eurofins Genomics

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Data Analysis Report: ONCOPANEL ALL-IN-ONE v1.4

Project / Study: FE-0242

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1 Results

1.1 Variant discovery

Single nucleotide variants (SNVs), Insertions and deletions (InDel) are detected in each sample using LoFreq[1], and are filtered based on mutation allele frequency (>1%) and coverage (≥ 10% of average coverage excluding duplicated fragments; coverage metrics can be found in chapter 2.5). Variants that pass these thresholds are summarised in the following table(s).

Table 1: Variant metrics for HD753_3, HD753_4.

	HD753_3	HD753_4
Total SNV	72893	72170
Known SNV	9817	9750
Unknown SNV	63076	62420
Total InDel	26616	28059
Known InDel	1145	1191
Unknown InDel	25471	26868

Known SNV / InDel: in reference variant databases (dbSNP, COSMIC[2] and / or ClinVar[3]).

Unknown SNV / InDel: currently not listed in reference variant database (as aforementioned).

1.2 Sample-wise known clinical significant variants

Variants detected are screened for known clinical significance in ClinVar (released 02. Oct 2017) [3] database. The ClinVar database aggregates information about genomic variation and its relationship to human health. It is hosted by the National Center for Biotechnology Information (NCBI). Detailed explanation of clinical significance in ClinVar database can be found at https://www.ncbi.nlm.nih.gov/clinvar/docs/clinsig/.

Variants which have clinical significance state as "Likely pathogenic", "Pathogenic" and "Drug response" are filtered from the complete list of variants and are reported in following table(s). For more detailed information navigate to the Clinvar database and type in the dbIDs of your variant of interest. Variant effects for multiple transcripts for the same variant are listed as separate entries. In case of multiple transcripts, transcripts which have missense, splice junction, UTR, frameshift, disruptive frameshift insertion / deletion variant types are listed.

1.2.1 HD753_3 Results

Table 2: Variants (SNV and InDels) in sample - **HD753_3.** Entries are sorted by gene.

Location	Gene	AA Change	Codon Change	Mutation Freq.	Depth	ClinVar ID	ClinVar Significance
chr7:87160618	ABCB1	p.S893A p.S829A	c.2677T>G c.2485T>G	64.9 %	1394x	166622	drug response
chr5:131931451	AC116366.3	. . . .	c.*2341delA c.*1321delA c.*2025delA c.*2155delA	15.0 %	1372x	408407	pathogenic

