somaticGermline TCRBOA7 - Report

Autor
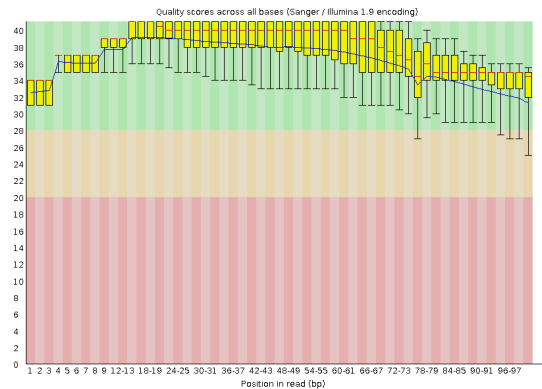
13. Oktober 2018

Inhaltsverzeichnis
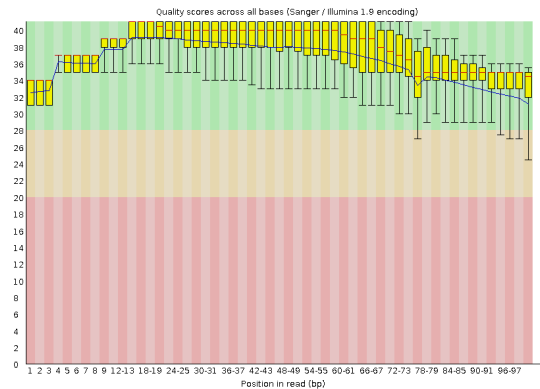
1 Qualität der Genomsequenzierung

1.1 Raw Quality

(a) Tumor Qualität

(b) Keimbahn Qualität

1.2 Base Quality Score Recalibration (BQSR)
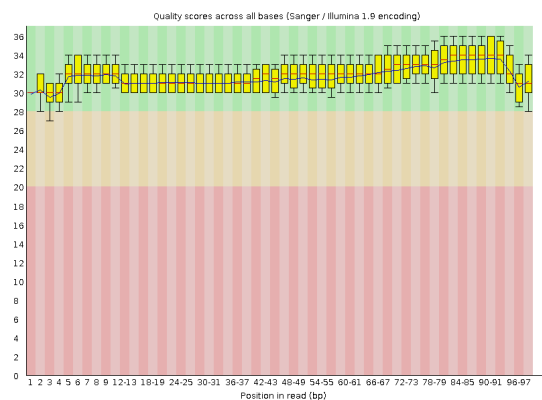
(c) Tumor Qualität nach BQSR
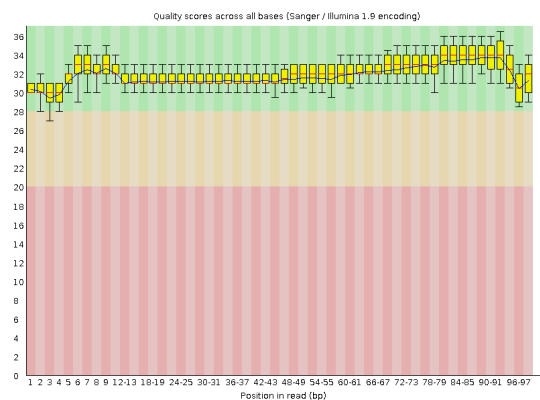
(d) Keimbahn Qualität nach BQSR

