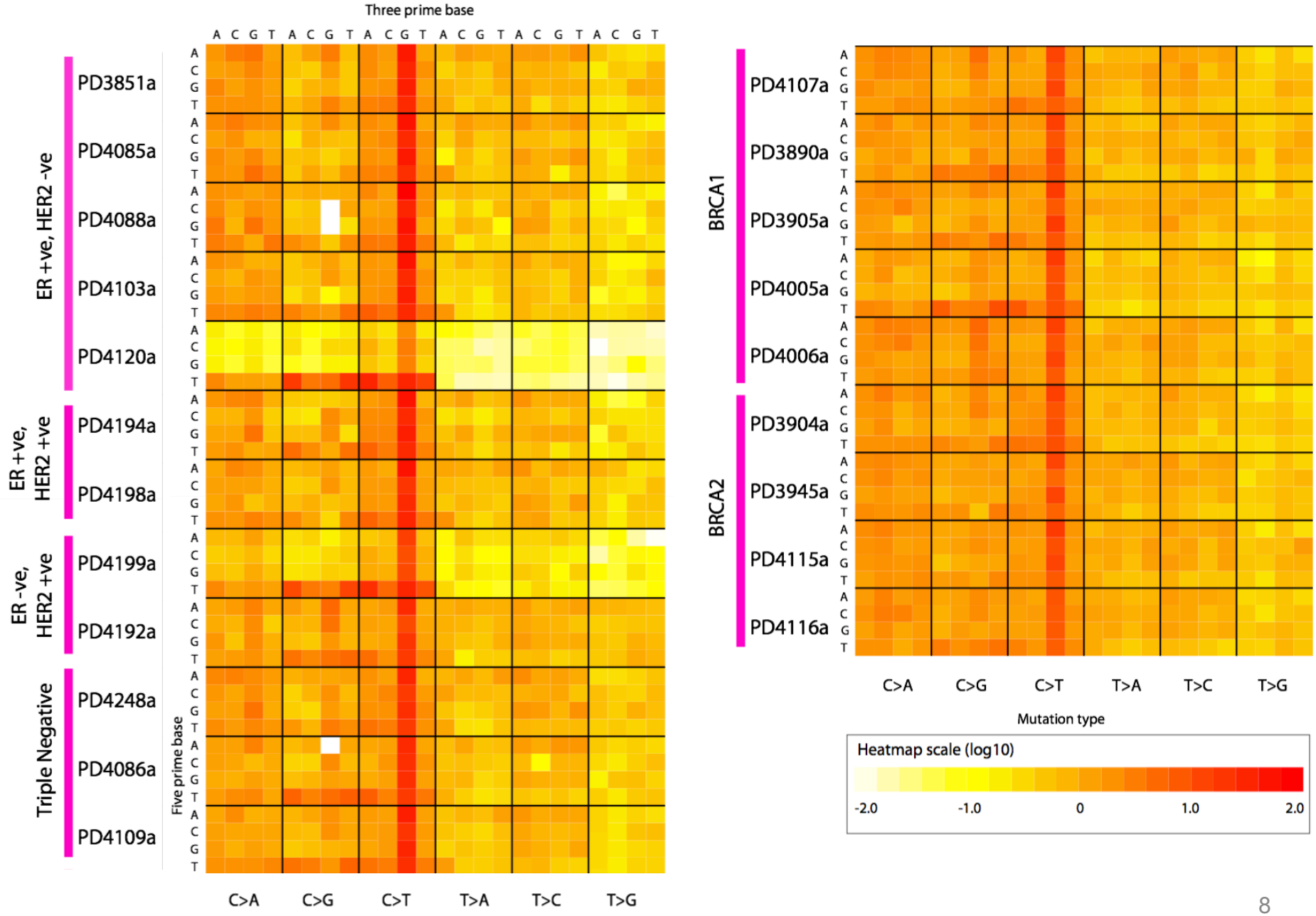


Figure 1. Genomic heatmap for base substitution frequency at trinucleotides context


Three prime base
A C G T A C G T A C G T A C G T A C G T A C G T
Five prime base
ER +ve, HER2 -ve
PD3851a
PD4085a
PD4088a
PD4103a
PD4120a
ER +ve, HER2 +ve
PD4194a
PD4198a
ER -ve, HER2 +ve
PD4199a
PD4192a
Triple Negative
PD4248a
PD4086a
PD4109a
BRCA1
PD4107a
PD3890a
PD3905a
PD4005a
PD4006a
BRCA2
PD3904a
PD3945a
PD4115a
PD4116a
C>A C>G C>T T>A T>C T>G
Mutation type
Heatmap scale (log10)
-2.0 -1.0 0 1.0 2.0