Location	Gene	AA Change	Codon Change	Mutation Freq.	Depth	ClinVar ID	ClinVar Significance
chr14:105246551	AKT1	. p.E17K	n.80G>A c.49G>A	5.4 %	948x	13983	pathogenic
chr10:96540410	AL583836.1	.	c.*394G>A	5.0 %	1191x	16899	drug response
chr10:96541616	AL583836.1	.	c.*439G>A	19.8 %	1024x	16897	drug response
chr20:31022441	ASXL1	p.G641fs p.G646fs	c.1919insG c.1934insG	4.5 %	661x	426927	pathogenic
chr11:108205832	ATM	p.V2716A	c.8147T>C	4.1 %	1861x	142700	pathogenic
chr17:63532584	AXIN2	p.G600fs p.G665fs	c.1799delG c.1994delG	5.3 %	452x	5880	pathogenic
chr19:49458970	BAX	p.R24fs p.E24fs p.E41fs	c.69delG c.70delG c.121delG	6.3 %	867x	9512	pathogenic
chr7:140453136	BRAF	. p.V207E p.V600E p.V28E	c.*1249T>A c.620T>A c.1799T>A c.83T>A	18.5 %	1685x	13961	pathogenic
chr17:41234451	BRCA1	.	c.*4110C>T	5.0 %	1824x	17675	pathogenic
chr13:32937354	BRCA2	p.I2675fs	c.8021insA	5.2 %	1044x	267050	pathogenic
chr9:21971186	CDKN2A	. p.P72L	c.*95C>T c.215C>T	8.1 %	211x	376310	likely pathogenic
chr15:93545433	CHD2	p.Q1392fs . .	c.4173insA c.*406insA c.*344insA	7.6 %	262x	218395	pathogenic
chr3:41266101	CTNNB1	p.S33Y p.S26Y	c.98C>A c.77C>A	5.6 %	1473x	17577	pathogenic
chr10:17113456	CUBN	p.S865N	c.2594G>A	4.6 %	798x	265086	pathogenic
chr19:41512841	CYP2B6	p.Q172H	c.516G>T	24.3 %	1945x	29671	drug response
chr19:41515263	CYP2B6	p.K262R	c.785A>G	25.2 %	547x	120171	drug response
chr10:96702047	CYP2C9	p.R144C	c.430C>T	9.0 %	1718x	8409	drug response
chr10:96741053	CYP2C9	p.I359L	c.1075A>C	5.7 %	1307x	8408	drug response
chr22:42524947	CYP2D6	. . . . .	c.353-1G>A c.440-1G>A c.506-1G>A n.1198-1G>A c.173-1G>A	32.4 %	550x	16889	drug response
chr22:42526694	CYP2D6	p.P34S p.P12S	c.100C>T c.34C>T	52.0 %	252x	16893	drug response
chr7:55242464	EGFR	p.E746_A750del p.E701_A705del .	c.2235_2249delGGAATTAAGAGAAGC c.2100_2114delGGAATTAAGAGAAGC c.*225_*239delGGAATTAAGAGAAGC	2.8 %	1960x	163343	drug response
chr7:55248998	EGFR	p.A767_V769ins . p.A722_V724ins	c.2300_2308insCCAGCGTGG c.*290_*298insCCAGCGTGG c.2165_2173insCCAGCGTGG	3.4 %	1442x	177678	drug response
chr22:41565529	EP300	p.D1399N	c.4195G>A	11.0 %	1138x	376401	likely pathogenic

Location	Gene	AA Change	Codon Change	Mutation Freq.	Depth	ClinVar ID	ClinVar Significance
chr8:118849384	EXT1	p.R129H p.R340H	c.386G>A c.1019G>A	11.4 %	1252x	265129	pathogenic
chr5:176520243	FGFR4	p.G23R p.G388R	c.67G>A c.1162G>A	35.0 %	443x	16326	pathogenic
chr19:3118942	GNA11	p.Q57L p.Q209L	c.170A>T c.626A>T	5.8 %	950x	376002	pathogenic
chr11:67352689	GSTP1	. p.I105V	c.*137A>G c.313A>G	61.6 %	1461x	37340	drug response
chr12:121432114	HNF1A	p.P291fs p.G226fs .	c.864delG c.677delG c.*304delG	6.3 %	748x	435424	pathogenic
chr7:142640113	KEL	p.L597P	c.1790T>C	16.0 %	1504x	31082	pathogenic
chr12:25398281	KRAS	p.G13D	c.38G>A	4.3 %	1689x	12580	pathogenic
chr15:66727451	MAP2K1	p.Q56P	c.167A>C	3.7 %	1341x	375978	pathogenic
chr15:66729147	MAP2K1	p.H119Y	c.355C>T	4.5 %	1772x	40741	pathogenic
chr5:79970914	MSH3	p.K383fs	c.1148delA	31.5 %	1272x	8738	pathogenic
chr2:48030639	MSH6	p.F56fs p.F1088fs . p.F958fs p.F786fs	c.165delC c.3261delC c.*2608delC c.2871delC c.2355delC	1.1 %	1595x	89363	pathogenic
chr2:48030639	MSH6	p.F786fs p.F1088fs . p.F958fs p.F56fs	c.2355insC c.3261insC c.*2608insC c.2871insC c.165insC	5.1 %	1595x	89364	pathogenic
chr17:29553477	NF1	p.P678fs p.P344fs . p.P712fs	c.2033delC c.1031delC c.*1434delC c.2135delC	5.6 %	1194x	428991	pathogenic
chr17:29553477	NF1	p.I345fs p.I679fs . p.I713fs	c.1031insC c.2033insC c.*1434insC c.2135insC	4.2 %	1194x	141513	pathogenic
chr3:178936091	PIK3CA	p.E545K	c.1633G>A	5.0 %	1291x	13655	pathogenic
chr3:178947865	PIK3CA	p.G914R	c.2740G>A	5.6 %	2226x	39703	pathogenic
chr3:178952085	PIK3CA	p.H1047R	c.3140A>G	14.4 %	1957x	13652	pathogenic
chr5:131931451	RAD50	p.K722fs . . p.?661fs	c.2165delA c.*1791delA c.*351delA c.1982delA	15.0 %	1372x	408407	pathogenic
chr12:21331549	SLCO1B1	p.V174A	c.521T>C	19.6 %	1539x	37346	drug response
chr7:141672604	TAS2R38	p.I296V	c.886A>G	58.6 %	2304x	2906	drug response
chr7:141673345	TAS2R38	p.A49P	c.145G>C	55.0 %	2233x	2904	drug response
chr17:7577559	TP53	p.S82F p.S230F p.S202F p.S109F p.S148F p.S241F	c.245C>T c.689C>T c.605C>T c.326C>T c.443C>T c.722C>T	5.9 %	752x	12359	pathogenic