1.3 Zusammenfassung

- Agilent SureSelect V6

- Paired end 100bp

- TD: 110 Mio. Reads

- GD: 114 Mio. Reads

- Gute Qualität der Reads

2 Coverage

Target Region Coverage
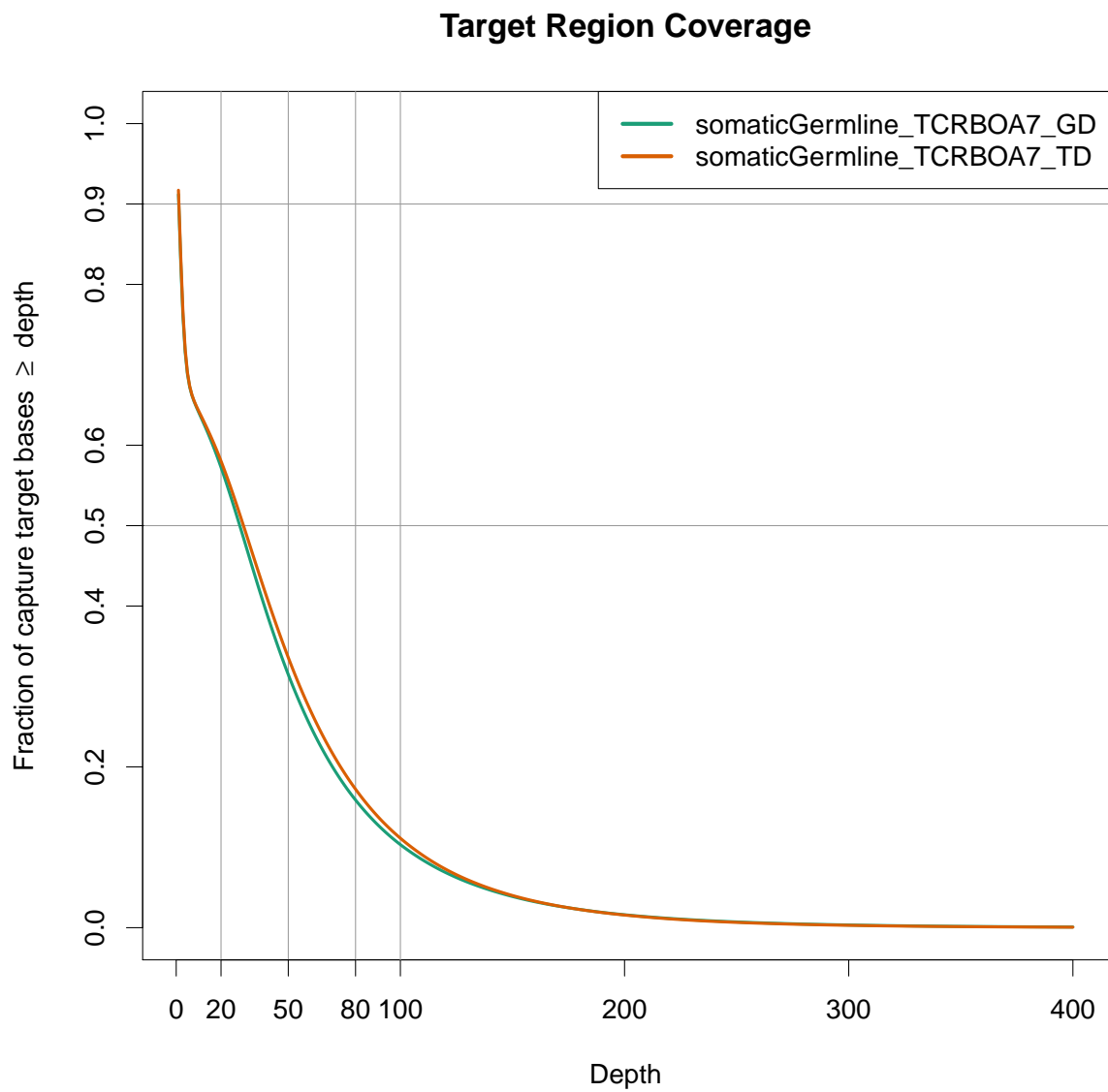
Abbildung 1: Coverage

2.1 Mean Coverage

```
## [1] "Mean Coverage somaticGermline_TCRBOA7_GD : 41.1569104"
## [1] "Mean Coverage somaticGermline_TCRBOA7_TD : 42.5843697"
```

3 Mutationsanalyse

3.1 Informationen zur Analyse

- Aligned zum Referenzgenom UCSC hg19

- Einschlusskriterien der Mutation

  – Mindestens 8 Reads pro Base
  – Seltene Mutationen (Minor-Allele Frequency (MAF) < 0.001, basierend auf gnomAD exome, ExAC, ESP6500 und 1000g)
  – Keine "Black-listed" Gene/Sequenzen
  – Variant Allele Frequency (VAF) $> 10\%$

- Analyse der Mutationen

  – Annotation bekannter Mutationen (Cosmic, Clinvar, dbSNP)
  – Ranking der Wichtigkeit (RVIS Score)
  – Strukturanalyse der mutierten Proteine (Condel, CADD)

