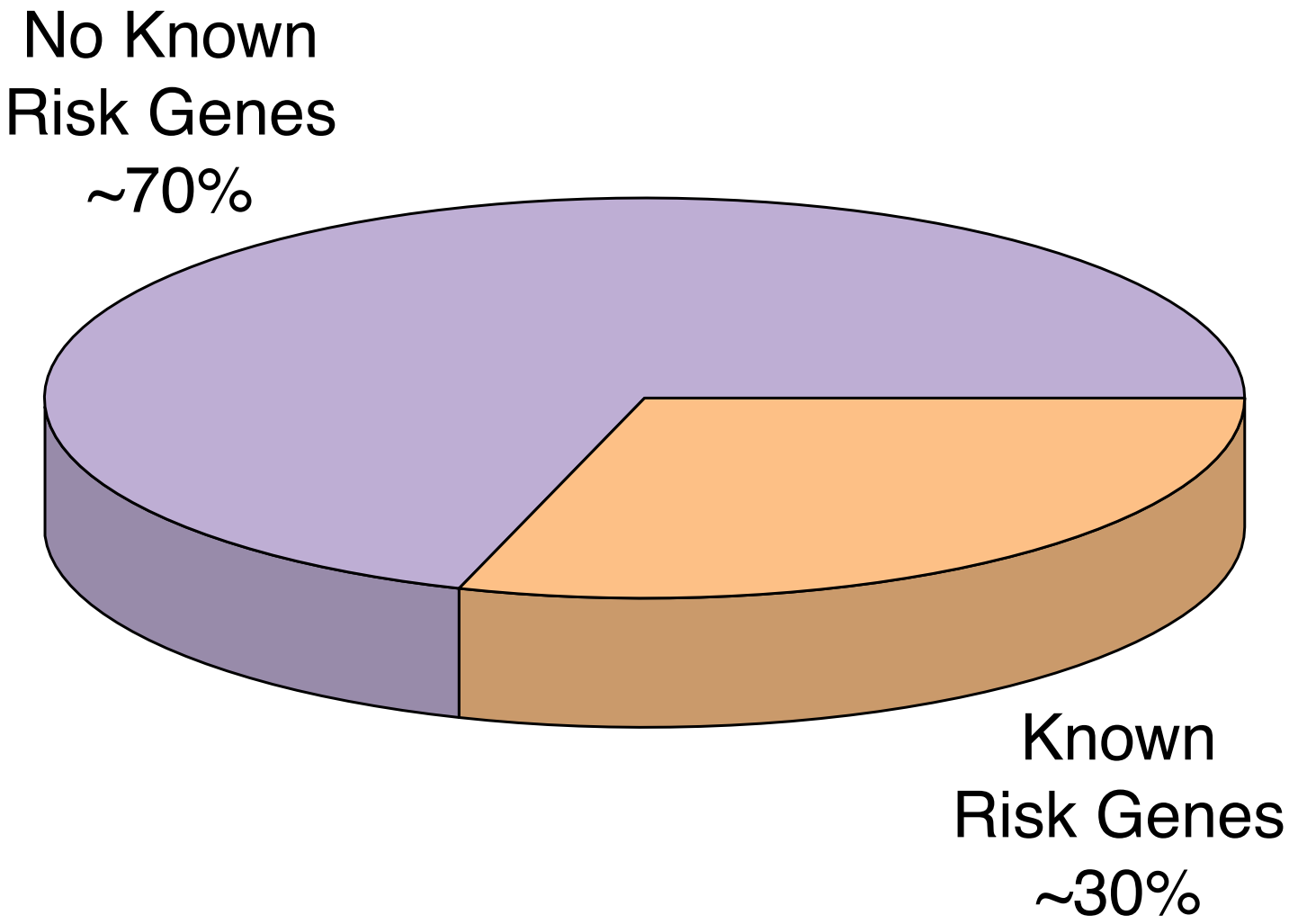
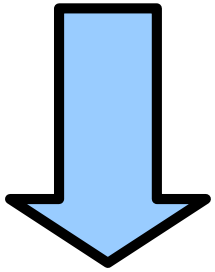
Familial Breast Cancer

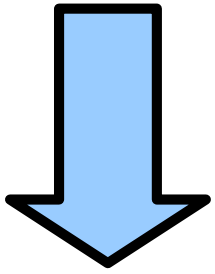


Stratton and Rahman, *Nature Genetics*, 2008

Exome-wide
DNA Variation



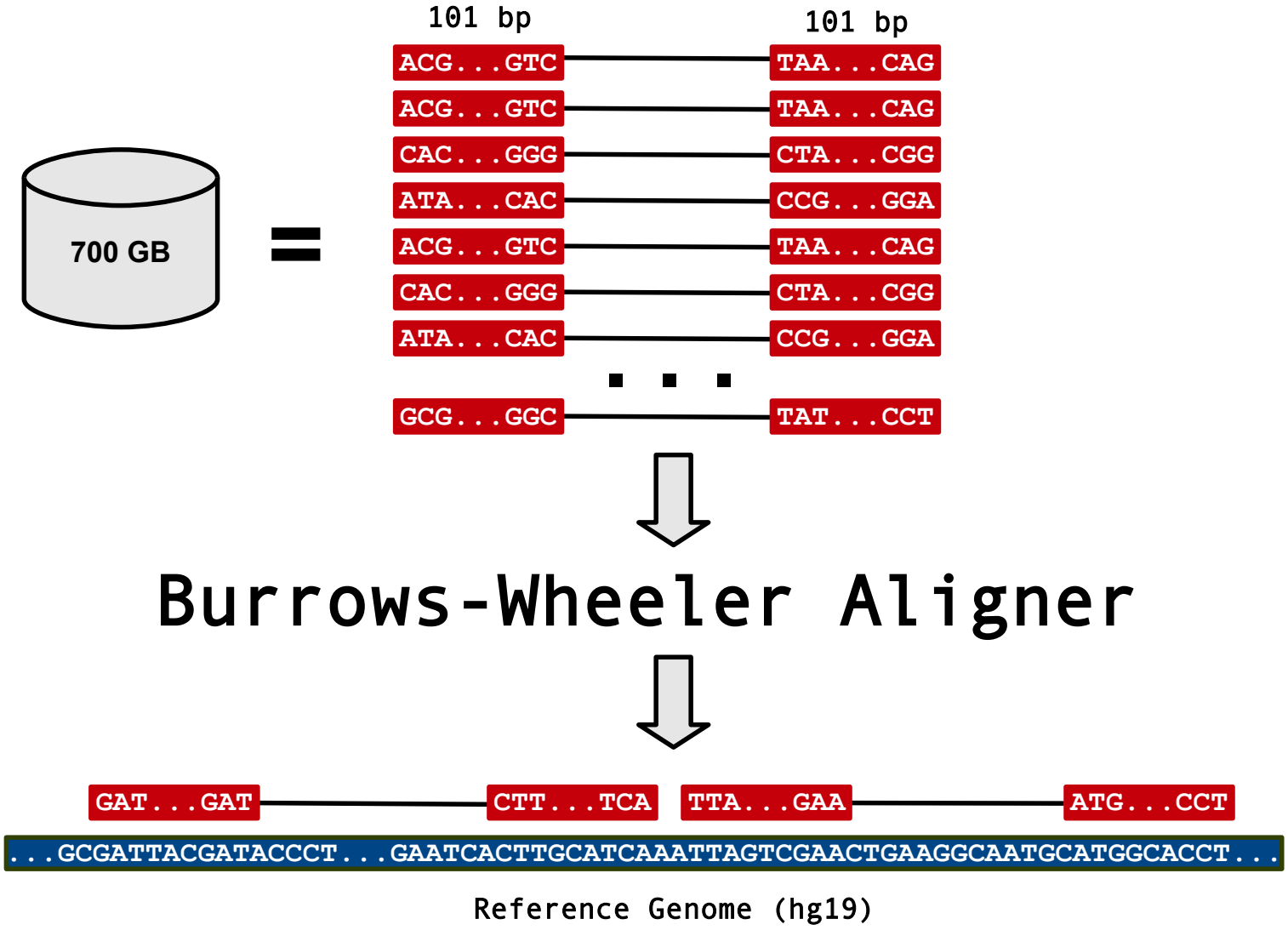
Impaired
Biological
Processes



Disease

Next Generation Sequencing

Read Mapping



Variant Calling

Single-Nucleotide Variant (SNV)