Location	Gene	AA Change	Codon Change	Mutation Freq.	Depth	ClinVar ID	ClinVar Significance
chr17:7577559	TP53	p.S148C p.S82C p.S241C p.S230C p.S109C p.S202C	c.443C>G c.245C>G c.722C>G c.689C>G c.326C>G c.605C>G	5.7 %	752x	177791	likely pathogenic
chr17:7579472	TP53	p.P33R p.P72R	c.98C>G c.215C>G	80.5 %	931x	12351	drug response
chr21:44524456	U2AF1	p.S34F . .	c.101C>T c.-186C>T c.-119C>T	8.1 %	677x	376025	likely pathogenic
chr21:44524456	U2AF1L5	p.S34F . .	c.101C>T c.-186C>T c.-119C>T	8.1 %	677x	376025	likely pathogenic
chr3:14187449	XPC	p.Q939K .	c.2815C>A c.*2268C>A	40.5 %	570x	190215	drug response

1.2.2 HD753_4 Results

Table 3: Variants (SNV and InDels) in sample - **HD753_4.** Entries are sorted by gene.

Location	Gene	AA Change	Codon Change	Mutation Freq.	Depth	ClinVar ID	ClinVar Significance
chr7:87160618	ABCB1	p.S893A p.S829A	c.2677T>G c.2485T>G	67.4 %	1281x	166622	drug response
chr5:131931451	AC116366.3	. . . .	c.*2341delA c.*1321delA c.*2025delA c.*2155delA	15.4 %	1267x	408407	pathogenic
chr14:105246551	AKT1	. p.E17K	n.80G>A c.49G>A	5.4 %	905x	13983	pathogenic
chr10:96540410	AL583836.1	.	c.*394G>A	4.1 %	1128x	16899	drug response
chr10:96541616	AL583836.1	.	c.*439G>A	20.8 %	942x	16897	drug response
chr20:31022441	ASXL1	p.G641fs p.G646fs	c.1919insG c.1934insG	4.1 %	580x	426927	pathogenic
chr11:108205832	ATM	p.V2716A	c.8147T>C	4.1 %	1653x	142700	pathogenic
chr17:63532584	AXIN2	p.G600fs p.G665fs	c.1799delG c.1994delG	5.6 %	393x	5880	pathogenic
chr19:49458970	BAX	p.E41fs p.R24fs p.E24fs	c.121insG c.69insG c.70insG	0.8 %	860x	9511	pathogenic
chr7:140453136	BRAF	. p.V207E p.V600E p.V28E	c.*1249T>A c.620T>A c.1799T>A c.83T>A	18.3 %	1597x	13961	pathogenic
chr17:41234451	BRCA1	.	c.*4110C>T	5.1 %	1712x	17675	pathogenic
chr13:32937354	BRCA2	p.I2675fs	c.8021insA	6.1 %	906x	267050	pathogenic
chr9:21971186	CDKN2A	. p.P72L	c.*95C>T c.215C>T	11.8 %	211x	376310	likely pathogenic
chr15:93545433	CHD2	p.Q1392fs . .	c.4173insA c.*406insA c.*344insA	11.5 %	252x	218395	pathogenic
chr3:41266101	CTNNB1	p.S33Y p.S26Y	c.98C>A c.77C>A	6.1 %	1382x	17577	pathogenic
chr10:17113456	CUBN	p.S865N	c.2594G>A	4.7 %	654x	265086	pathogenic
chr19:41512841	CYP2B6	p.Q172H	c.516G>T	25.8 %	1905x	29671	drug response
chr19:41515263	CYP2B6	p.K262R	c.785A>G	24.5 %	477x	120171	drug response
chr10:96702047	CYP2C9	p.R144C	c.430C>T	10.4 %	1648x	8409	drug response
chr10:96741053	CYP2C9	p.I359L	c.1075A>C	5.2 %	1253x	8408	drug response
chr22:42524947	CYP2D6	. . . . .	c.353-1G>A c.440-1G>A c.506-1G>A n.1198-1G>A c.173-1G>A	34.1 %	554x	16889	drug response
chr22:42526694	CYP2D6	p.P34S p.P12S	c.100C>T c.34C>T	53.3 %	242x	16893	drug response