3.2 Somatische Mutationen und Loss of Heterozygosity (LoH)

Somatic SNV
Somatic InDel
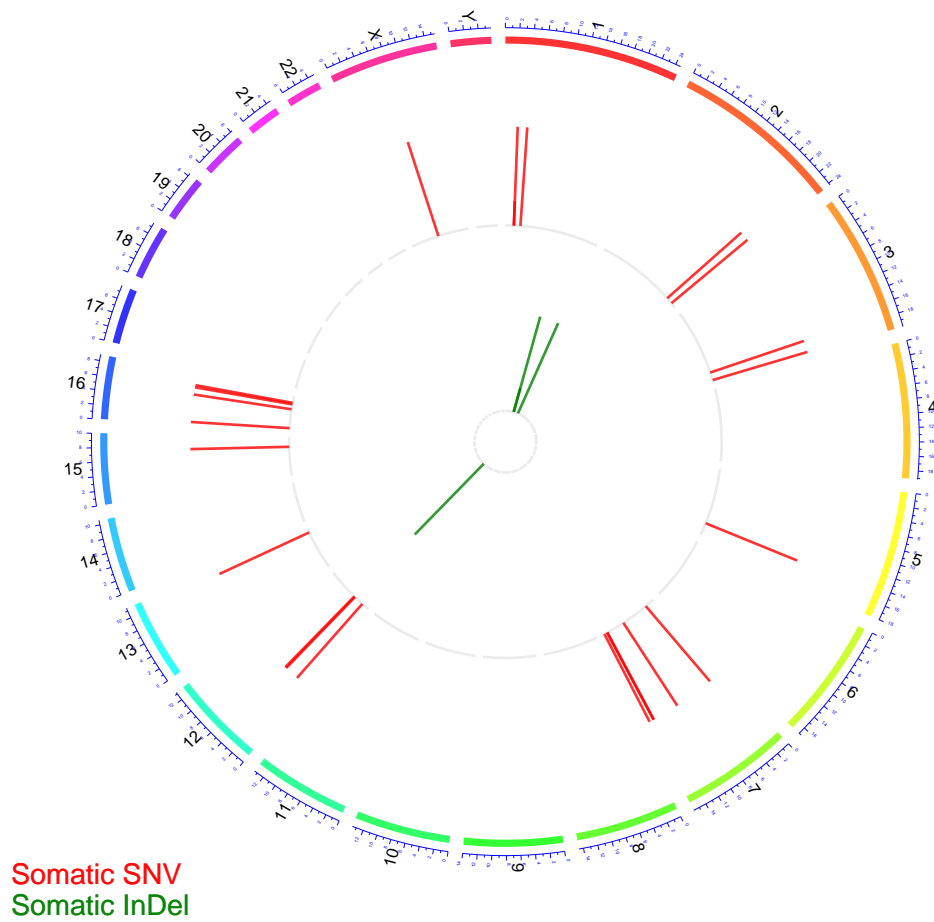
Abbildung 2: Circos Plot

Tabelle 1: Zusammenfassung der identifizierten Mutationen

Mutationstype	Number of exonic	Zygosity	TS	OG	HS
somatic SNV	0	homozygous	0	0	0
somatic SNV	22	heterozygous	2	0	0
LoH SNV	0	-	0	0	0
somatic InDel	0	homozygous	0	0	0
somatic InDel	3	heterozygous	1	0	0
LoH InDel	0	-	0	0	0

- 25 somatische Mutationen (exonisch)

- 0 Loss of Heterozygosity (LoH)

- Insgesamt 25 Mutationen

- Mutationslast 3.79/Mb

Tabelle 2: Tumorsuppressoren und Onkogene - Überblick

Symbol	Gene Name	TSG	OG	HS
KMT2D	lysine methyltransferase 2D	1	0	0
CREBBP	CREB binding protein	1	0	0
KMT2D	lysine methyltransferase 2D	1	0	0