GATGACCCGGCCTTATGCAACTAGAT

GATGACCCGGCCATATGCAACTAGAT

Insertion Variant

TATGACCCGGCCTTATTACGCAACTAGAT

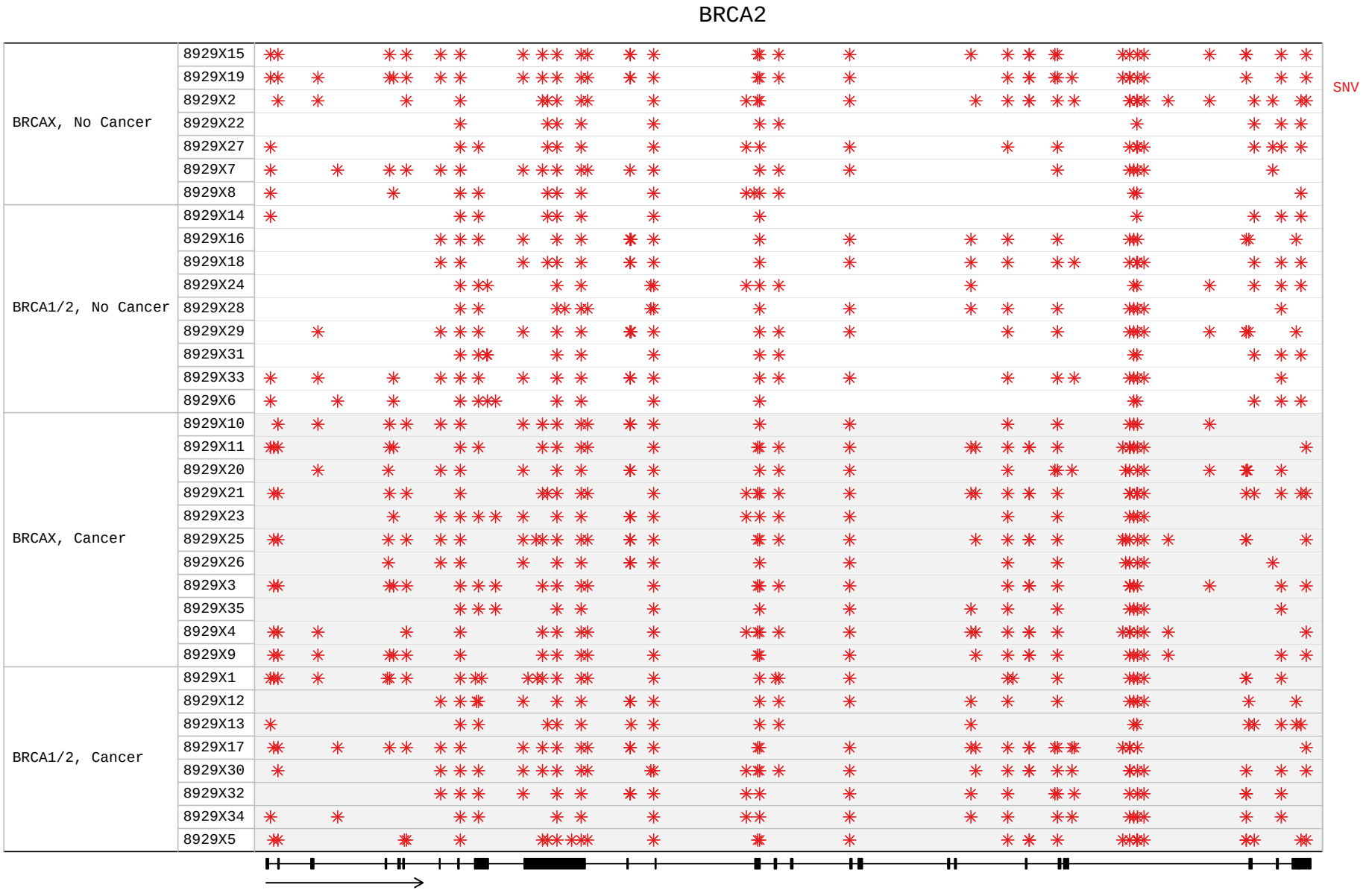
TATGACCCGGCCATAT---GCAACTAGAT

Deletion Variant

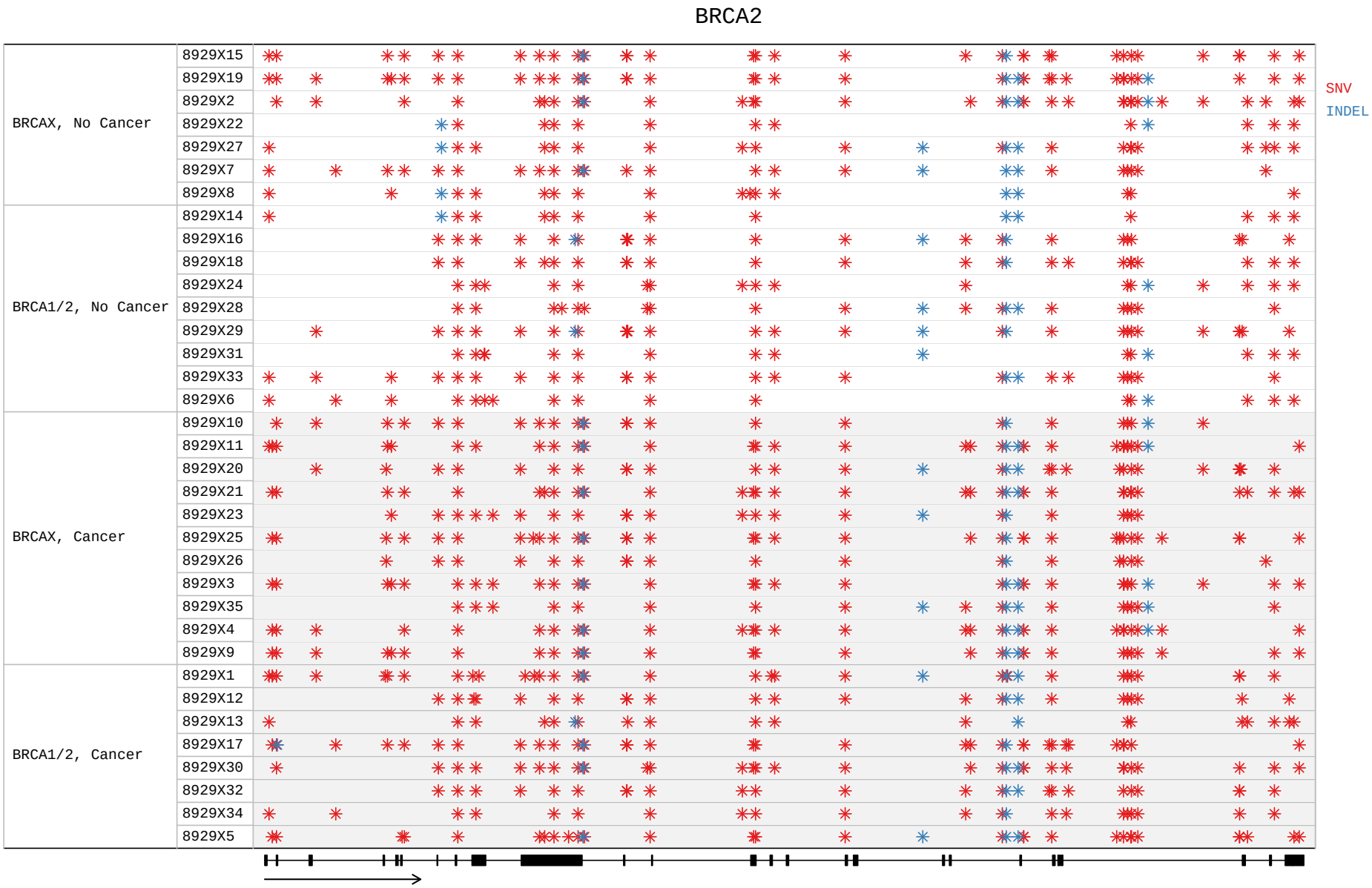
GATTA--ACCCGGCCTTATGCAACTAGAT

GATTATGACCCGGCCATATGCAACTAGAT

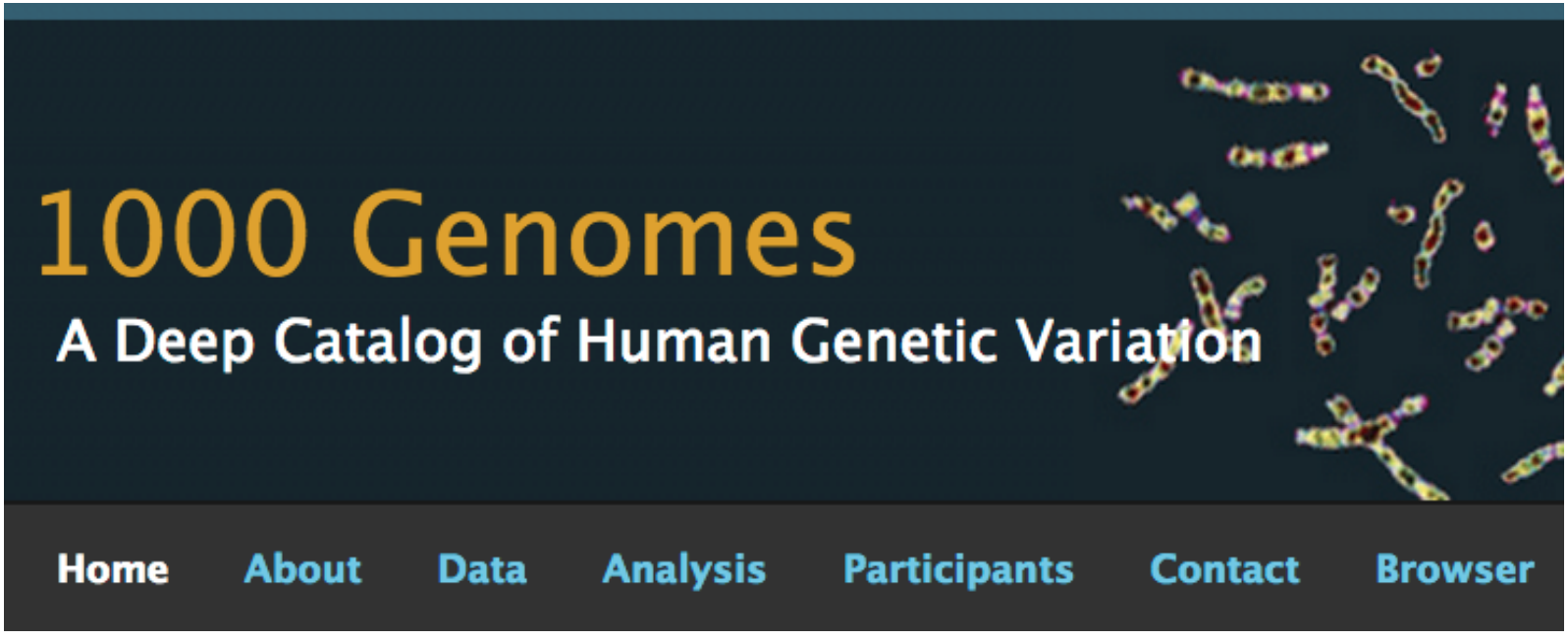
Single Nucleotide Variants - Initial Set

