NEXT GENERATION SEQUENCING: FIRST RESULTS IN BREAST CANCER

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Outline

- New genes
- New mutation signatures
- Subclonal diversification

ARTICLE

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Whole-genome analysis informs breast cancer response to aromatase inhibition

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LETTER

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The landscape of cancer genes and mutational processes in breast cancer

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ARTICLE

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Comprehensive molecular portraits of human breast tumours

The Cancer Genome Atlas Network*

LETTER

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The clonal and mutational evolution spectrum of primary triple-negative breast cancers

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ARTICLE

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The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups

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LETTER

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Sequence analysis of mutations and translocations across breast cancer subtypes

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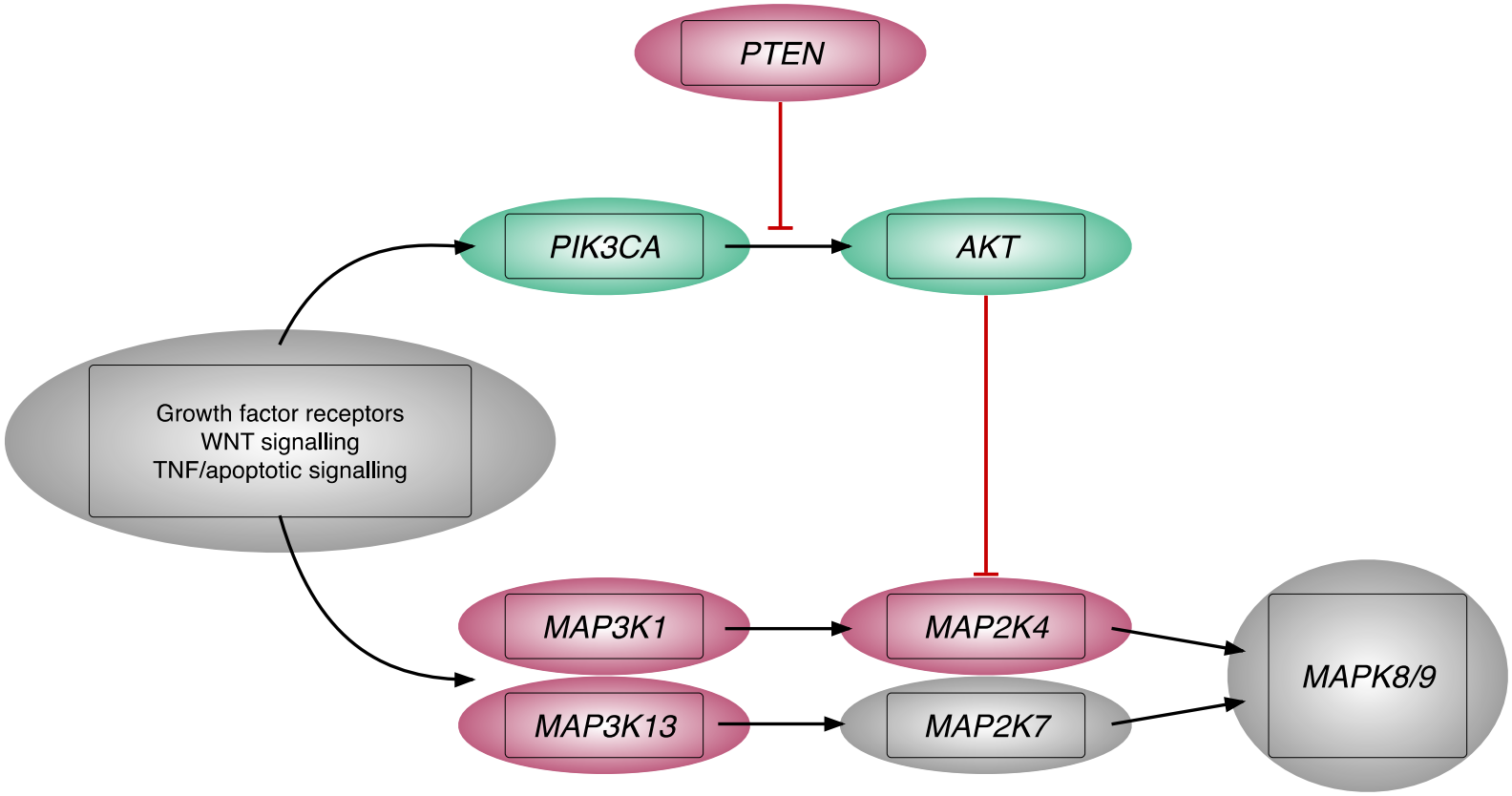
Recurrent breast cancer genes – 2011

Gene	Frequency
PIK3CA	35%
TP53	35%
GATA3	11%
MAP3K1	8%
CDH1	7%
PTEN	3%
AKT1	2%
RB1	2%
BRCA1 & BRCA2	3%