3.3 Tumorsuppressoren und Onkogene

Tabelle 3: Tumorsuppressoren und Onkogene

Symbol	Gene Name	Exonic Function	Aminoacid Change	VAF	Zygosity	Reads	TSG	OG	HS	TARGET	MAF	CADD	Condel	CLINSIG	COSMIC
KMT2	lysine methyltransferase 2D	stopgain	p.Gln170*	34.09%	het	15|44	1	0	0	.	NA	35.0	NA	NA	NA
CREBB	CREB binding protein	nonsynonymous SNV	p.Ser1436Arg	55.56%	het	10|18	1	0	0		NA	23.8	D	NA	ID=COSM5948954
KMT2	lysine methyltransferase 2D	frameshift deletion	p.Phe4576fs	30.56%	het	11|36	1	0	0	.	NA	NA	NA	NA	NA

3.4 Somatische Mutationen (top20 nach VAF)

Tabelle 4: somatische Mutationen

Symbol	Gene Name	Exonic Function	Aminoacid Change	VAF	Zygosity	Reads	TSG	OG	HS	TARGET	MAF	CADD	Condel	CLINSIG	COSMIC
CREBBP	CREB binding protein	nonsynonymous SNV	p.Ser1436Arg	55.56%	het	10|18	1	0	0		NA	23.800	D	NA	ID=COSM5948954
KIAA2022		nonsynonymous SNV	p.Thr1118Ile	51.28%	het	20|39	0	0	0	.	NA	8.520	N	NA	ID=COSM4111048
HSPG2	heparan sulfate proteoglycan 2	nonsynonymous SNV	p.Val3402Met	40.91%	het	9|22	0	0	0	.	6.52e-05	32.000	D	Uncertain significance	ID=COSM1339041
KMT2D	lysine methyltransferase 2D	stopgain	p.Gln170*	34.09%	het	15|44	1	0	0	.	NA	35.000	NA	NA	NA
NAALADL2	N-acetylated alpha-linked acidic dipeptidase like 2	nonsynonymous SNV	p.Lys17Thr	32.61%	het	15|46	0	0	0	.	NA	22.800	N	NA	NA
CUL1	cullin 1	nonsynonymous SNV	p.Tyr228Cys	32.04%	het	33|103	0	0	0	.	NA	28.600	D	NA	ID=COSM3259576
CCDC168	coiled-coil domain containing 168	nonsynonymous SNV		30.59%	het	26|87	0	0	0	.	NA	2.672	NA	NA	NA
KMT2D	lysine methyltransferase 2D	frameshift deletion	p.Phe4576fs	30.56%	het	11|36	1	0	0	.	NA	NA	NA	NA	NA

Tabelle 4: somatische Mutationen *(continued)*

Symbol	Gene Name	Exonic Function	Aminoacid Change	VAF	Zygosity	Reads	TSG	OG	HS	TARGET	MAF	CADD	Condel	CLINSIG	COSMIC
SLC38A4	solute carrier family 38 member 4	nonsynonymou SNV	p.Ile30Val	30.09%	het	34|11:	0	0	0	.	NA	0.004	N	NA	NA
ST3GAL2	ST3 beta-galactoside alpha-2,3-sialyltransferas 2	nonsynonymou SNV	p.Ser69Ile	27.5%	het	11|40	0	0	0	.	NA	14.600	N	NA	NA
UBE3C	ubiquitin protein ligase E3C	nonsynonymou SNV	p.Val129Gly	25%	het	9|36	0	0	0	.	NA	23.900	N	NA	NA
SLCO1C1	solute carrier organic anion transporter family member 1C1	nonsynonymou SNV	p.Pro377Gln	25%	het	27|10!	0	0	0	.	NA	25.400	D	NA	NA
CHD9	chromodomain helicase DNA binding protein 9	nonsynonymou SNV	p.Pro2699Ser	25%	het	18|72	0	0	0	.	NA	0.531	N	NA	NA
DENND4B	DENN domain containing 4B	nonframeshift insertion		23.81%	het	5|23	0	0	0	.	NA	NA	NA		NA
CPS1	carbamoyl-phosphate synthase 1	nonsynonymou SNV	p.Ala519Asp	23.73%	het	14|59	0	0	0	.	NA	34.000	D	NA	NA
C2orf83	chromosome 2 open reading frame 83	nonsynonymou SNV	p.Phe13Leu	23.68%	het	9|38	0	0	0	.	NA	23.800	D	NA	NA