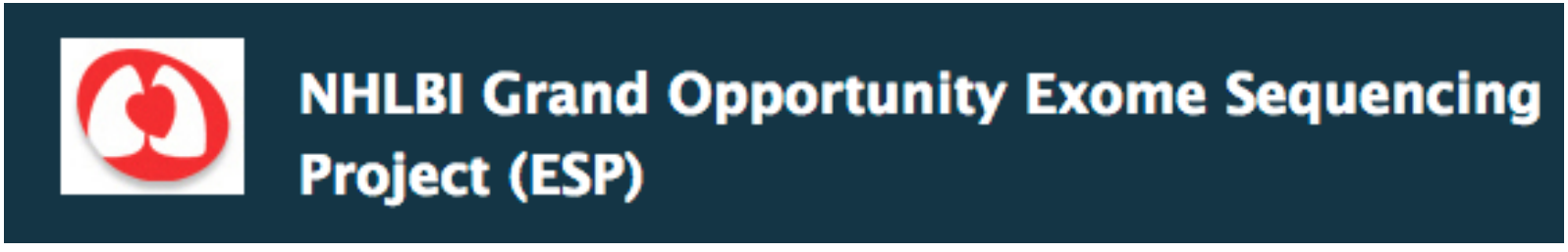


SNVs and Indels - Initial Set

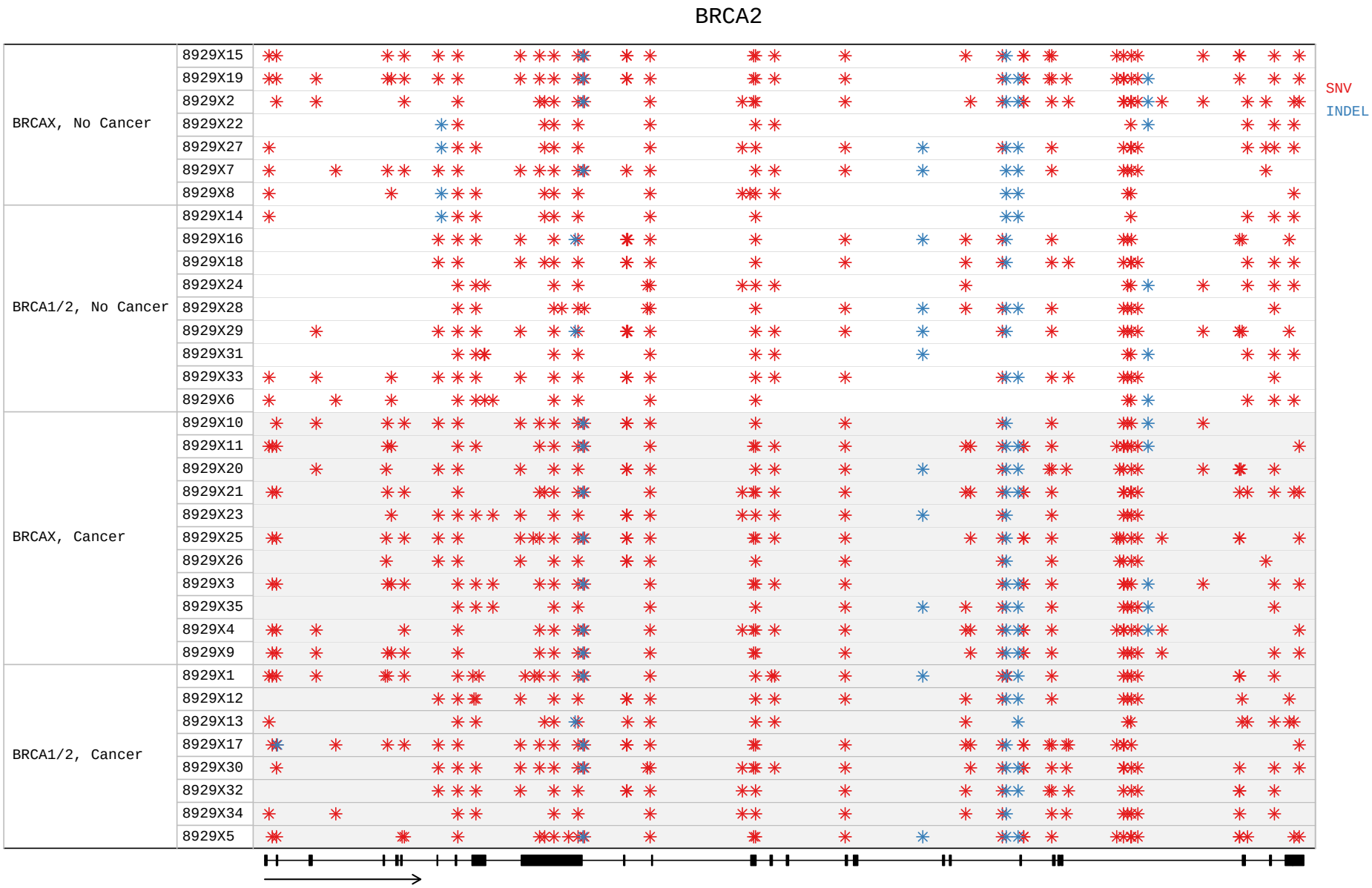


Publicly Available Resources

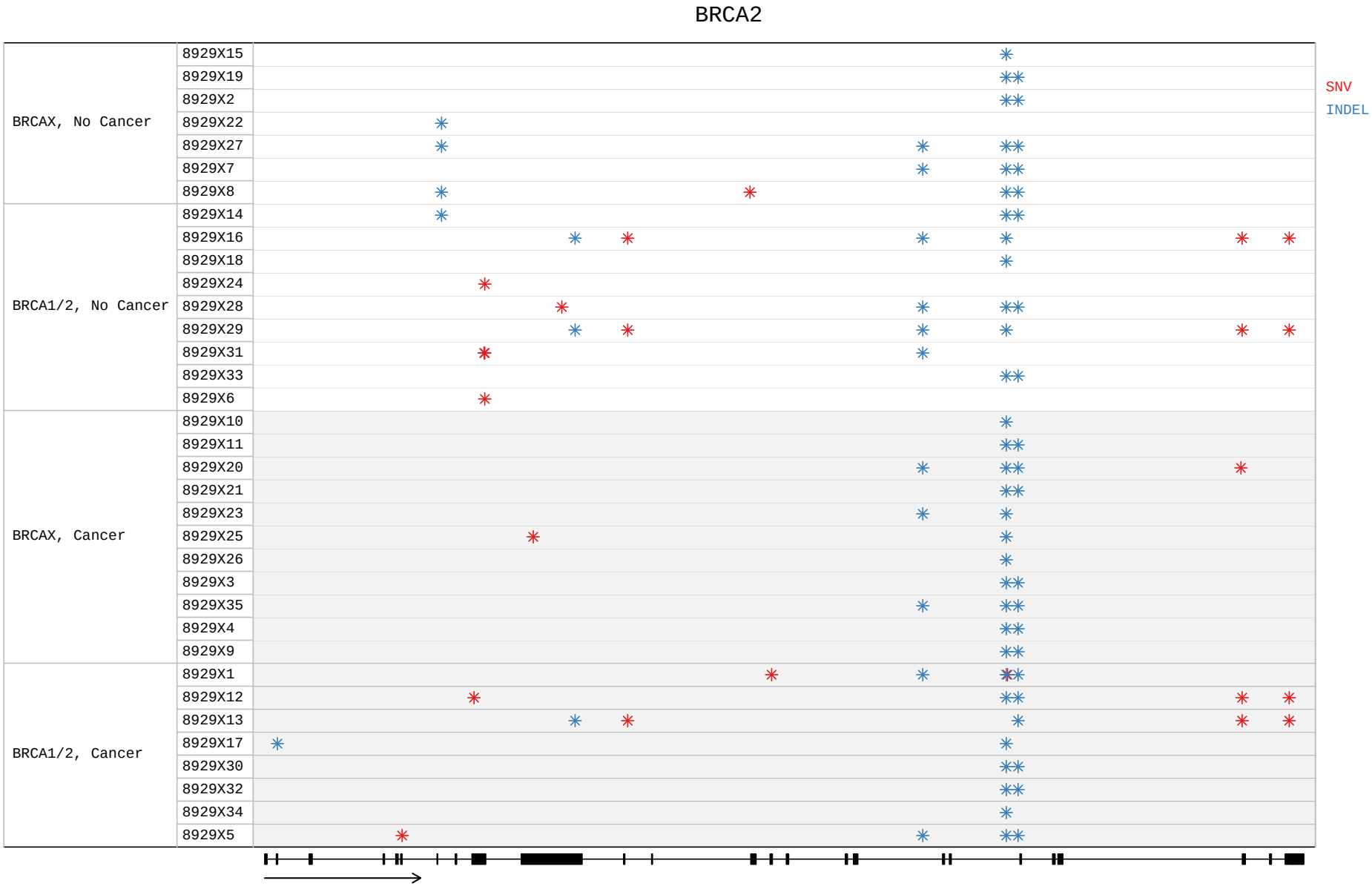




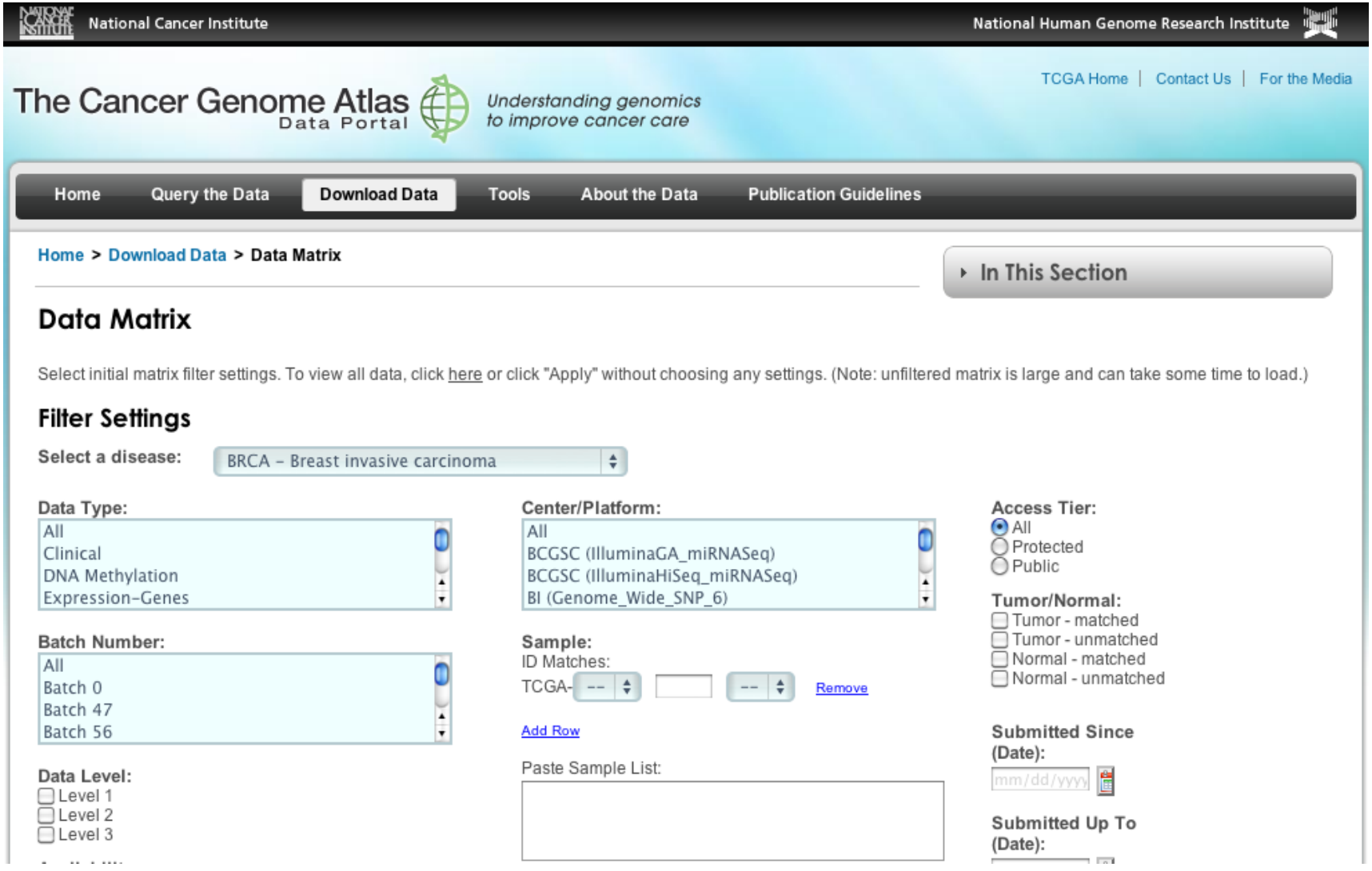