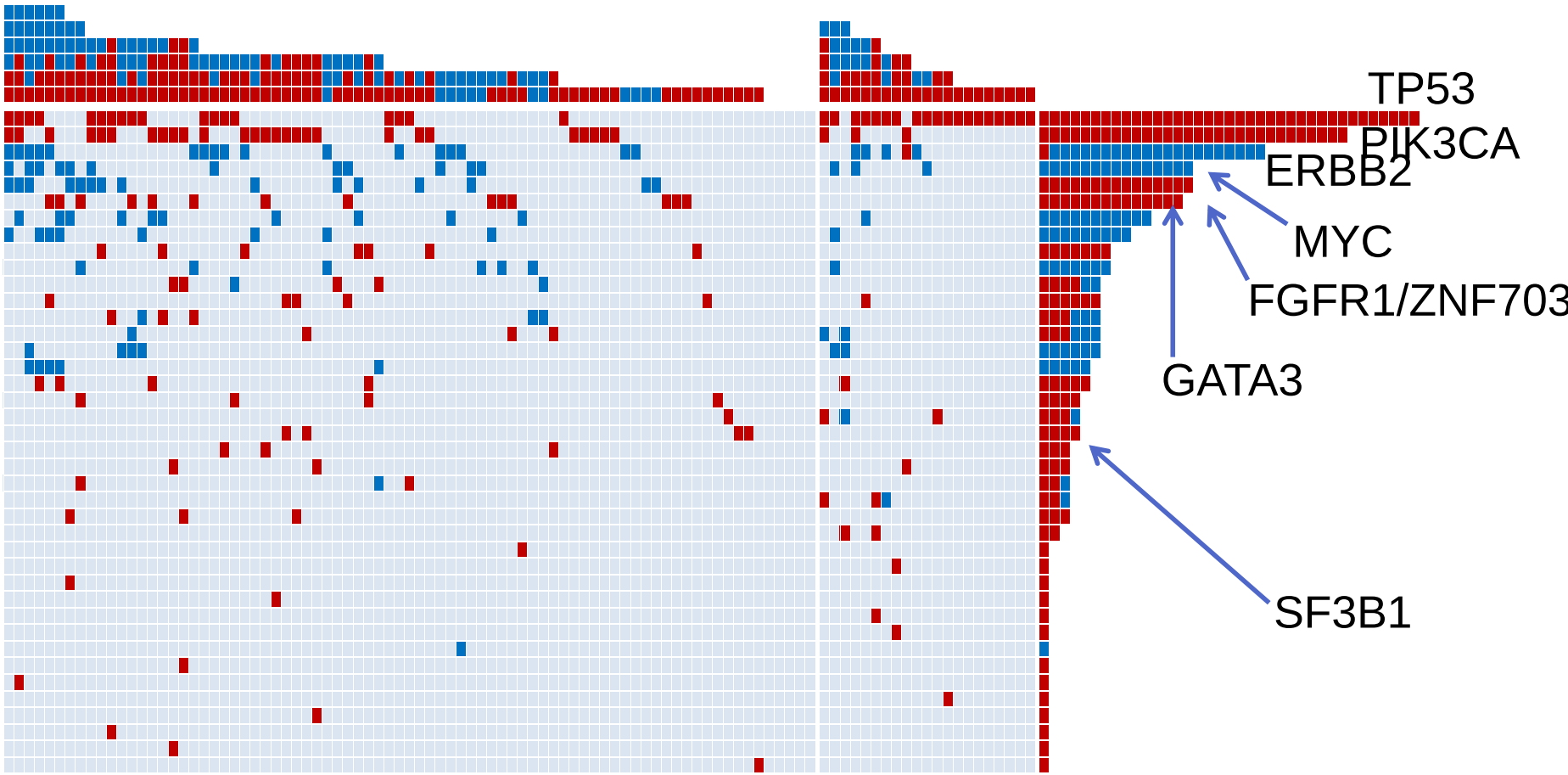
Recurrent breast cancer genes – 2012

Gene	Frequency	Gene	Number of studies
PIK3CA	35%	MAP2K4	3
TP53	35%	TBX3	2
GATA3	11%	RUNX1	3
MAP3K1	8%	CBFB	3
CDH1	7%	PIK3R1	1
PTEN	3%	SF3B1	3
AKT1	2%	NF1	1
RB1	2%	PTPN22	1
BRCA1 & BRCA2	3%	CCND3	1
MLL3	3	CDKN1B	3
CASP8	1	MAP3K13	1
SMARCD1	1	NCOR1	1