Tabelle 4: somatische Mutationen *(continued)*

Symbol	Gene Name	Exonic Function	Aminoacid Change	VAF	Zygosity	Reads	TSG	OG	HS	TARGET	MAF	CADD	Condel	CLINSIG	COSMIC
SPINK5	serine peptidase inhibitor, Kazal type 5	nonsynonymous SNV	p.Gly551Arg	22.88%	het	35|153	0	0	0	.	NA	0.039	N	NA	NA
NFE2L3	nuclear factor, erythroid 2 like 3	stopgain	p.Gln614*	22.41%	het	13|58	0	0	0	.	NA	38.000	NA	NA	NA
CDH5	cadherin 5	nonsynonymous SNV	p.Arg402Lys	22.22%	het	6|27	0	0	0	.	1.79e-05	0.028	N	NA	NA
CSK	C-terminal Src kinase	nonsynonymous SNV	p.Glu438Lys	20%	het	4|20	0	0	0	.	NA	20.900	N	NA	NA

3.5 LoH

```
## [1] "No LoH!"
```

3.6 Funktionelle Analysen

GO

Tabelle 5: Ergebnisse GO Analyse, top 20

Term	Count	Size	p-value	adj.P.Val
stimulatory C-type lectin receptor signaling pathway	3	124	3.56e-04	1e+00
innate immune response activating cell surface receptor signaling pathway	3	126	3.74e-04	1e+00
immune response-activating cell surface receptor signaling pathway	4	414	4.30e-04	1e+00
immune response-regulating cell surface receptor signaling pathway	4	446	6.17e-04	1e+00
immune response-activating signal transduction	4	558	1.66e-03	1e+00
immune response-regulating signaling pathway	4	591	2.15e-03	1e+00
activation of immune response	4	611	2.47e-03	1e+00
regulation of immune response	5	971	2.55e-03	1e+00
innate immune response-activating signal transduction	3	277	3.50e-03	1e+00
activation of innate immune response	3	284	3.73e-03	1e+00
cellular response to nitrogen compound	4	588	3.97e-03	1e+00
positive regulation of innate immune response	3	327	5.53e-03	1e+00
positive regulation of immune response	4	749	5.76e-03	1e+00
regulation of defense response	4	678	6.51e-03	1e+00
sulfur compound metabolic process	3	371	8.15e-03	1e+00
regulation of innate immune response	3	391	9.16e-03	1e+00
cellular response to endogenous stimulus	5	1230	1.11e-02	1e+00
positive regulation of defense response	3	420	1.12e-02	1e+00
single-organism metabolic process	10	4234	1.16e-02	1e+00
innate immune response	4	867	1.28e-02	1e+00

Consensus

Tabelle 6: Ergebnisse Consensus Analyse, top 20

Term	Count	Size	p-value	adj.P.Val	Symbol
Wnt Mammals	3	119	3.23e-04	2.72e-01	CREBBP| HSPG2| CUL1

Reactome

Tabelle 7: Ergebnisse Reactome Analyse, top 20

Term	Count	Size	p-value	adj.P.Val
Circadian Clock	3	69	6.30e-05	3.85e-02
Disease	6	828	2.56e-04	7.65e-02
Signaling by Wnt	3	297	4.49e-03	1.89e-01
Developmental Biology	5	1029	5.26e-03	2.01e-01
Metabolism	7	2076	6.71e-03	2.25e-01
Diseases of signal transduction	3	361	7.79e-03	2.27e-01
Generic Transcription Pathway	4	856	1.43e-02	3.48e-01
Signal Transduction	7	2517	1.66e-02	3.72e-01