SNVs and Indels - Initial Set



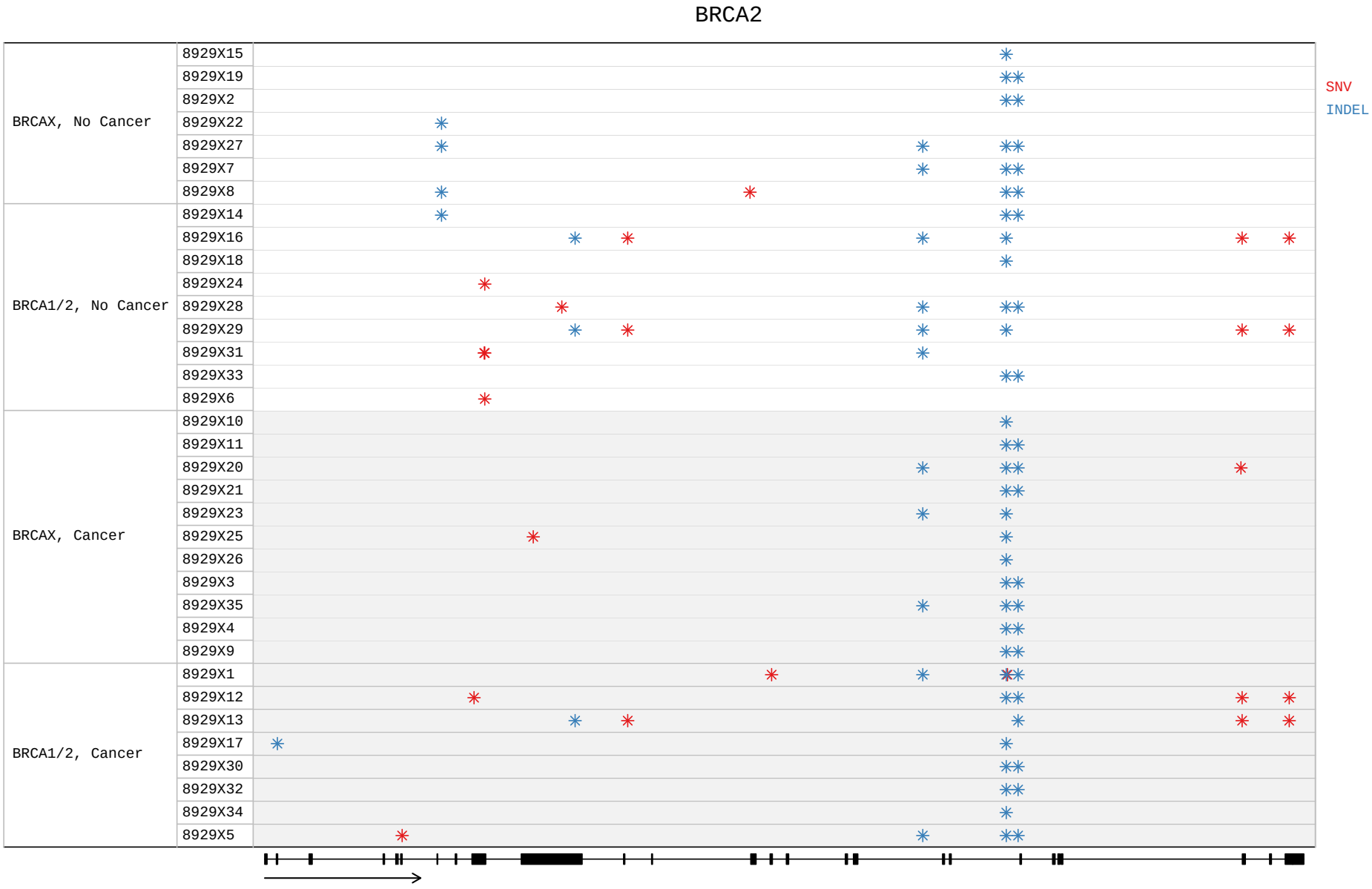
Minus 1000 Genomes and ESP Common Variants



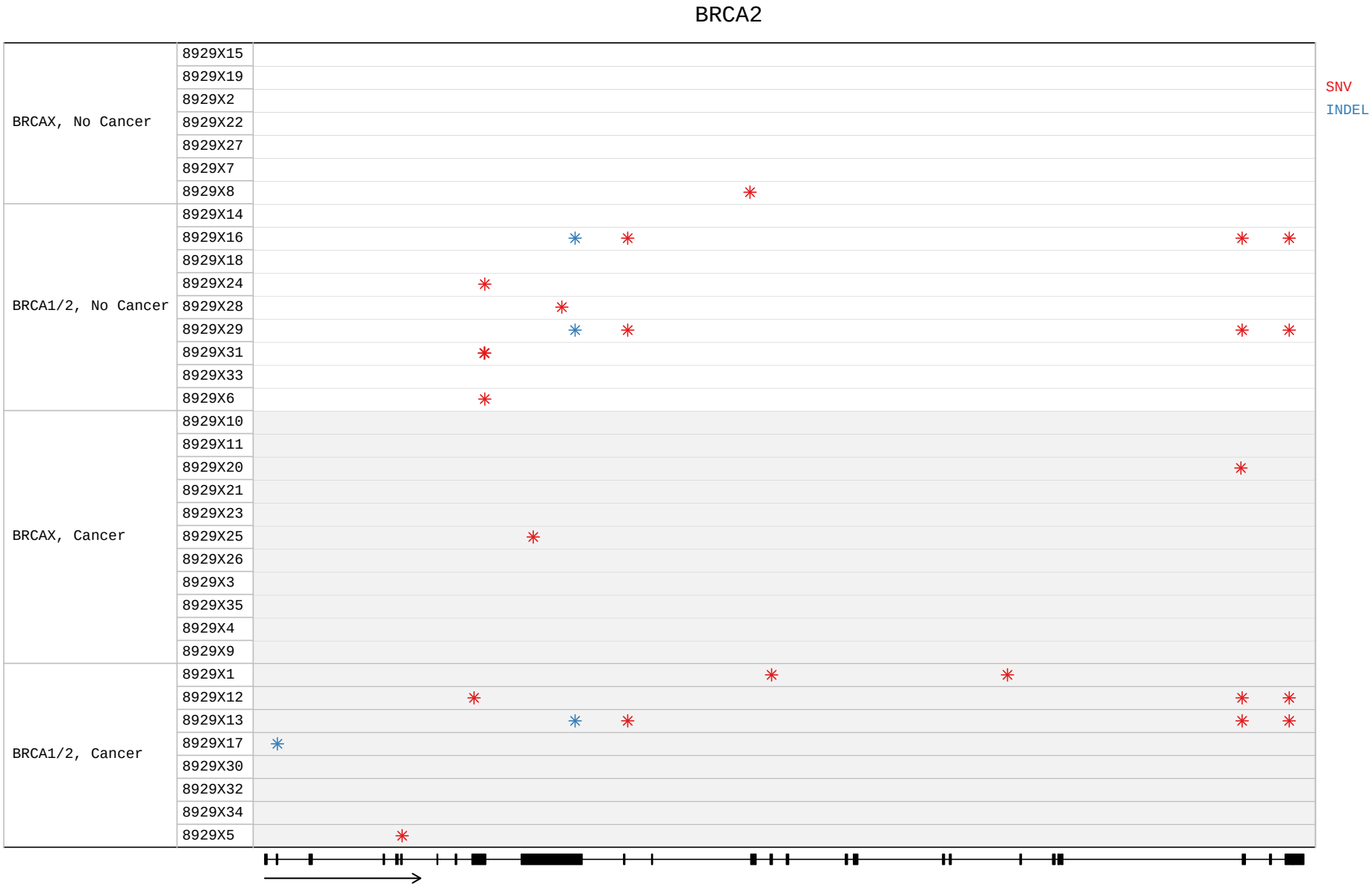
The Cancer Genome Atlas (TCGA)