JUN-kinase pathway in breast cancer



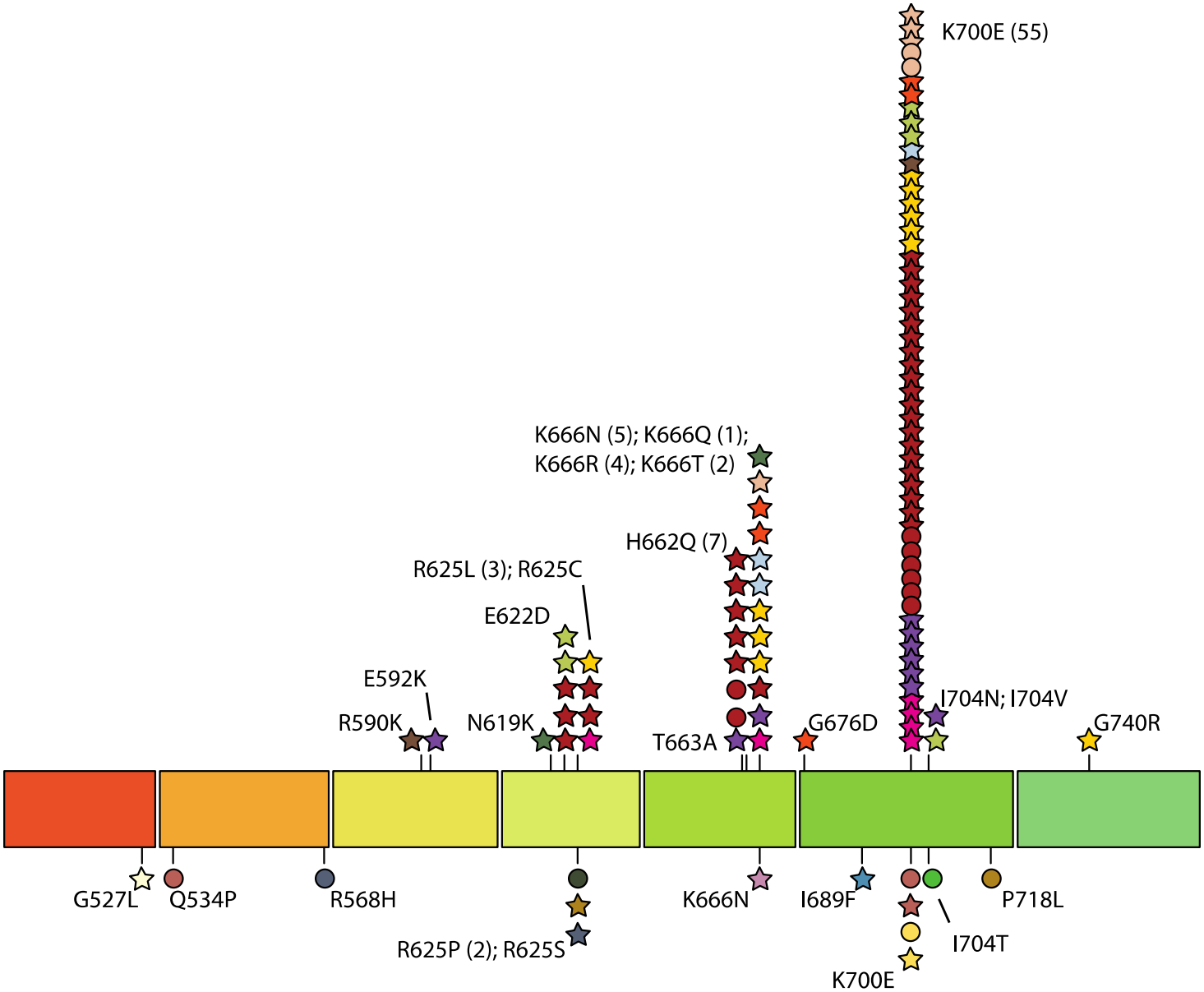
Distribution of oncogenic changes



ER-positive patients ER-negative patients

SF3B1 mutations

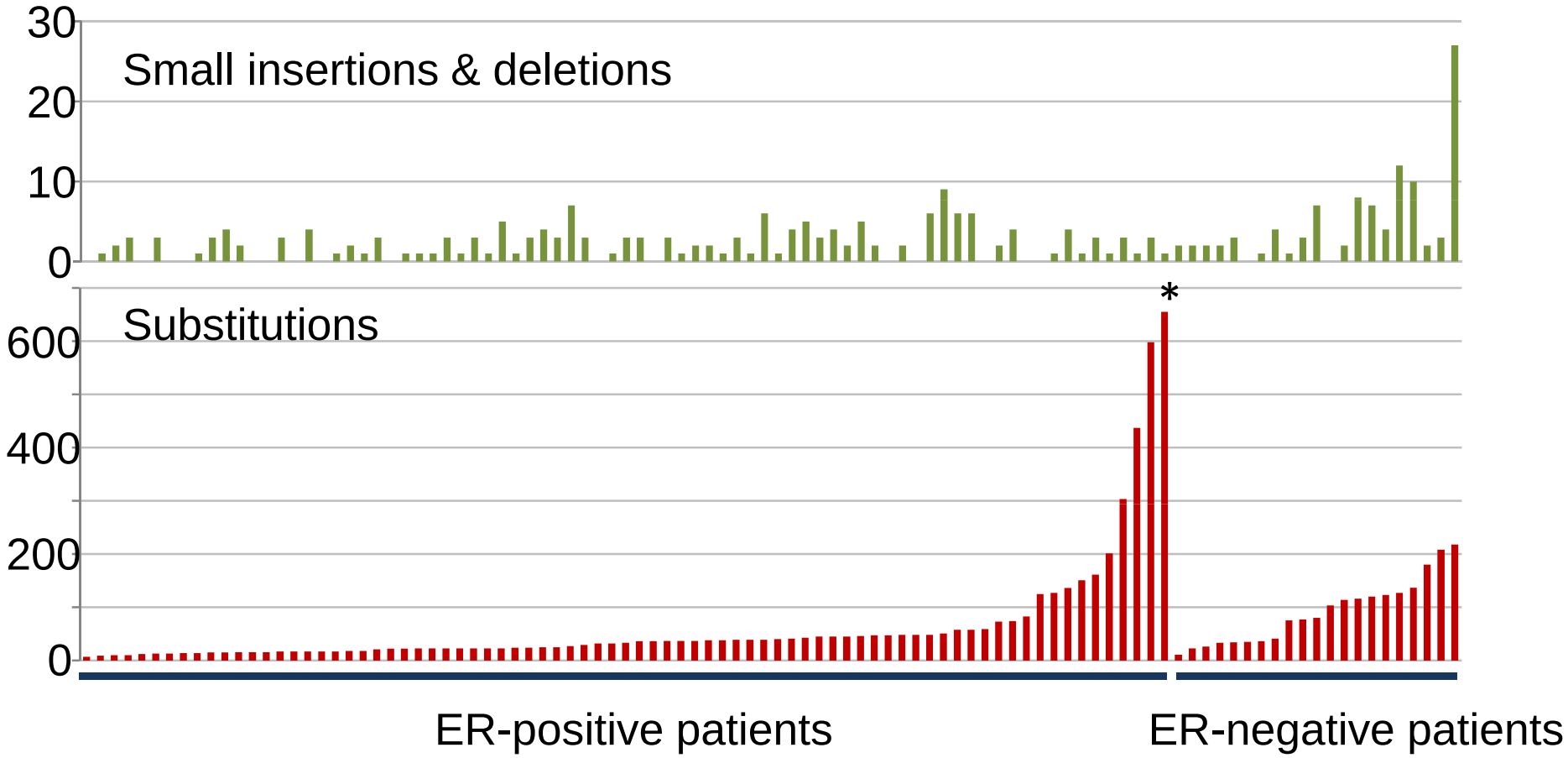
Papaemmanuil et al, NEJM 2011



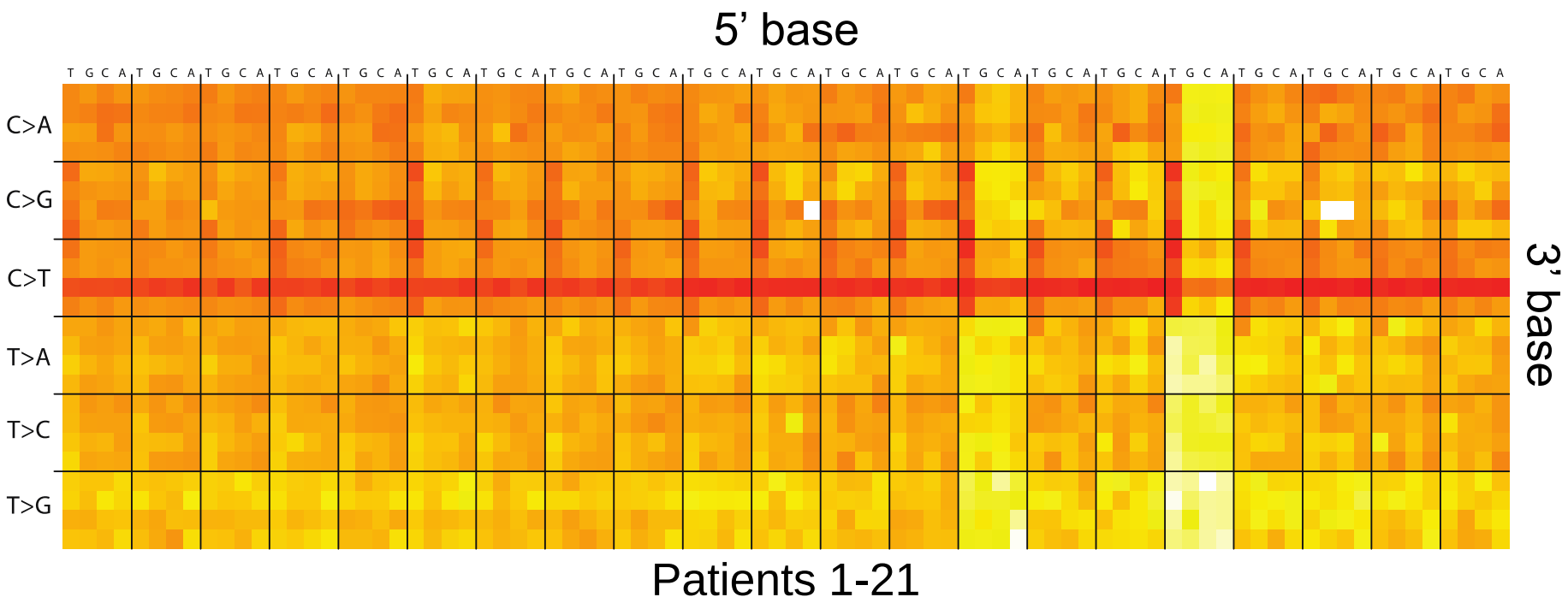
