

# Landscape of somatic mutations in inflammatory breast cancer whole-genome sequences

Xiaotong Li

# Number of somatic variants in each call set

Filters	# Ours	# PCAWG	Intersection	% (sensitivity)
None (“ACCEPT” by MuTect)	10,701	4,336	4,139	0.9545664
	29,338	23,360	23,066	0.9874144
	6,951	1,478	1,411	0.9546685
Filter 1 (NOT dbSNP)	8,000	3,926	3,696	0.9414162
	25,811	22,179	21,687	0.9778169
	4,599	1,311	1,244	0.948894
Filter 2 (NOT dbSNP & Mask)	3,910	2,841	2,734	0.9623372
	18,539	17,345	16,997	0.9799366
	1,670	934	905	0.9689507
Ours: Filter 2 vs. PCAWG: Original	3,910	4,336	2,911	0.67/0.74
	18,539	23,360	17,569	0.75/0.95
	1,670	1,478	980	0.66/0.59

# Mutation Frequency of TP53

- PCAWG original call set
  - selected 3 samples as examples
  - 2 samples reported coding mutations in TP53, 1 mutation each.
    - nonsynonymous; preMatureStop
- These two mutations are **in** current call set as well!
- NOT dbSNP **!=** NOVEL
  - COSMIC

NOT dbSNP vs. NOVEL	3910	3,876
	18,539	18,462
	1,670	1,663

~0.5% (~20 per sample) mutations are annotated as “COSMIC”, which were missed previously; This small number may change the entire story!!

# Filters for somatic mutations calling

- include “COSMIC”
- **NOT** apply “MASK”?
- Mutation rate of TP53 in PCAWG set
- Check recipe from PCAWG

# PCAWG pipeline

- **Thousand Genomes phase 3** occurrence fraction if found
- multiple callers that made this call (Not called by enough callers in ensemble)
  - MuTect (broad); dkfz (German); MuSE (MD Anderson); sanger
- **COSMIC v76**
- **dbSNP, build 147**
- repeat masker region
- known-somatic dbSNP variant
- Sanger Tower: possible artifact
- Suspected C>A oxo-guanine signature in some samples (Failed OXOG oxidative artifact filter)
- SNV is located near indel
- Sequencing Bias
- PCR Bias
- 1000Genome variant with insufficient somatic evidence
- Overlaps germline Haplotype call
- Presence in Panel of Normals
- Variant no longer seen under remapping
- Likely artifact or call in PAR region: Y-chromosome variant in female donor

- From the output of MuTect:
  - remove dbSNP
  - keep NOVEL
  - keep COSMIC
- remove “common” (allele frequency >1% ) variants from 1000G

# IBC calls

- From the output of MuTect:
  - remove dbSNP
  - keep NOVEL
  - keep COSMIC (COSMIC; dbSNP&COSMIC)

```
10 COSMIC
32307 DBSNP
10 DBSNP+COSMIC
188800 NOVEL
```

- remove “common” (estimated allele frequency >1%) variants from 1000G
  - 773 variants be filtered in this step
- Final calls: 188,047 variants
- Annotated by FunSeq2
  - TP53: Altered in 11/20(55.00%) samples