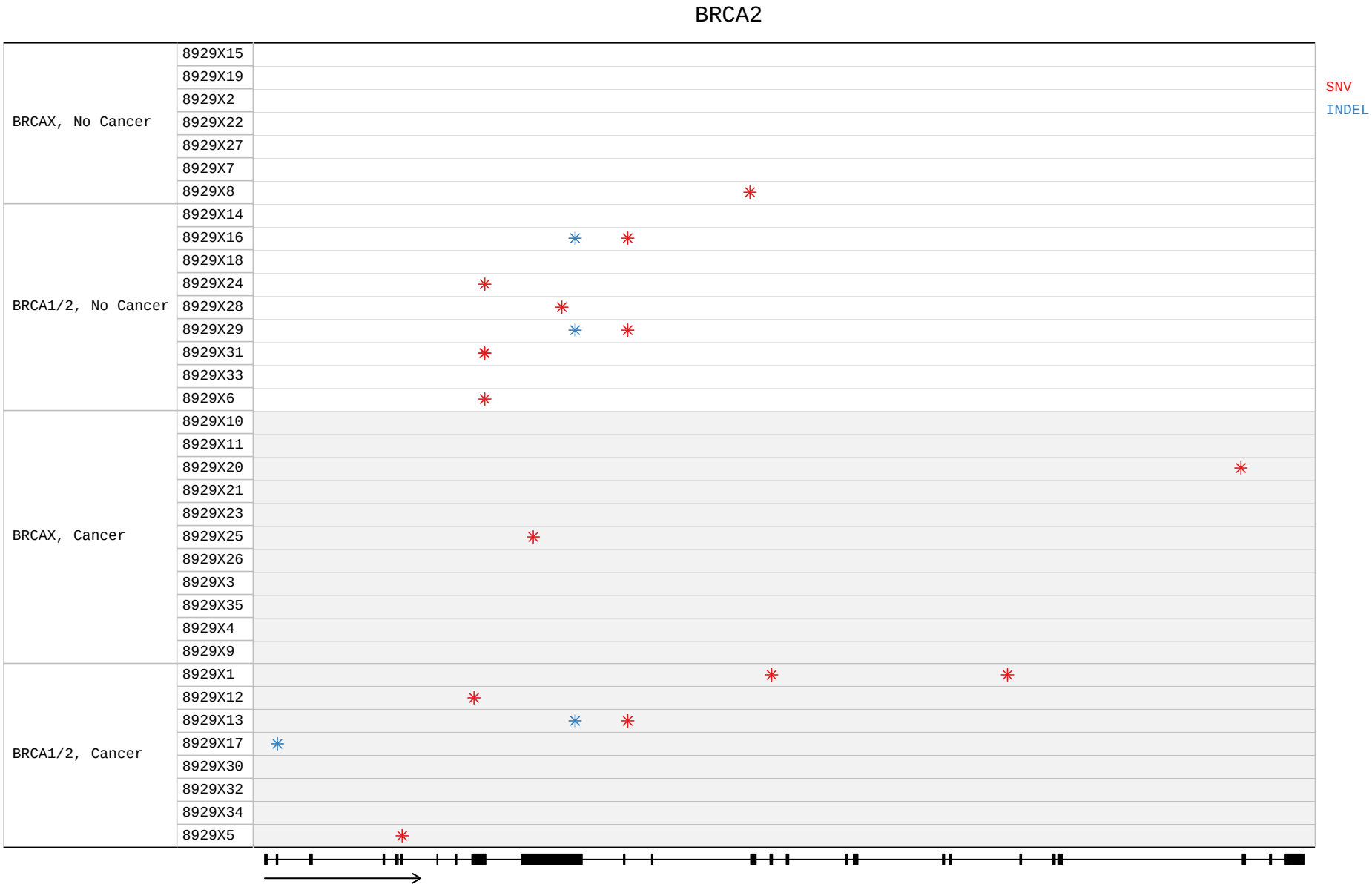
Before


BRCA2
BRCAX, No Cancer
8929X15
8929X19
8929X2
8929X22
8929X27
8929X7
8929X8
BRCA1/2, No Cancer
8929X14
8929X16
8929X18
8929X24
8929X28
8929X29
8929X31
8929X33
8929X6
BRCAX, Cancer
8929X10
8929X11
8929X20
8929X21
8929X23
8929X25
8929X26
8929X3
8929X35
8929X4
8929X9
BRCA1/2, Cancer
8929X1
8929X12
8929X13
8929X17
8929X30
8929X32
8929X34
8929X5
SNV
INDEL

Minus TCGA Common Variants



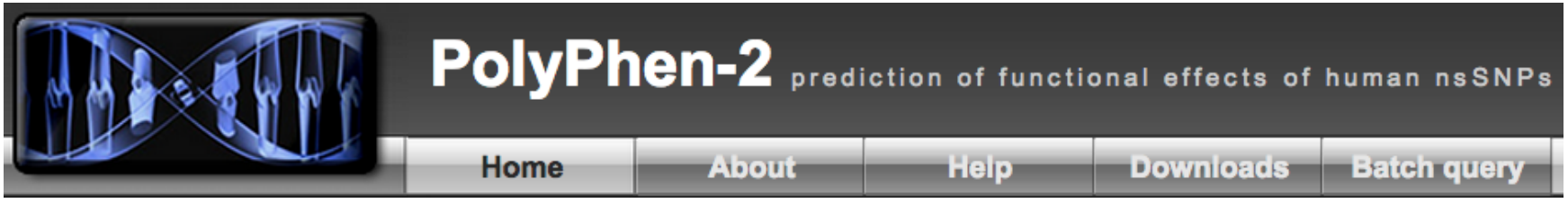
Minus “Internal” Common Variants

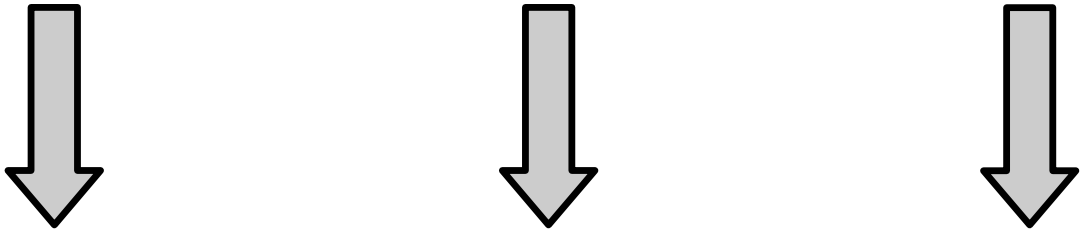



Reference
GAT CGT TGT ACG TCG GGT AAT GAG
D R C T D G N E
Non-Synonymous Variant
GAT CGT TGT ACG TGG GGT AAT GAG
D R C T W G N E
Stop Gained
GAT CGT TGT ACG TAG GGT AAT GAG
D R C T STOP
Frameshift
GAT C-- TGT ACG TCG GGT AAT GAG
GAT CTG TAC GTC GGG TAA TGA G
D L Y V G STOP