Outline

- New genes
- New mutation signatures
- Subclonal diversification

Frequency of coding mutations

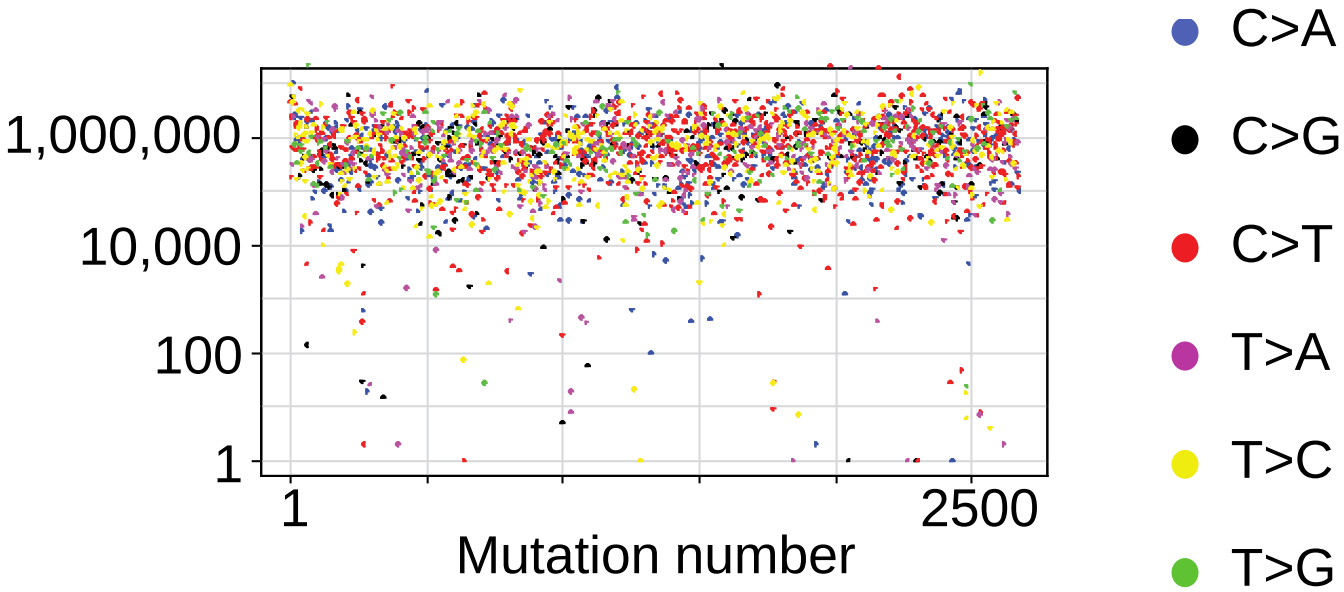


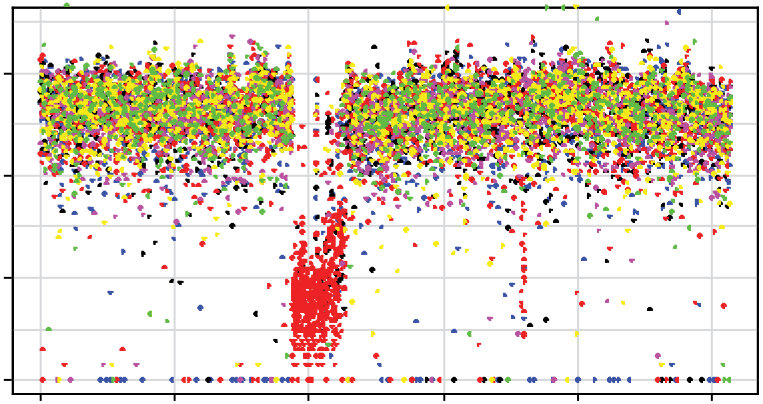
Mutation patterns breast cancer genomes

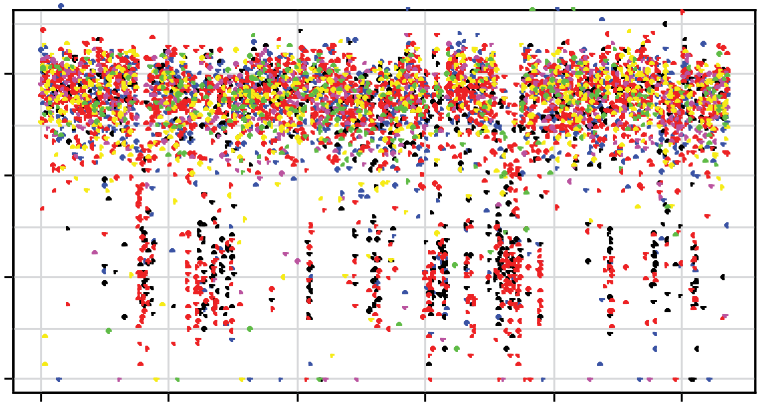