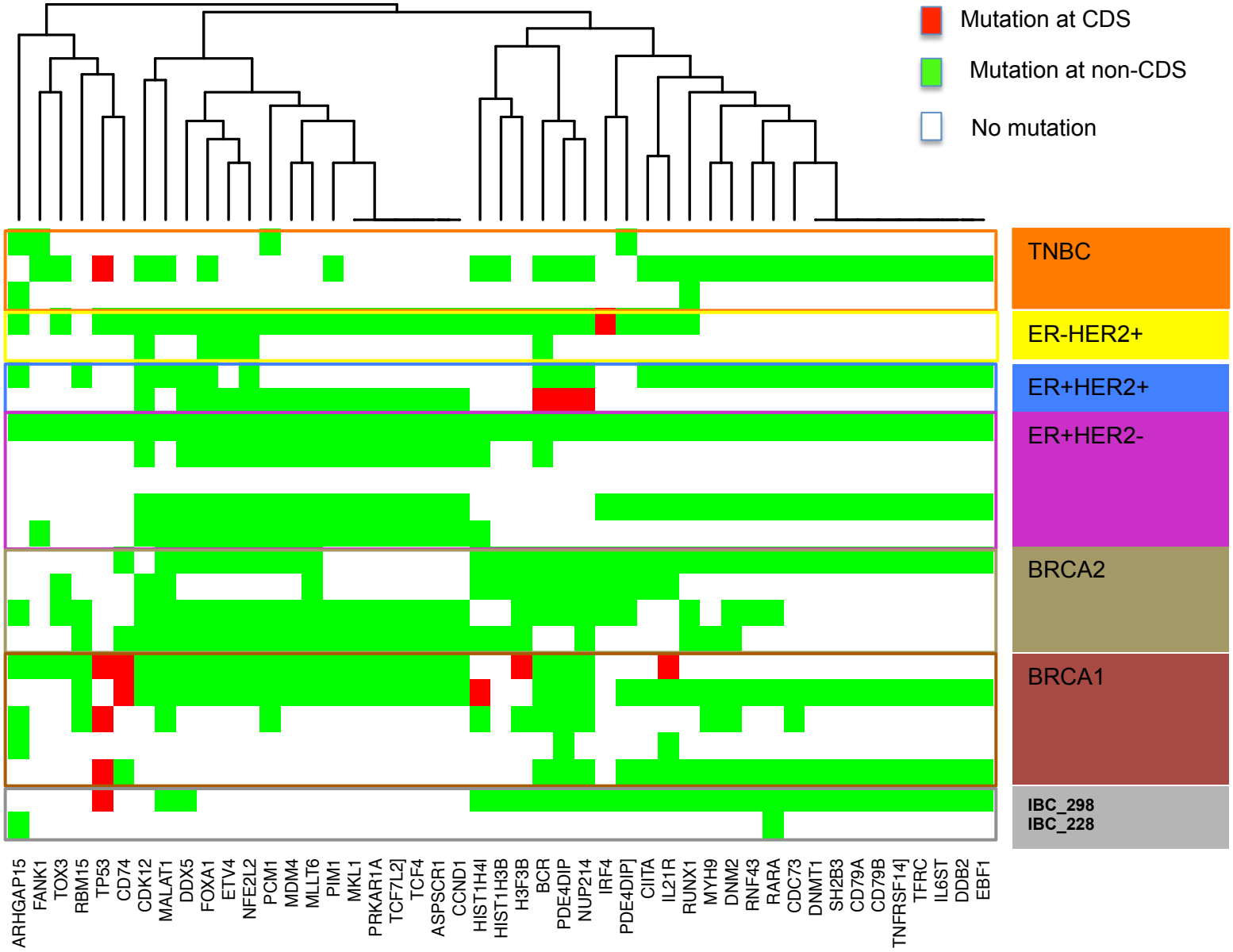


Figure 2. Genes with somatic variants prioritized by FunSeq2

Annotation of Genes with Mutations Present in All Breast Cancer

ENSG00000105369	CD79a molecule, immunoglobulin-associated alpha
KEGG_PATHWAY	B cell receptor signaling pathway, Primary immunodeficiency,
ENSG00000007312	CD79b molecule, immunoglobulin-associated beta
KEGG_PATHWAY	B cell receptor signaling pathway,
ENSG00000130816	DNA (cytosine-5-)-methyltransferase 1
KEGG_PATHWAY	Cysteine and methionine metabolism,
ENSG00000111252	SH2B adaptor protein 3
KEGG_PATHWAY	Neurotrophin signaling pathway,
ENSG00000179583	class II, major histocompatibility complex, transactivator
KEGG_PATHWAY	Antigen processing and presentation, Primary immunodeficiency,
ENSG00000134574	damage-specific DNA binding protein 2, 48kDa
KEGG_PATHWAY	Nucleotide excision repair, p53 signaling pathway, Ubiquitin mediated proteolysis,
ENSG00000079805	dynamin 2
KEGG_PATHWAY	Endocytosis, Fc gamma R-mediated phagocytosis,
ENSG00000103522	interleukin 21 receptor
KEGG_PATHWAY	Cytokine-cytokine receptor interaction, Jak-STAT signaling pathway,
ENSG00000134352	interleukin 6 signal transducer (gp130, oncostatin M receptor)
KEGG_PATHWAY	Cytokine-cytokine receptor interaction, Jak-STAT signaling pathway,
ENSG00000100345	myosin, heavy chain 9, non-muscle
KEGG_PATHWAY	Tight junction, Regulation of actin cytoskeleton, Viral myocarditis,
ENSG00000131759	retinoic acid receptor, alpha
KEGG_PATHWAY	Pathways in cancer, Acute myeloid leukemia,
ENSG00000159216	runt-related transcription factor 1
KEGG_PATHWAY	Pathways in cancer, Chronic myeloid leukemia, Acute myeloid leukemia,
ENSG00000072274	transferrin receptor (p90, CD71)
KEGG_PATHWAY	Endocytosis, Hematopoietic cell lineage,
ENSG00000157873	tumor necrosis factor receptor superfamily, member 14 (herpesvirus entry mediator)
KEGG_PATHWAY	Cytokine-cytokine receptor interaction,

Annotation of Genes with Mutations Absent in IBC Samples

ENSG00000198625	Mdm4 p53 binding protein homolog (mouse)
KEGG_PATHWAY	p53 signaling pathway,
ENSG00000110092	cyclin D1
KEGG_PATHWAY	Cell cycle, p53 signaling pathway, Wnt signaling pathway, Focal adhesion, Jak-STAT sig cancer, Pancreatic cancer, Endometrial cancer, Glioma, Prostate cancer, Thyroid cancer leukemia, Acute myeloid leukemia, Small cell lung cancer, Non-small cell lung cancer, V