J. Craig Venter™ INSTITUTE

SIFT

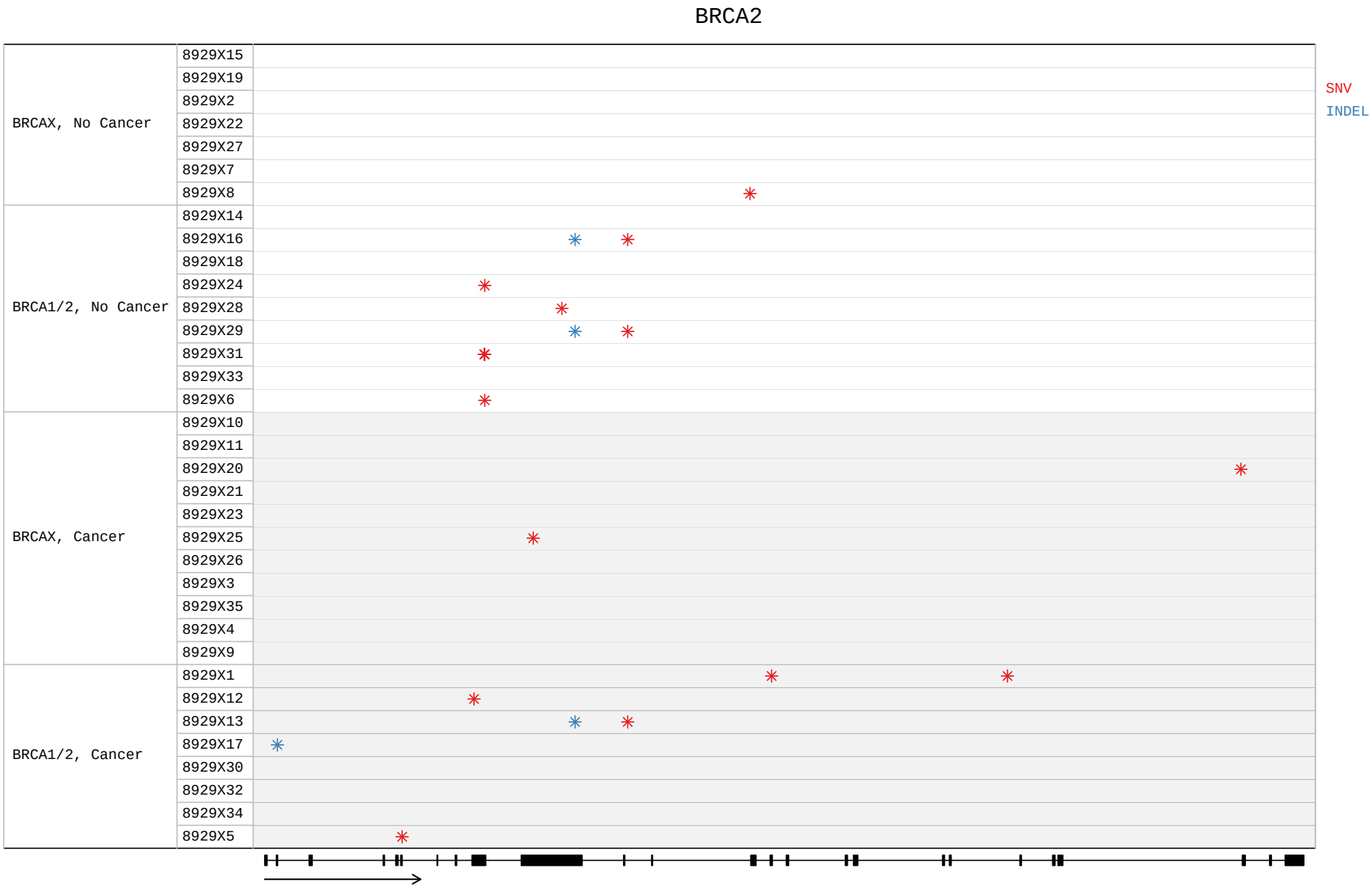




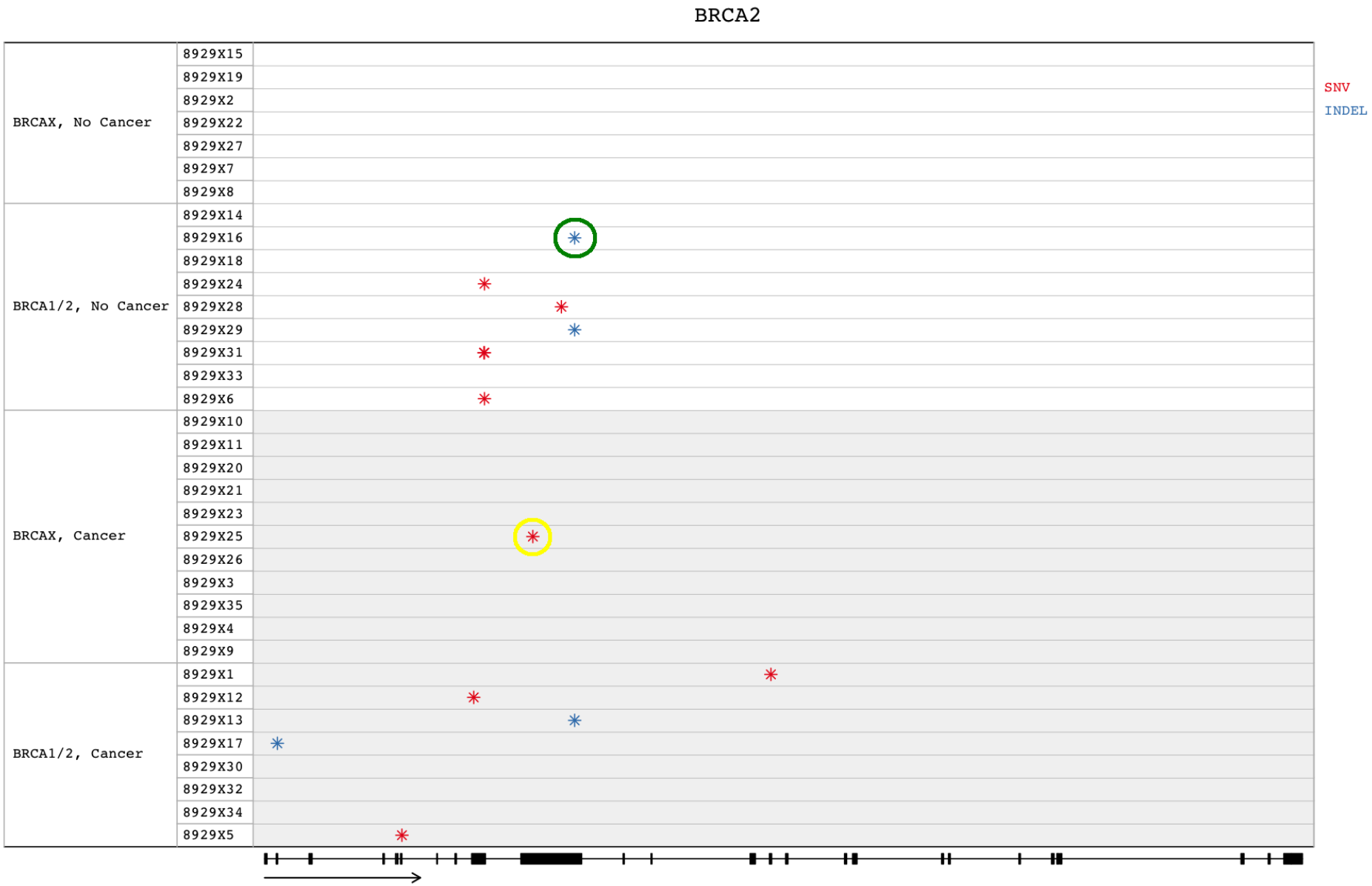
Condel

CONsensus DELeteriousness score of missense SNVs

Before


BRCA2
BRCAX, No Cancer
BRCA1/2, No Cancer
BRCAX, Cancer
BRCA1/2, Cancer
8929X15
8929X19
8929X2
8929X22
8929X27
8929X7
8929X8
8929X14
8929X16
8929X18
8929X24
8929X28
8929X29
8929X31
8929X33
8929X6
8929X10
8929X11
8929X20
8929X21
8929X23
8929X25
8929X26
8929X3
8929X35
8929X4
8929X9
8929X1
8929X12
8929X13
8929X17
8929X30
8929X32
8929X34
8929X5
SNV
INDEL

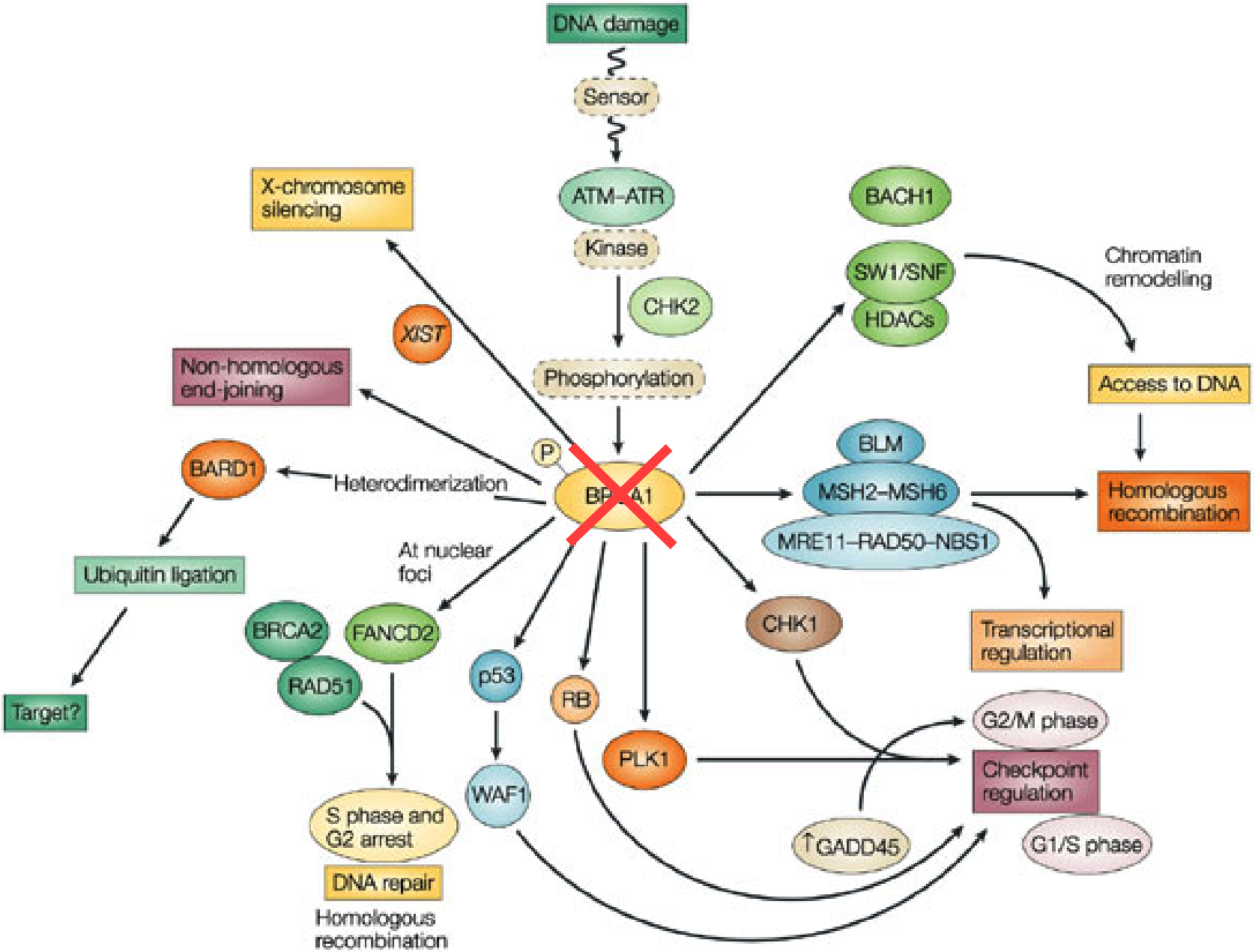
Final Variants

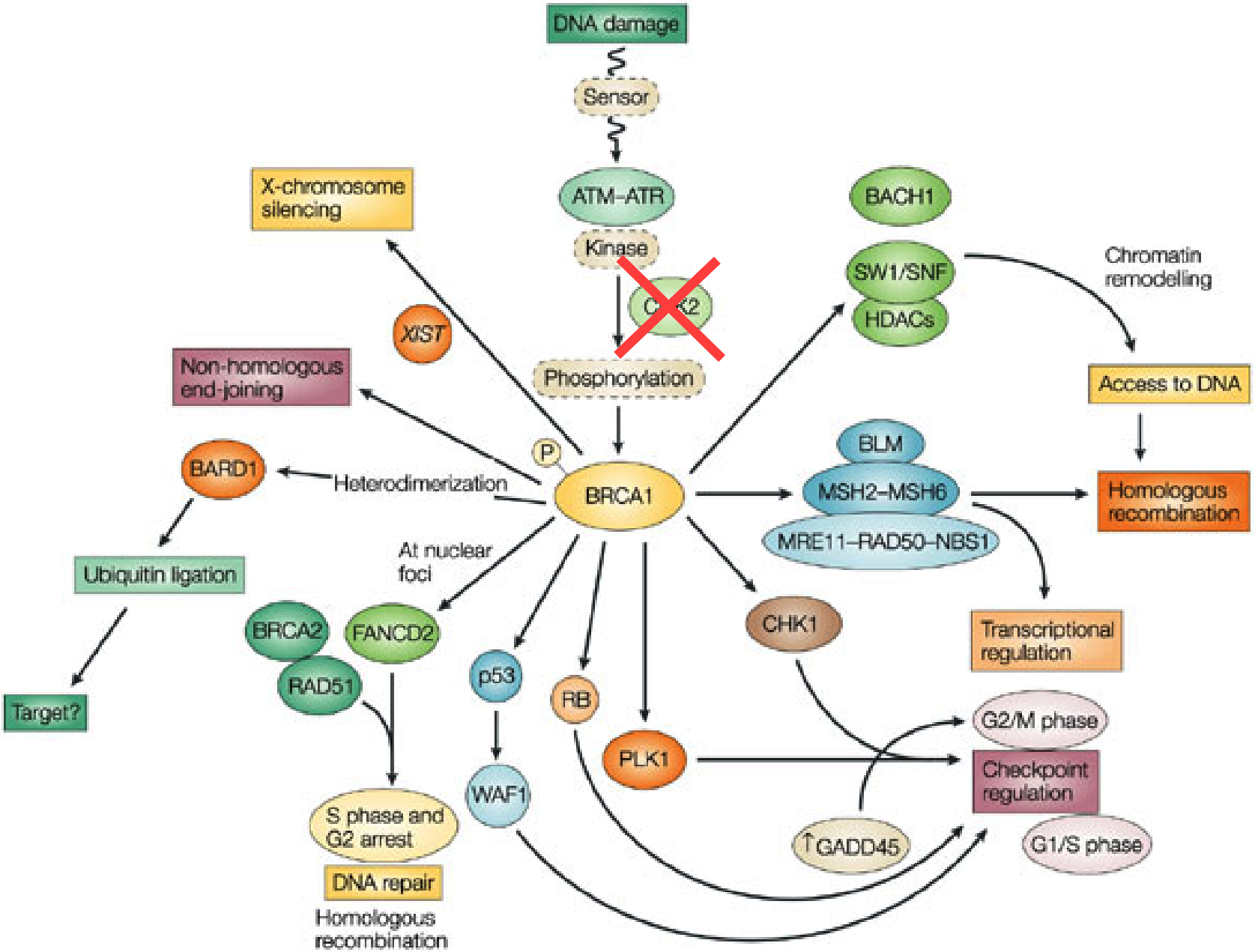


Final Variant Count

2822 variants (80.6 per sample)

2089 genes (1.35 variants per gene)