Location	Gene	AA Change	Codon Change	Mutation Freq.	Depth	ClinVar ID	ClinVar Significance
chr7:55242464	EGFR	p.E746_A750del p.E701_A705del .	c.2235_2249delGGAATTAAGAGAAGC c.2100_2114delGGAATTAAGAGAAGC c.*225_*239delGGAATTAAGAGAAGC	2.6 %	1911x	163343	drug response
chr7:55248998	EGFR	p.A767_V769ins . p.A722_V724ins	c.2300_2308insCCAGCGTGG c.*290_*298insCCAGCGTGG c.2165_2173insCCAGCGTGG	4.5 %	1325x	177678	drug response
chr22:41565529	EP300	p.D1399N	c.4195G>A	9.8 %	1018x	376401	likely pathogenic
chr8:118849384	EXT1	p.R129H p.R340H	c.386G>A c.1019G>A	11.1 %	1140x	265129	pathogenic
chr5:176520243	FGFR4	p.G23R p.G388R	c.67G>A c.1162G>A	28.7 %	401x	16326	pathogenic
chr19:3118942	GNA11	p.Q57L p.Q209L	c.170A>T c.626A>T	4.3 %	857x	376002	pathogenic
chr11:67352689	GSTP1	. p.I105V	c.*137A>G c.313A>G	58.7 %	1398x	37340	drug response
chr12:121432114	HNF1A	p.P291fs p.G226fs .	c.864delG c.677delG c.*304delG	5.0 %	723x	435424	pathogenic
chr7:142640113	KEL	p.L597P	c.1790T>C	17.4 %	1431x	31082	pathogenic
chr12:25398281	KRAS	p.G13D	c.38G>A	4.6 %	1534x	12580	pathogenic
chr15:66727451	MAP2K1	p.Q56P	c.167A>C	5.1 %	1213x	375978	pathogenic
chr15:66729147	MAP2K1	p.H119Y	c.355C>T	5.0 %	1676x	40741	pathogenic
chr5:79970914	MSH3	p.K383fs	c.1148delA	30.6 %	1058x	8738	pathogenic
chr2:48030639	MSH6	p.F56fs p.F1088fs . p.F958fs p.F786fs	c.165delC c.3261delC c.*2608delC c.2871delC c.2355delC	0.9 %	1662x	89363	pathogenic
chr2:48030639	MSH6	p.F786fs p.F1088fs . p.F958fs p.F56fs	c.2355insC c.3261insC c.*2608insC c.2871insC c.165insC	5.2 %	1662x	89364	pathogenic
chr17:29553477	NF1	p.I345fs p.I679fs . p.I713fs	c.1031insC c.2033insC c.*1434insC c.2135insC	4.8 %	1140x	141513	pathogenic
chr17:29553477	NF1	p.P678fs p.P344fs . p.P712fs	c.2033delC c.1031delC c.*1434delC c.2135delC	5.8 %	1140x	428991	pathogenic
chr16:23646980	PALB2	p.M1fs p.M296fs	c.1delA c.886delA	0.3 %	1369x	143979	pathogenic
chr3:178936091	PIK3CA	p.E545K	c.1633G>A	4.8 %	1238x	13655	pathogenic
chr3:178947865	PIK3CA	p.G914R	c.2740G>A	4.6 %	2110x	39703	pathogenic
chr3:178952085	PIK3CA	p.H1047R	c.3140A>G	15.2 %	1846x	13652	pathogenic