ENSG00000137193	pim-1 oncogene
KEGG_PATHWAY	Jak-STAT signaling pathway, Acute myeloid leukemia,
ENSG00000108946	protein kinase, cAMP-dependent, regulatory, type I, alpha (tissue specific extinguisher 1)
KEGG_PATHWAY	Apoptosis, Insulin signaling pathway,
ENSG00000148737	transcription factor 7-like 2 (T-cell specific, HMG-box)
KEGG_PATHWAY	Wnt signaling pathway, Adherens junction, Melanogenesis, Pathways in cancer, Colorec Thyroid cancer, Basal cell carcinoma, Acute myeloid leukemia, Arrhythmogenic right ve

Cancer Cell
Article

p53-Mediated Senescence Impairs the Apoptotic Response to Chemotherapy and Clinical Outcome in Breast Cancer

James G. Jackson,[1] Vinod Pant,[1] Qin Li,[1,5] Leslie L. Chang,[1] Alfonso Quintás-Cardama,[2] Daniel Garza,[1] Omid Tavana,[3] Peirong Yang,[1] Taghi Manshouri,[2] Yi Li,[6] Adel K. El-Naggar,[4] and Guillermina Lozano[1,*]

Significance

Approximately one-third of human breast cancers harbor mutations in the tumor suppressor gene *TP53*. The long-held paradigm that wild-type p53 mediates apoptosis resulting in a favorable chemotherapy response is less clear in breast cancer because many reports conflict, including some suggesting that tumors harboring *TP53* mutations respond more favorably. Here, we show that wild-type p53 activity is paradoxically detrimental to chemotherapy response because, unlike mutant *p53* tumors, *p53* wild-type tumors can avoid aberrant mitoses by undergoing arrest, which is followed by expression of cytokines in senescent cells that can stimulate cell proliferation and tumor relapse. Furthermore, our data demonstrate that in order to accurately predict clinical response of *TP53*-mutated tumors, the status of the second allele must be determined.

response even in the context of heterozygous *p53* point mutations or absence of p21. Thus, we show that wild-type *p53* activity hinders chemotherapy response and demonstrate the need to reassess the paradigm for *p53* in cancer therapy.

Next Steps

- Base substitution frequency at wider sequence context (3bp→20bp)
- Similar pipelines for germline mutations
- More methods/framework analyzing somatic mutations
- Combine more published data sources and compare IBC with other types of breast cancer
- Integrate more sequencing data of IBC samples