DNA damage
Sensor
ATM–ATR
Kinase
CHK2
Phosphorylation
X-chromosome silencing
XIST
Non-homologous end-joining
BARD1
Heterodimerization
Ubiquitin ligation
Target?
At nuclear foci
BRCA2
FANCD2
RAD51
S phase and G2 arrest
DNA repair
Homologous recombination
p53
WAF1
RB
PLK1
CHK1
BACH1
SW1/SNF
HDACs
Chromatin remodelling
Access to DNA
BLM
MSH2–MSH6
MRE11–RAD50–NBS1
Homologous recombination
Transcriptional regulation
G2/M phase
Checkpoint regulation
↑GADD45
G1/S phase


DNA damage
Sensor
ATM–ATR
Kinase
CHK2
Phosphorylation
X-chromosome silencing
XIST
Non-homologous end-joining
BARD1
Heterodimerization
P
BRCA1
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At nuclear foci
BRCA2
FANCD2
RAD51
S phase and G2 arrest
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PLK1
CHK1
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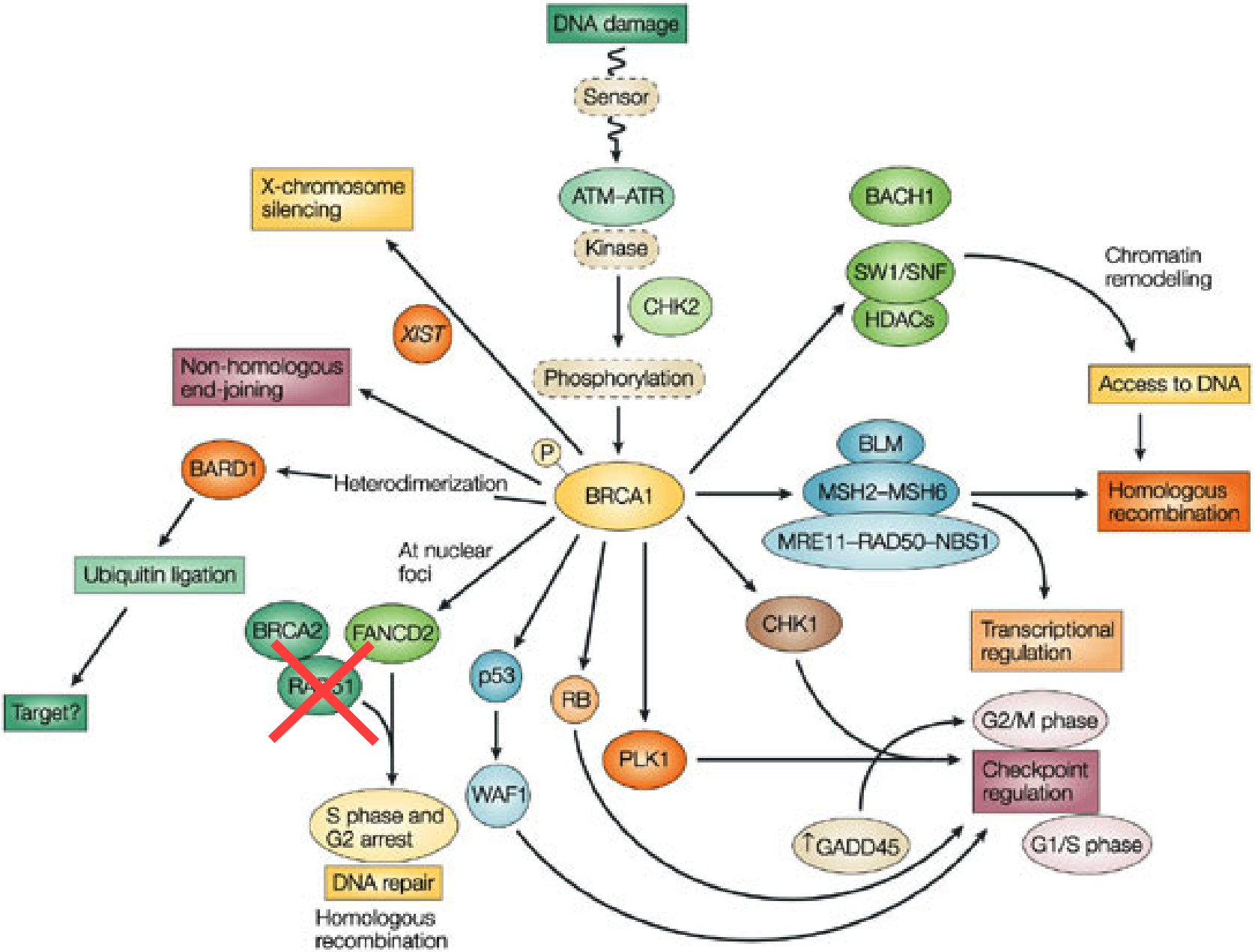
Homologous recombination
Transcriptional regulation
G2/M phase
Checkpoint regulation
↑GADD45
G1/S phase