# Non-IBC calls

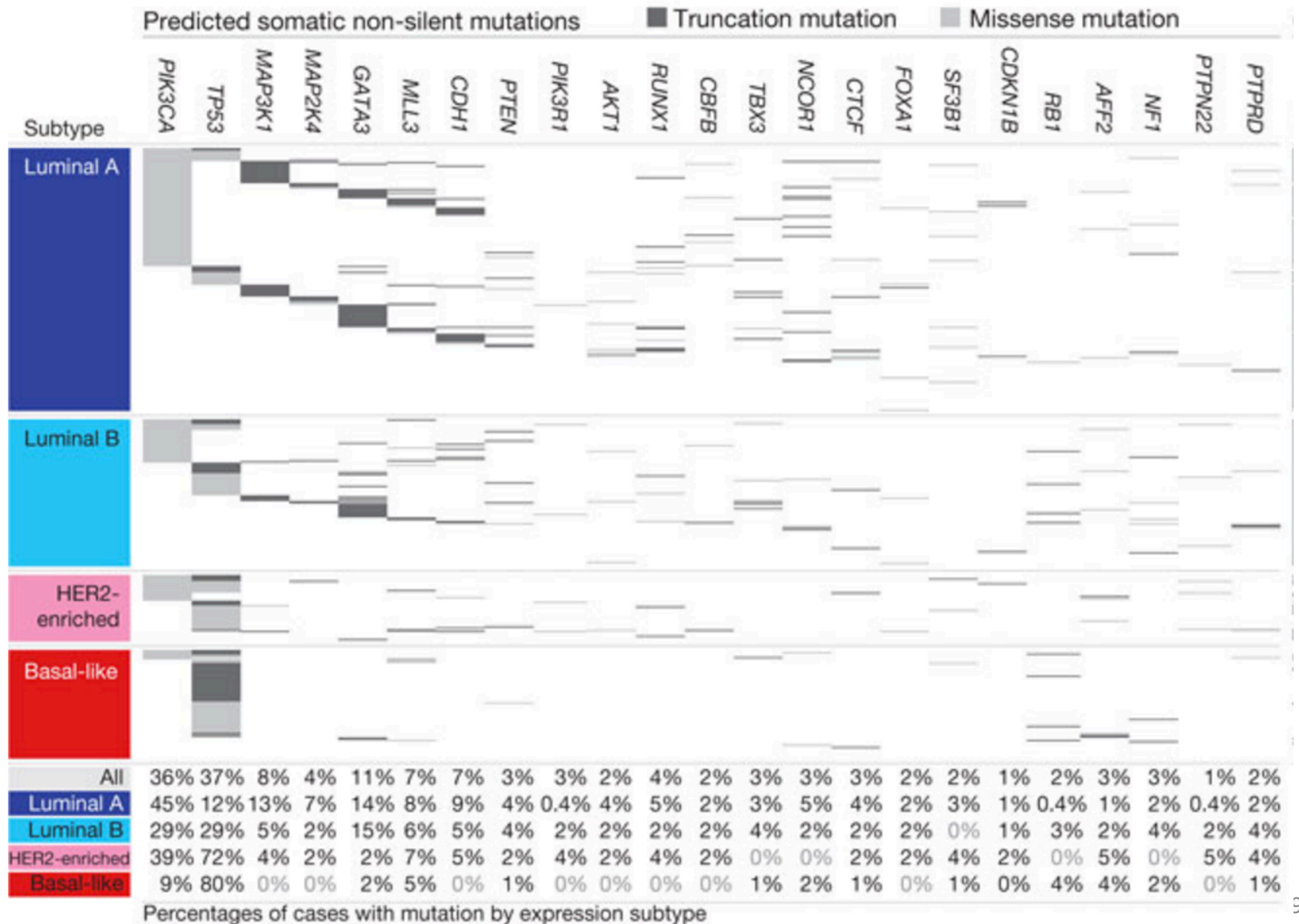
- From the output of MuTect:
  - remove dbSNP
  - keep NOVEL
  - keep COSMIC (COSMIC; dbSNP&COSMIC)

```
86 COSMIC
106567346 DBSNP
822 DBSNP+COSMIC
15913363 NOVEL
```

- remove “common” (estimated allele frequency >1%) variants from 1000G
  - 521,743 variants be filtered in this step
- Final calls: 15,392,528 variants
- Annotated by FunSeq2
  - TP53: Altered in 3/23 (13.04%) samples



# 10 most significantly mutated genes from 800 WXS analysis on Nature



# Mutation Rate under new fileters

Gene*	IBC	Non-IBC	PCAWG
PIK3CA	1/20 (5%)	2/23 (8.70%)	49/198 (24.75%)
<b>TP53</b>	<b>11/20 (55%)</b>	<b>3/23 (13.04%)</b>	<b>71/198 (35.86%)</b>
MAP3K1	0	0	6/198 (3.03%)
MAP2K4	0	0	2/198 (1.01%)
GATA3	0	0	3/198 (1.52%)
MLL3	0	0	0
CDH1	0	0	0
PTEN	0	0	6/198 (3.03%)
PIK3R1	0	1/23 (4.35%)	1/198 (0.51%)
RUNX1	1/20 (5%)	0	0

\* 10 most significantly mutated genes from 800 WXS analysis on Nature

# Top mutated genes in each study

gene_list	freq	rate
IBC		
TP53	11	0.55
DPCR1	7	0.35
FLG2	5	0.25
FKSG63	4	0.2
ZNF57	3	0.15
GRIN2A	3	0.15
TTN	3	0.15
FAM47C	3	0.15
RP11-1055B8.7	3	0.15
AKT1	3	0.15

Non-IBC		
AHCYL1	6	0.26086957
TPM3	6	0.26086957
MAML2	6	0.26086957
KRT18	6	0.26086957
RRBP1	6	0.26086957
FAM136A	6	0.26086957
FRG1B	6	0.26086957
UTP3	6	0.26086957
HLA-DRB1	6	0.26086957
FRMPD3	6	0.26086957

PCAWG		
TP53	71	0.35858586
PIK3CA	49	0.24747475
TTN	36	0.18181818
MUC16	18	0.09090909
USH2A	12	0.06060606
SYNE1	11	0.05555556
XIRP2	11	0.05555556
FSIP2	11	0.05555556
LRP2	11	0.05555556
PLEC	11	0.05555556