Nik-Zainal et al, Cell 2012; 979-993
Nik-Zainal et al, Cell 2012; 994-1007

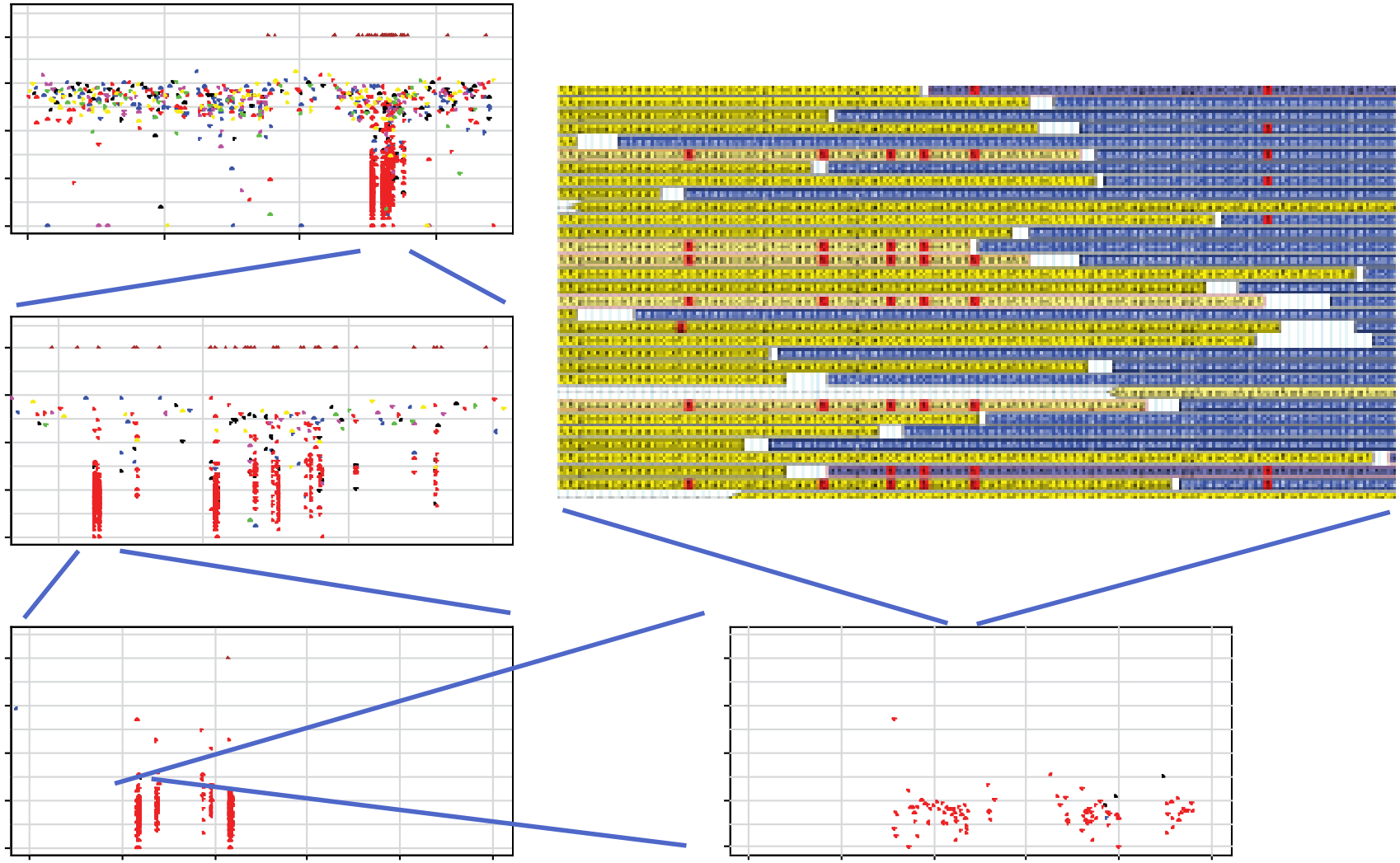
Clustering of mutations



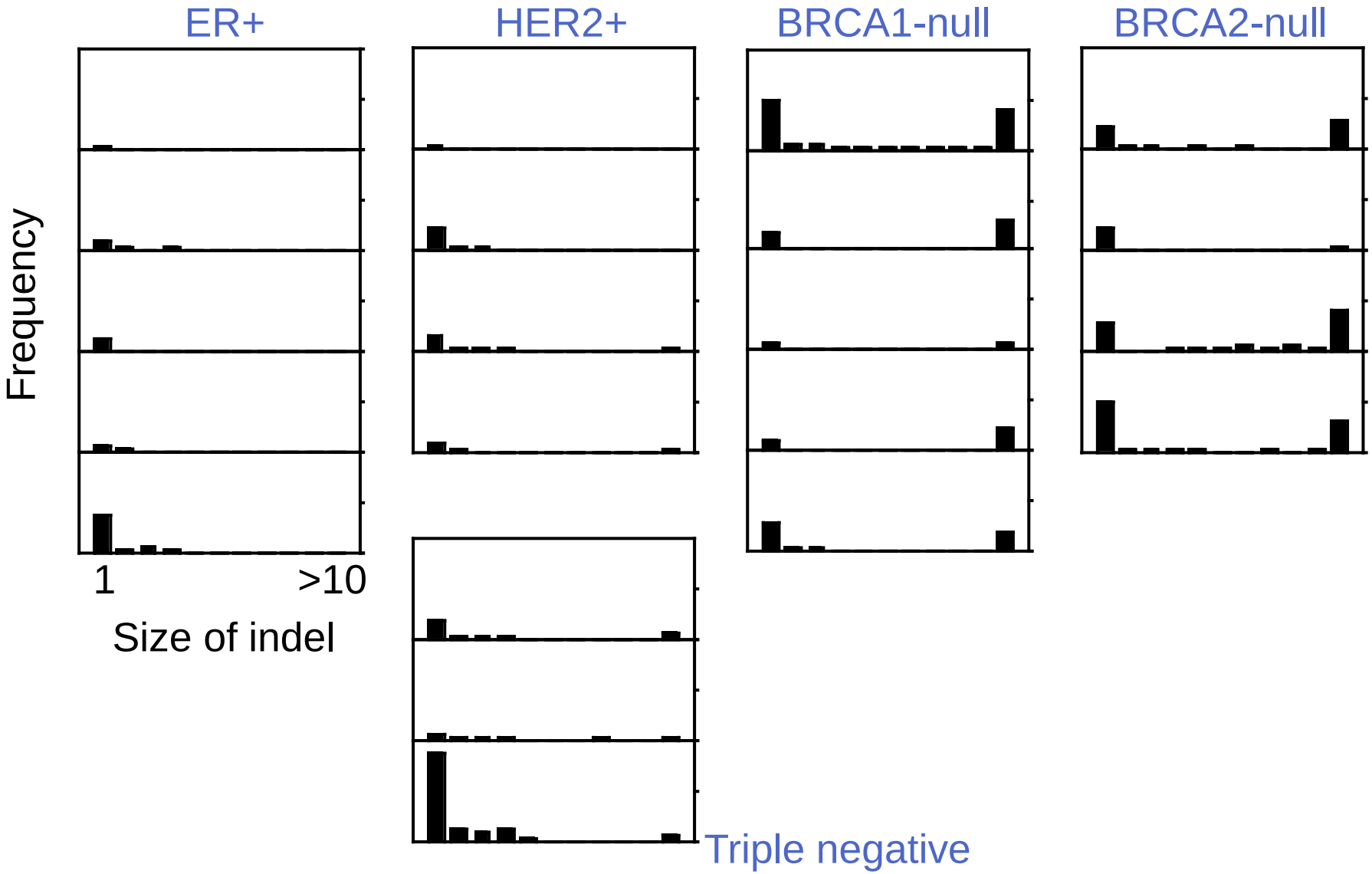




Clustering of mutations



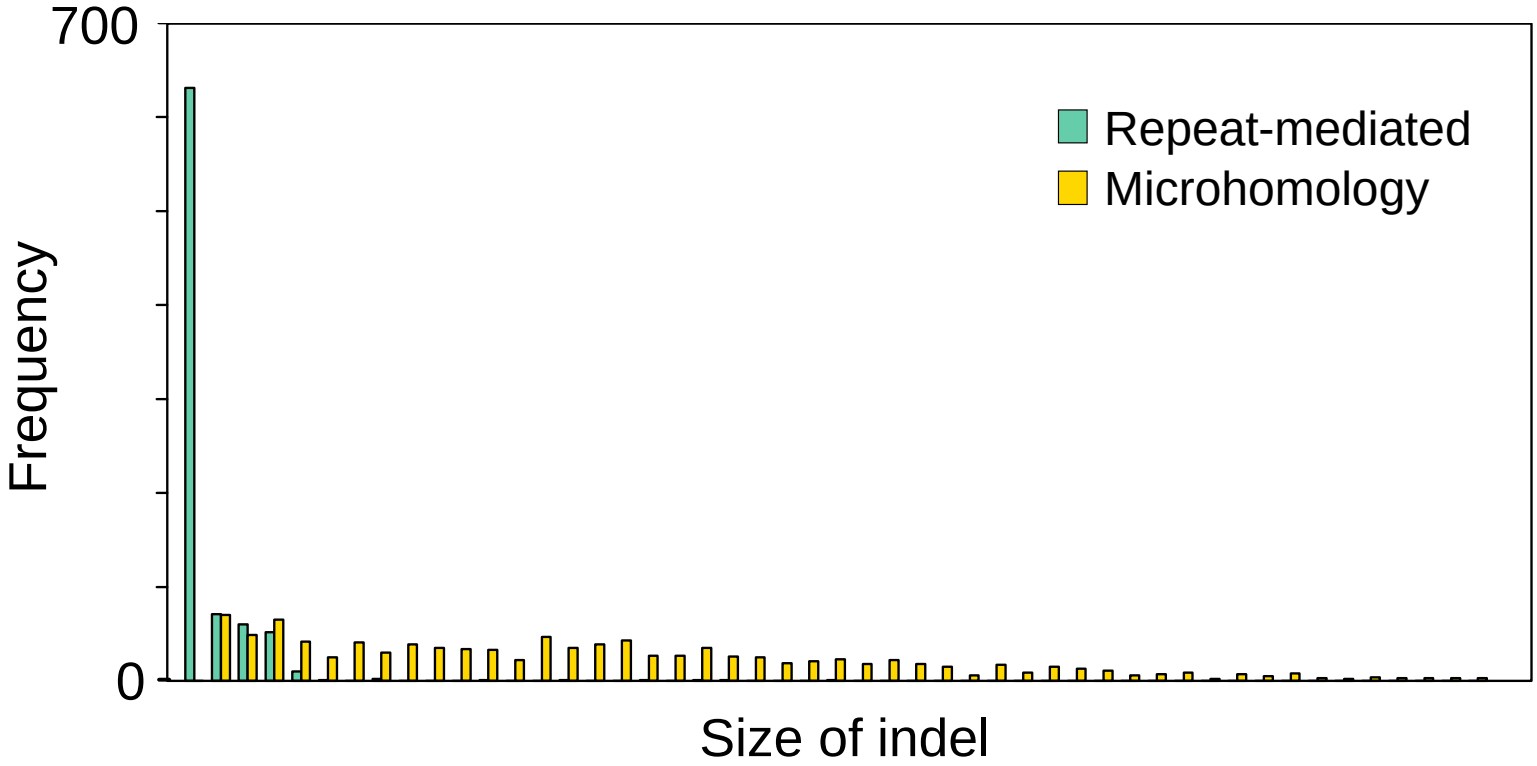
Indels


ER+
HER2+
BRCA1-null