Hallmarks of Cancer

Tabelle 8: Ergebnisse Hallmarks Analyse, top 20

Term	Count	Size	p-value	adj.P.Val
NA	NA	NA	NA	NA

3.7 Wichtige Signalwege

Tabelle 9: Important Pathways

Pathway	Symbol	Gene Name	Exonic Function	VAF	Reads	Aminoacid Change	TARGET	MAF	CADD	Condel	CLINSIG	COSMIC
PI3K-AKT-mTOR	RRAGC	Ras related GTP binding C	nonsynon SNV	15.69%	8|51	p.Pro118Leu	.	0	29.9	D	NA	ID=COSM1315890
RAF-MEK-ERK	CREBBP	CREB binding protein	nonsynon SNV	55.56%	10|18	p.Ser1436Arg		None	23.8	D	NA	ID=COSM5948954
Cell Cycle	CUL1	cullin 1	nonsynon SNV	32.04%	33|103	p.Tyr228Cys	.	None	28.6	D	NA	ID=COSM3259576
Tyrosine Kinases	CSK	C-terminal Src kinase	nonsynon SNV	20%	4|20	p.Glu438Lys	.	None	20.9	N	NA	None

4 Copy Number Variation

4.1 Anzahl CNVs

```
## [1] "#CNVs: 67"
```
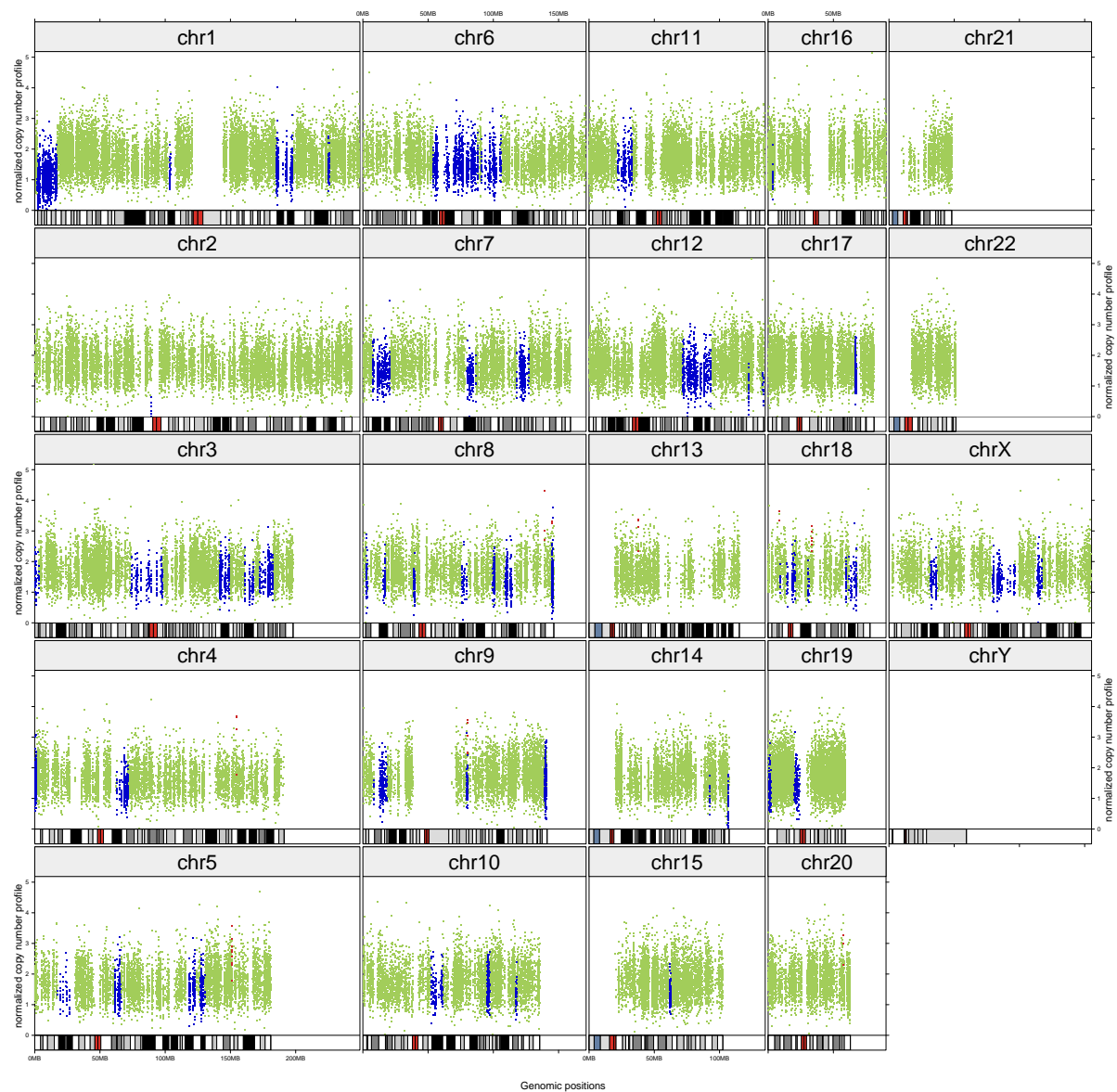
4.2 CNV Plots
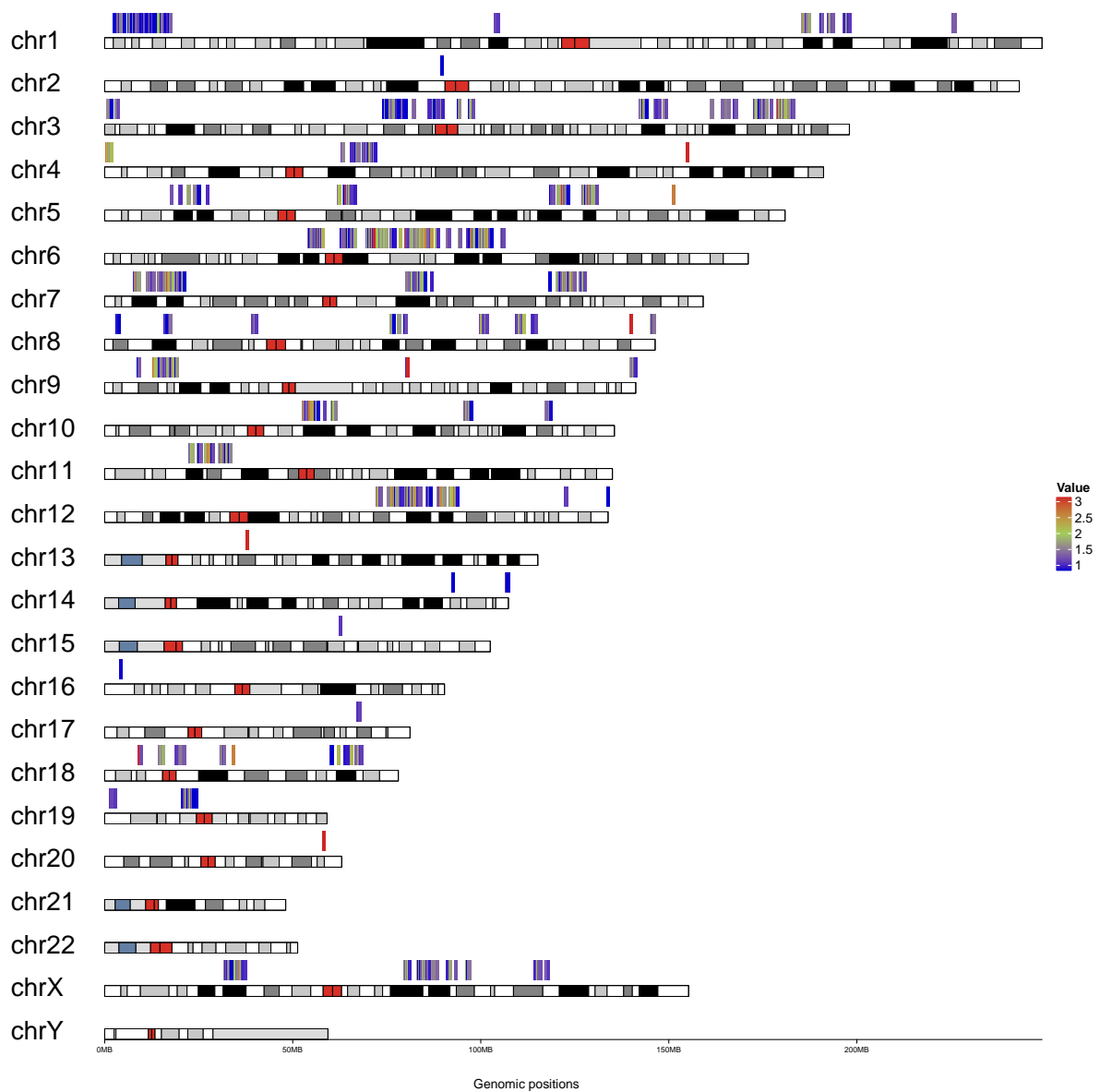