DNA damage
Sensor
ATM–ATR
Kinase
CHK2
Phosphorylation
X-chromosome silencing
XIST
Non-homologous end-joining
BARD1
Heterodimerization
P
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Target?
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BRCA2
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PLK1
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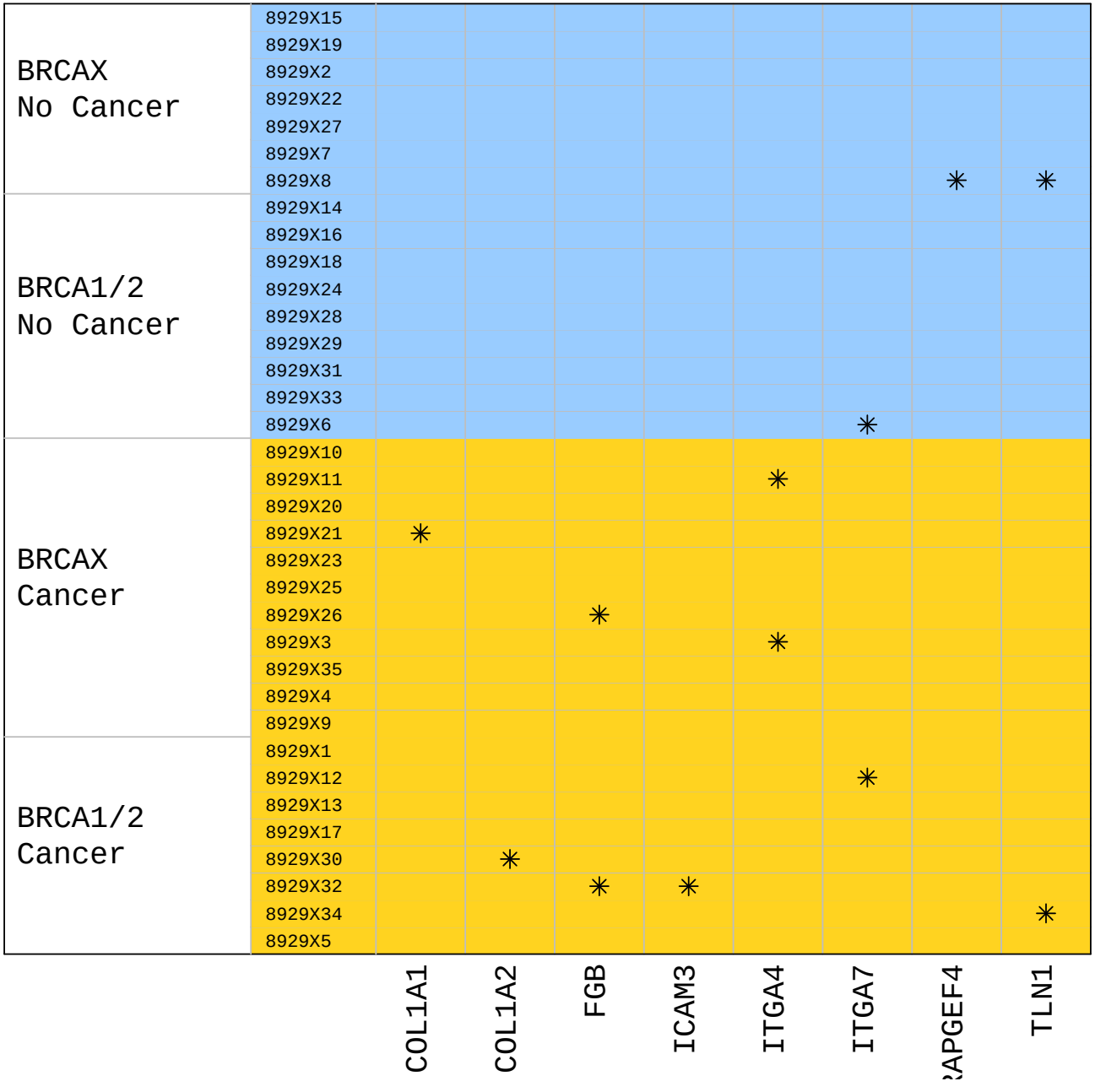
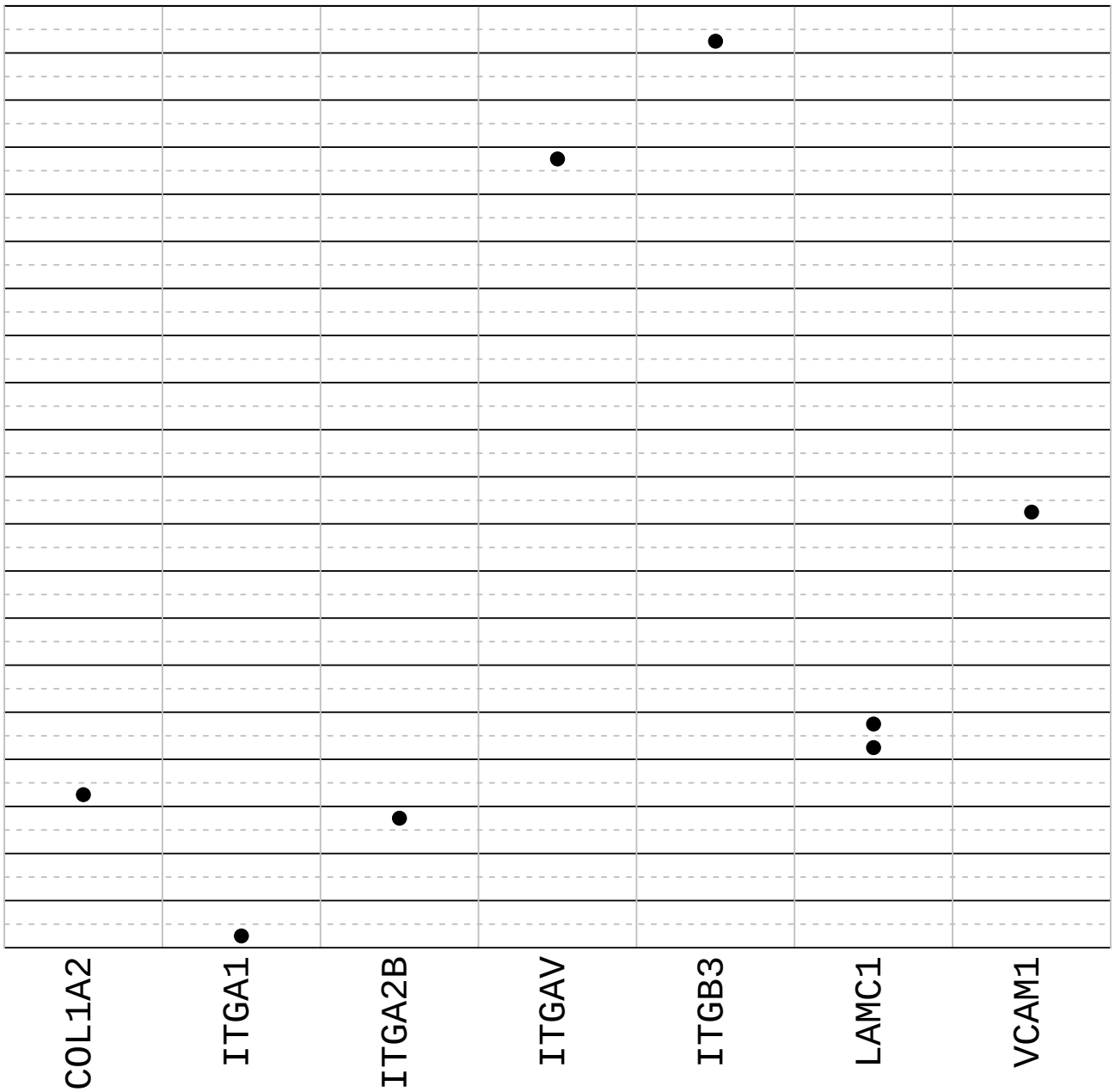
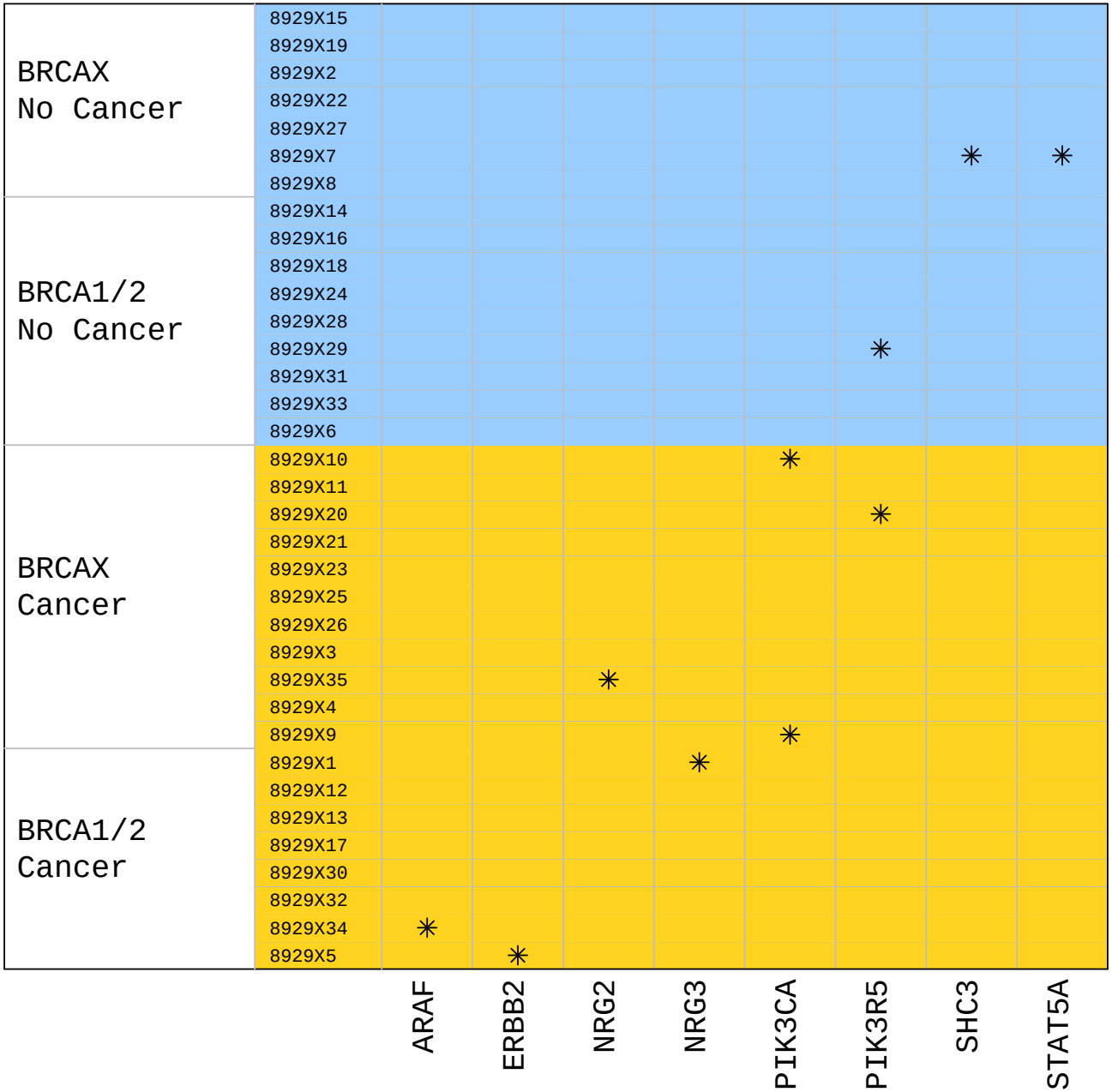
Chromatin remodelling
Access to DNA
BLM
MSH2–MSH6
MRE11–RAD50–NBS1
Homologous recombination
Transcriptional regulation
G2/M phase
Checkpoint regulation
↑GADD45
G1/S phase

Integrin cell-surface interactions

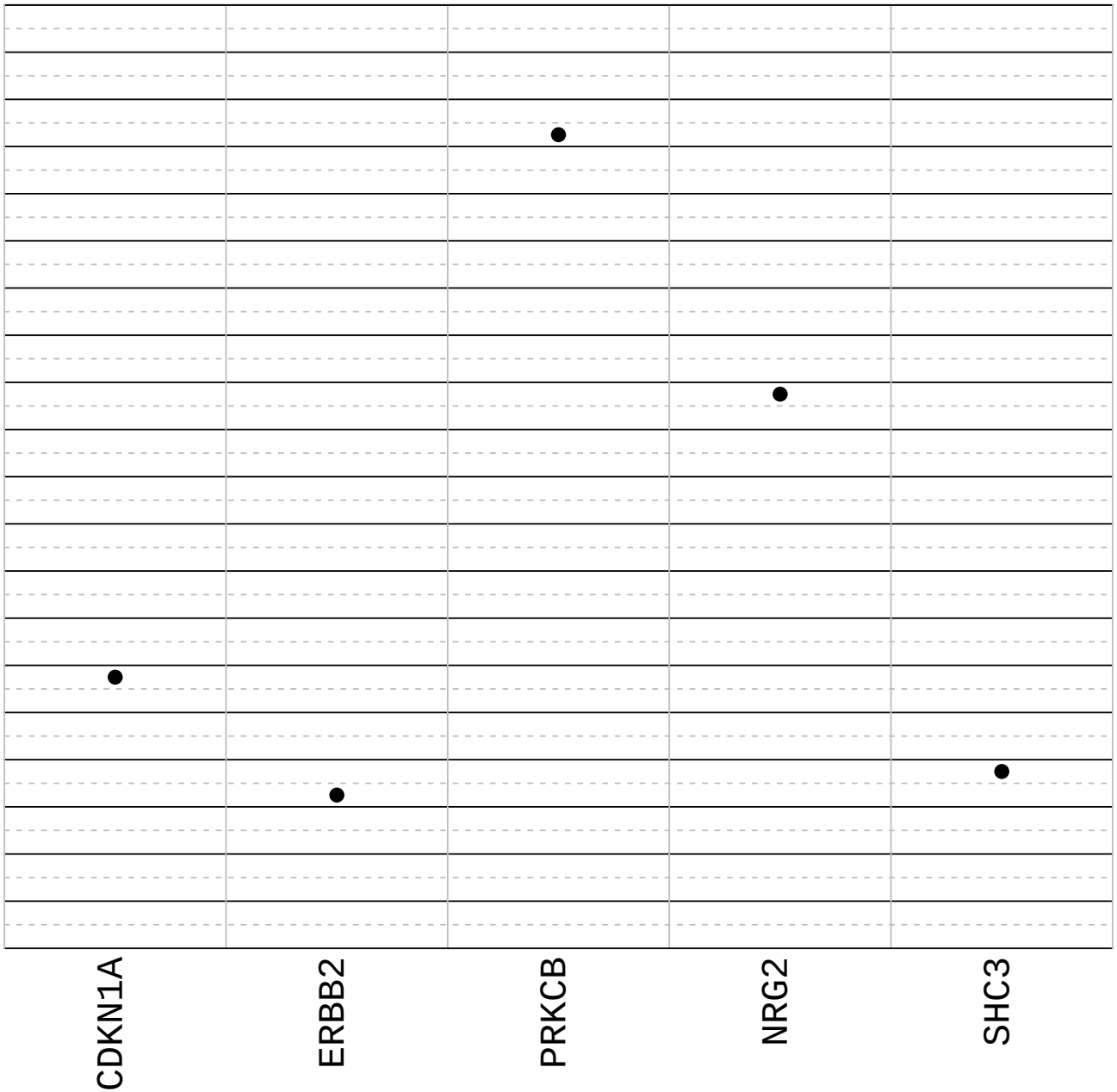



Integrin cell−surface interactions
COL1A2
ITGA1
ITGA2B
ITGAV
ITGB3
LAMC1
VCAM1

ERBB Signaling Pathway



ERBB Signaling Pathway



Top Pathway Results

Pathway	AUC	Controls Mutated	Cancer Mutated
Integrin cell surface interactions	0.687	3/16	9/19
Cell adhesion molecules	0.682	2/16	8/19
PI3K Signaling System	0.676	4/16	10/19
Citrate/Krebs cycle	0.678	0/16	7/19
Fructose and mannose metabolism	0.668	1/16	7/19
ERBB signaling pathway	0.658	3/16	7/19

Pathways that performed well in both analyses are known to play a role in tumor development!