BRCA2-null
Frequency
1
>10
Size of indel
Triple negative

Indel signature in BRCA-null tumours

- Microhomology (feature of NHEJ):

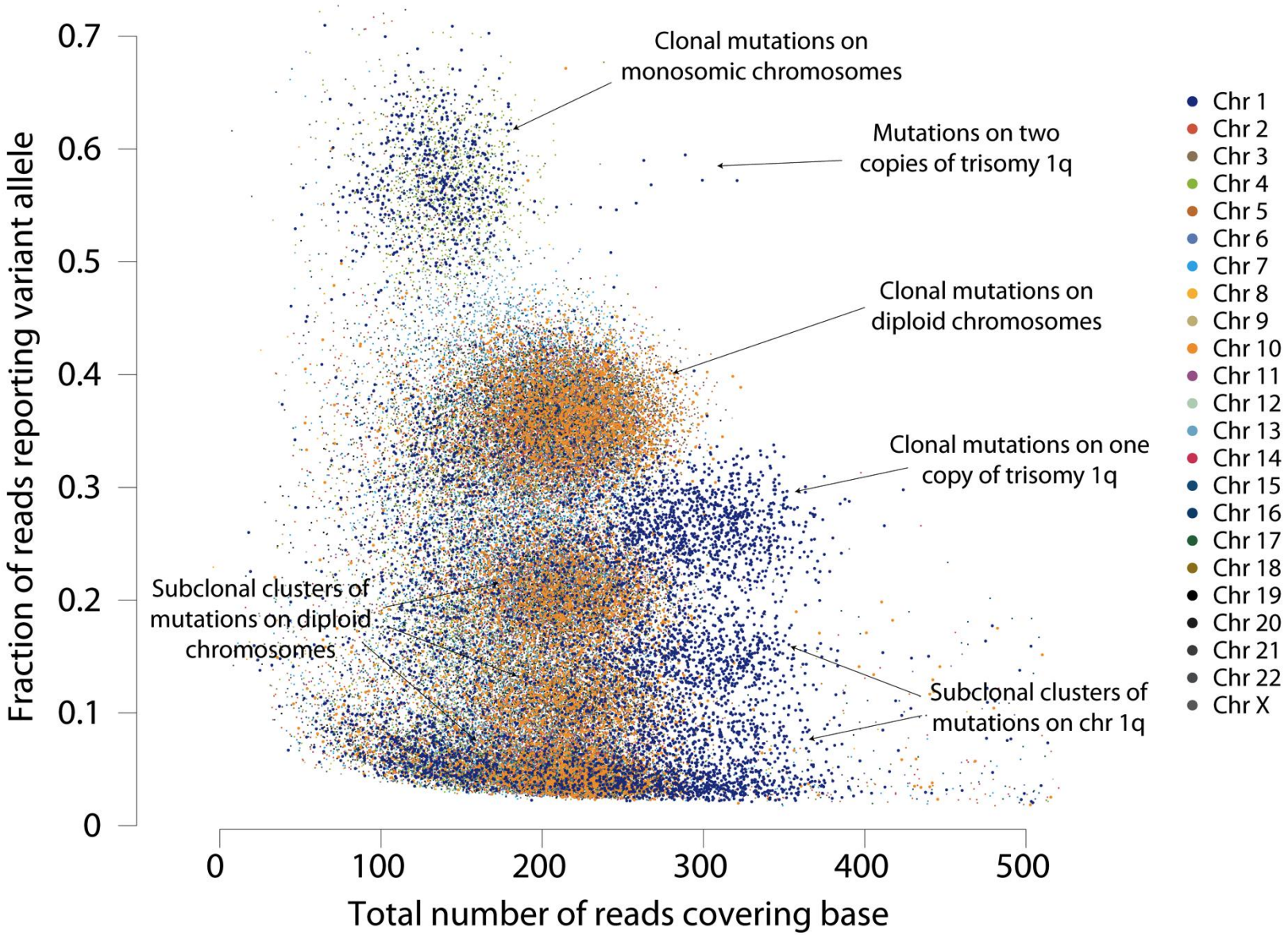
```
ACCTGGCATTGTGCACGTTGACAGTAGCTGCACCCAGTCGCTGGGCA
ACCTGGCATTGTGCAC---------------CCAGTCGCTGGGCA
```