Abbildung 3: Copy Number Variation

Abbildung 4: Copy Number Variation - Ideogram

4.3 Tumorsuppressoren

Tabelle 10: Tumorsuppressoren

chr	copy.number	status	TumorSuppressor
1	1	loss	SDHB,SPEN,ERRFI1
1	1	loss	CDC73
3	1	loss	ATR
16	1	loss	CREBBP
19	1	loss	STK11

4.4 Onkogene

Tabelle 11: Onkogene

chr	copy.number	status	Oncogene
1	1	loss	MTOR,PIK3CD
3	1	loss	PIK3CA
7	1	loss	ETV1
7	1	loss	HGF
18	1	loss	BCL2

4.5 Funktionelle Analyse der CNVs

GAIN

Tabelle 12: Ergebnisse GO Analsye - GAIN, top 20

Term	Count	Size	p-value	adj.P.Val
None	None	None	NA	NA

LOSS

Tabelle 13: Ergebnisse GO Analyse - LOSS, top 20

Term	Count	Size	p-value	adj.P.Val
phospholipid scrambling	5	12	4.00e-03	1e+00
cellular glucuronidation	6	17	4.26e-03	1e+00
regulation of skeletal muscle fiber development	4	10	1.20e-02	1e+00
regulation of circadian sleep/wake cycle, wakefulness	3	6	1.51e-02	1e+00
circadian sleep/wake cycle, wakefulness	3	6	1.51e-02	1e+00
uronic acid metabolic process	6	22	1.68e-02	1e+00
glucuronate metabolic process	6	22	1.68e-02	1e+00
protein import into peroxisome matrix	4	12	2.42e-02	1e+00
positive regulation of fever generation	3	7	2.45e-02	1e+00
positive regulation of skeletal muscle fiber development	3	7	2.45e-02	1e+00
spermidine metabolic process	3	8	3.64e-02	1e+00
regulation of fever generation	3	8	3.64e-02	1e+00
diaphragm development	3	8	3.64e-02	1e+00
negative regulation of mesenchymal cell proliferation	3	8	3.64e-02	1e+00
primary amino compound metabolic process	4	14	4.17e-02	1e+00

5 Analyse der Mutationssignaturen

- Nur somatische Mutationen werden berücksichtigt

- Nur Signaturen, die mehr als 1% aller SNVs beinhalten, werden verwendet

- Die Signautren basieren auf den aktuellen *COSMIC Mutation Signatures* `http://cancer.sanger.ac.uk/cosmic/signatures`

- *AC3* wird als *BRCAness* bezeichnet

Tabelle 14: Ergebnisse Mutationssignatur Analyse

Signature	Process	Percentage
AC1	spontaneous deamination	3.57
AC3	defect DNA DSB repair hom. recomb.	17.24
AC10	altered POL E	2.31
AC14	unknown	1.23
AC15	defect DNA MMR	5.22
AC16	unknown	27.87
AC19	unknown	22.43
AC25	unknown	6.52
AC27	unknown	3.07
AC28	unknown	2.31
AC30	unknown	8.22

6 Versionsinfo

6.1 Genome
- UCSC hg19

6.2 Programmversionen
- FastQC: 0.11.5

- Trimmomatic: 0.36

- BWA: 0.7.15

- bam-readcount: 0.8.0

- samtools 1.4.1

- GATK: 3.6

- picard-tools: 2.9.2

- VarScan: 2.4.3

- annovar 2017-07-17

- bedtools: 2.26.0

- Control-FREEC: 11.0

- Java: 1.8.0_121

6.3 Annovar Datenbanken
- refGene GRCh37 (20170601)

- esp6500siv2_all (20141222)

- avsnp150 (dbSNP) (20170929)

- clinvar_20170905 (20171003)

- 1000g2015aug_all (20150824)

- cosmic84 (20180213)

- exac03 (20151129)

- gnomad_exome (20170311)

- cadd13 (20170123)