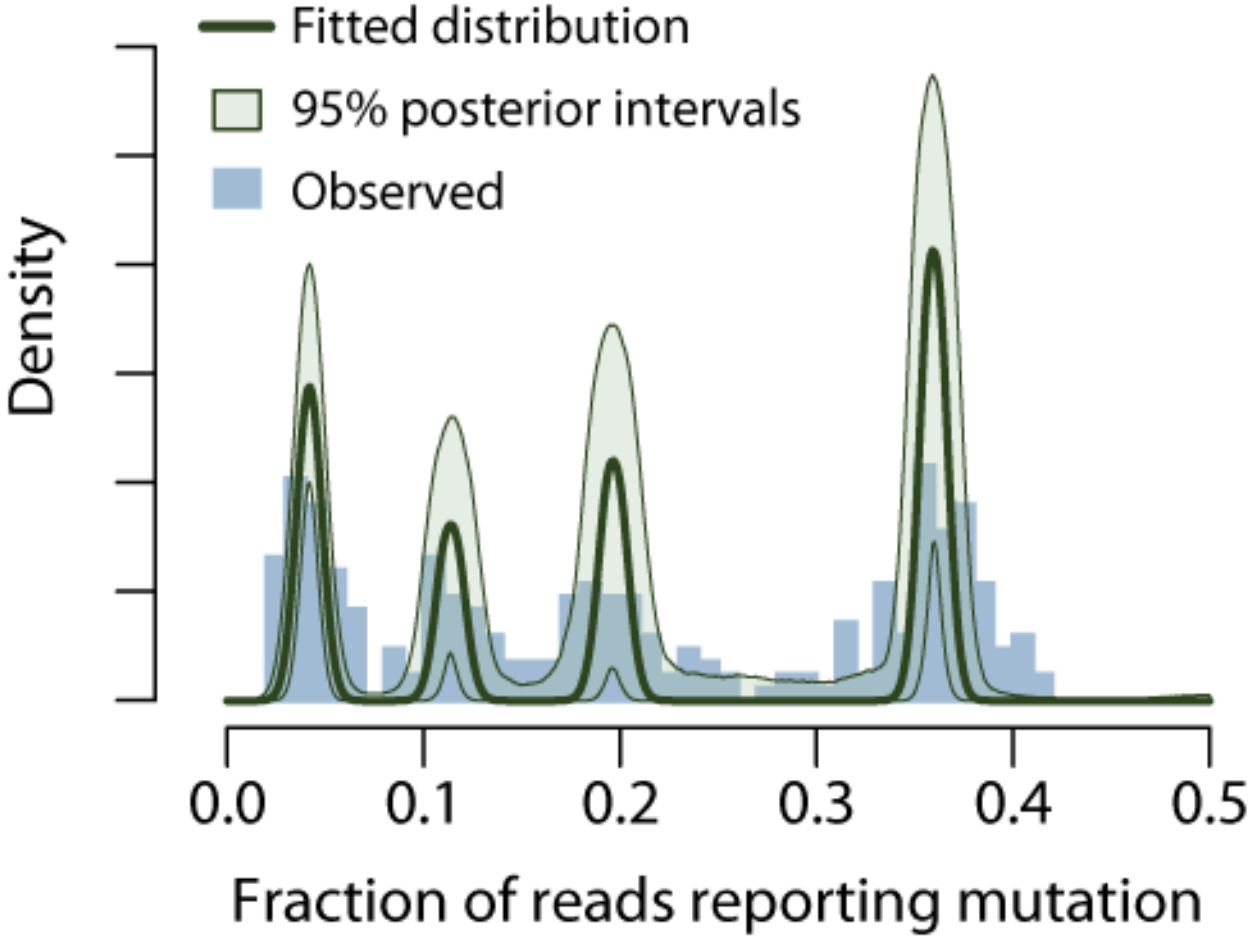
Outline

- New genes
- New mutation signatures
- Subclonal diversification

Point mutations

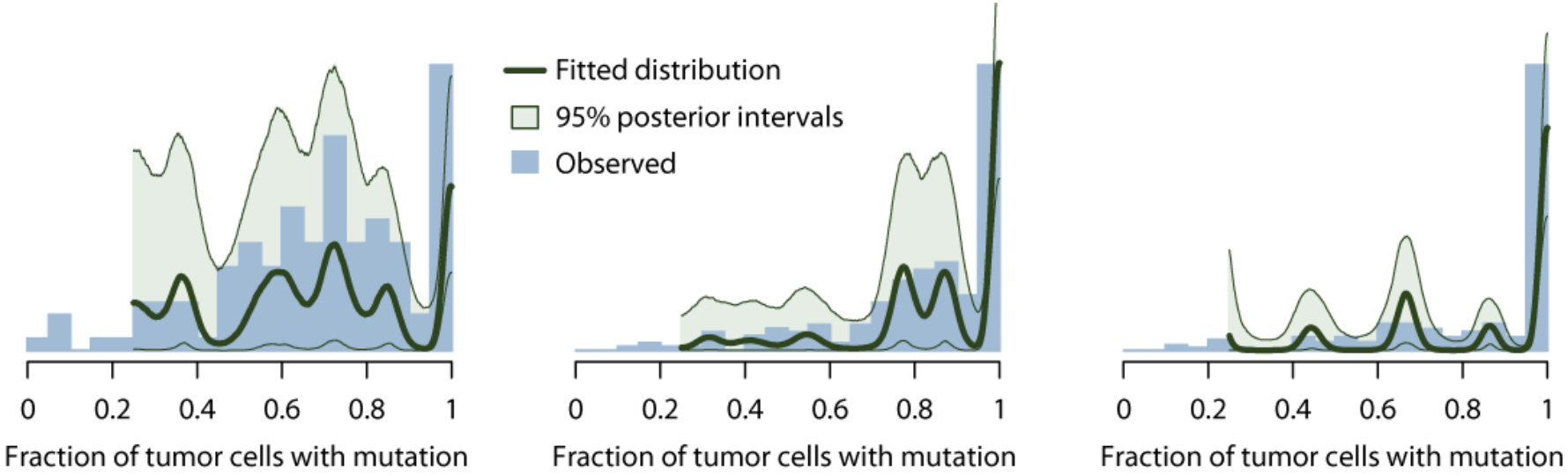


Clusters of subclonal mutations

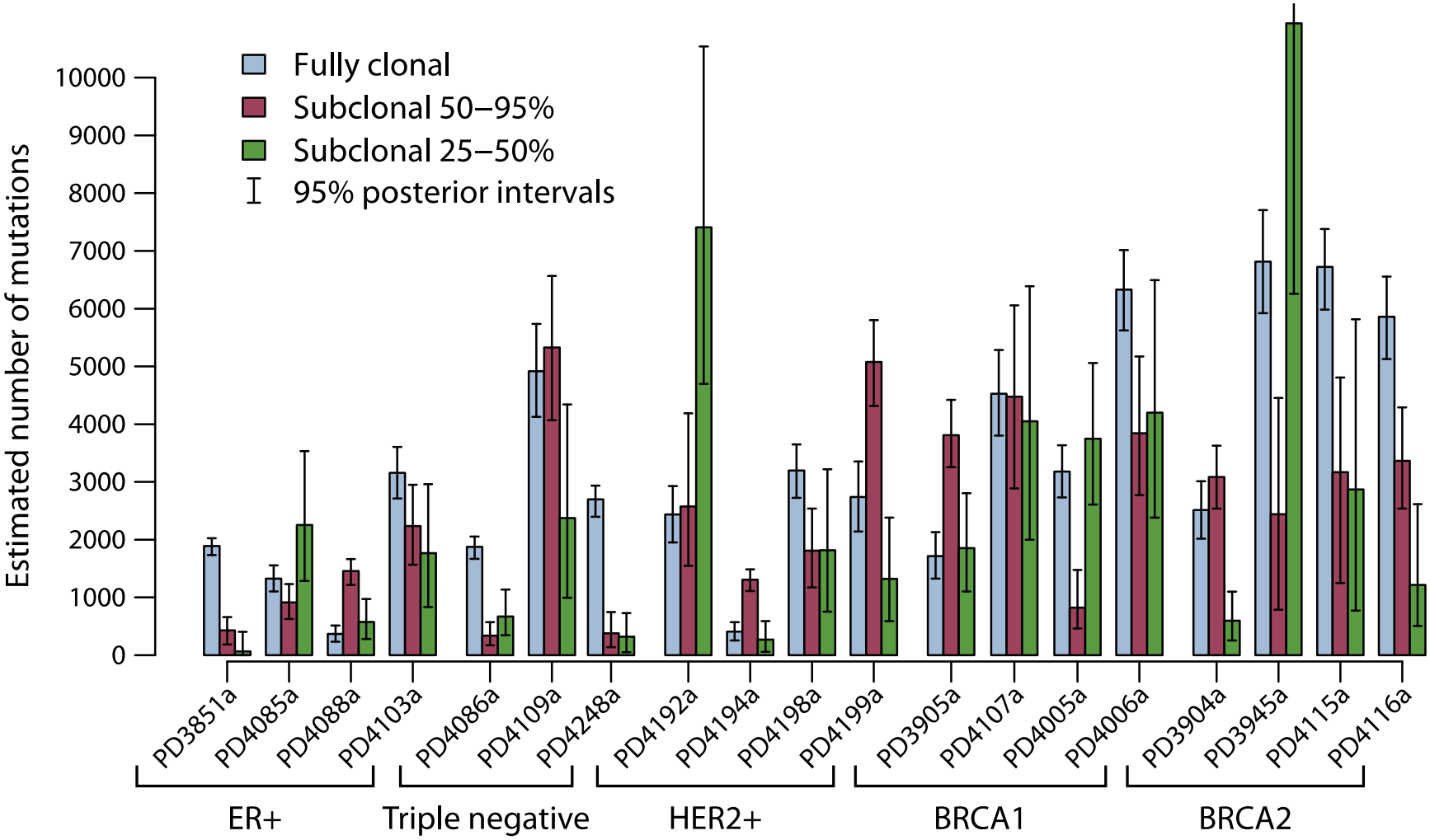


Subclonal point mutations

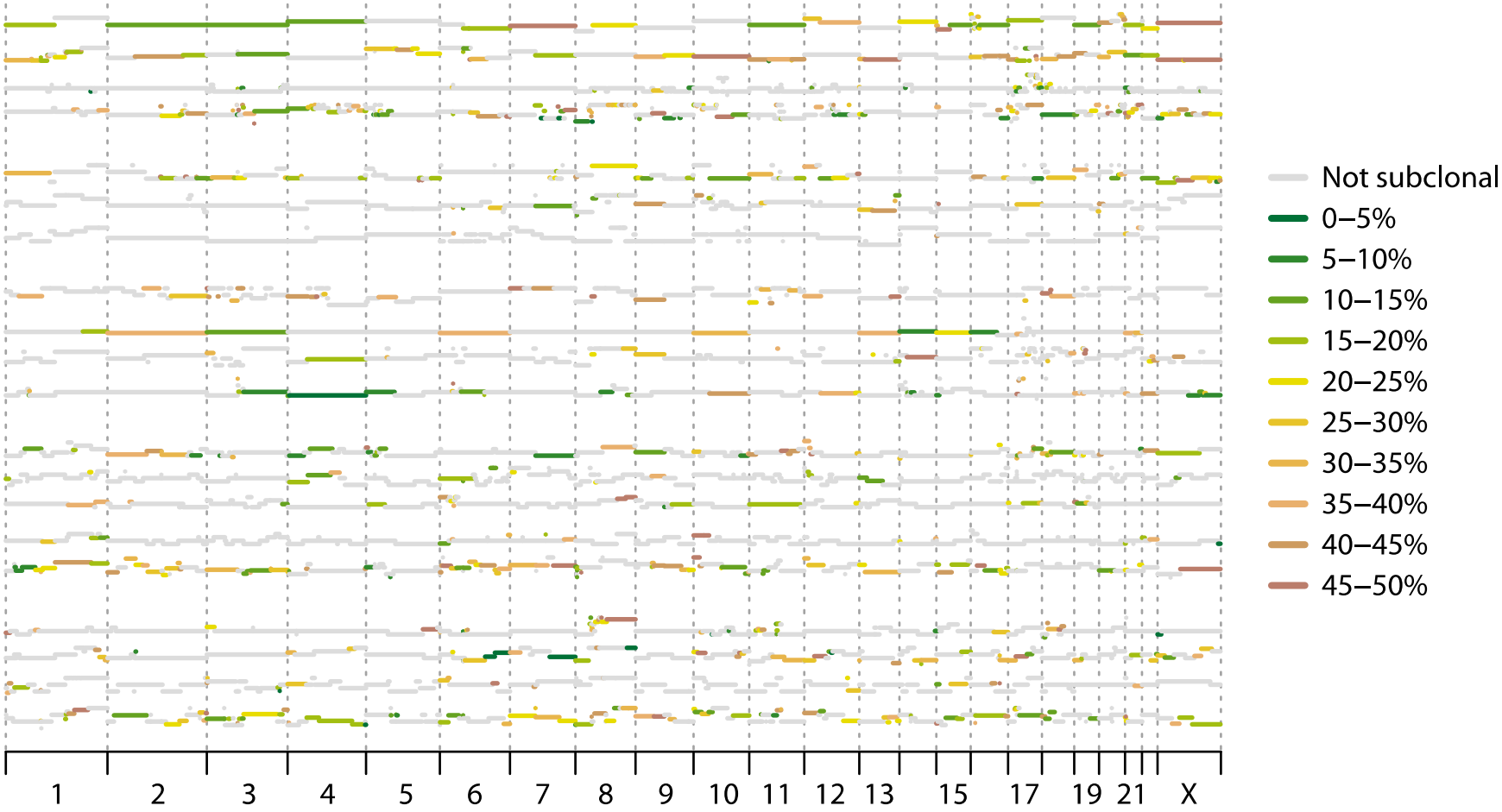
- Estimated by deep sequencing of PCR product across mutated base



Subclonal point mutations



Subclonal structural variation in 20 breast cancers



Summary

- Large number of new breast cancer genes
  - JUN-kinase pathway target for inactivation
  - Frequent involvement of genes implicated in haematological cancers
- Many new mutation signatures
  - Evolve late in the development of breast cancer
  - Contribute 100s-1000s of mutations
- Extensive subclonal diversification
  - Both point mutations and large-scale copy number alterations
  - Likely to underpin heterogeneity of treatment response

Cancer Genome Project

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