Location	Gene	AA Change	Codon Change	Mutation Freq.	Depth	ClinVar ID	ClinVar Significance
chr5:131931451	RAD50	p.K722fs . . p.?661fs	c.2165delA c.*1791delA c.*351delA c.1982delA	15.4 %	1267x	408407	pathogenic
chr12:21331549	SLCO1B1	p.V174A	c.521T>C	18.1 %	1494x	37346	drug response
chr7:141672604	TAS2R38	p.I296V	c.886A>G	59.1 %	2209x	2906	drug response
chr7:141673345	TAS2R38	p.A49P	c.145G>C	54.4 %	2126x	2904	drug response
chr17:7577559	TP53	p.S148C p.S82C p.S241C p.S230C p.S109C p.S202C	c.443C>G c.245C>G c.722C>G c.689C>G c.326C>G c.605C>G	4.2 %	782x	177791	likely pathogenic
chr17:7577559	TP53	p.S82F p.S230F p.S202F p.S109F p.S148F p.S241F	c.245C>T c.689C>T c.605C>T c.326C>T c.443C>T c.722C>T	6.8 %	782x	12359	pathogenic
chr17:7579472	TP53	p.P33R p.P72R	c.98C>G c.215C>G	81.2 %	807x	12351	drug response
chr21:44524456	U2AF1	p.S34F . .	c.101C>T c.-186C>T c.-119C>T	8.2 %	622x	376025	likely pathogenic
chr21:44524456	U2AF1L5	p.S34F . .	c.101C>T c.-186C>T c.-119C>T	8.2 %	622x	376025	likely pathogenic
chr3:14187449	XPC	p.Q939K .	c.2815C>A c.*2268C>A	34.0 %	580x	190215	drug response

1.3 Copy number analysis

Copy number variations (CNV) are detected using the software package CNVkit[4] which uses normalized read depths to infer copy number evenly across the exome/genome. CNVkit uses both the on-target reads and the nonspecifically captured off-target reads to calculate log2 copy ratios across the genome for each sample. Briefly, off-target bins are assigned from the genomic positions between targeted regions, with the average off-target bin size being much larger than the average on-target bin to match their read counts. Both the on and off target locations are then separately used to calculate the mean read depth within each interval. The on and off target read depths are then combined, normalized to a reference derived from control samples, corrected for several systematic biases (GC content, sequence complexity and targets) to result in a final table of log2 copy ratios. Then, the segmentation algorithm uses log2 ratio values to infer discrete copy number events.Copy number events with minimum 100 x coverage are reported.

Table 4: Case vs Control setup.

Case	Control(s)
HD753_3	NA12878_Pv2_052017_CNV_R1, NA12878_Pv2_052017_CNV_R2
HD753_4	NA12878_Pv2_052017_CNV_R1, NA12878_Pv2_052017_CNV_R2

Table 5: Summary of CNV events detected in each sample.

Sample	Duplication Events	Deletion Events
HD753_3	24	10
HD753_4	23	14

1.3.1 HD753_3 Results

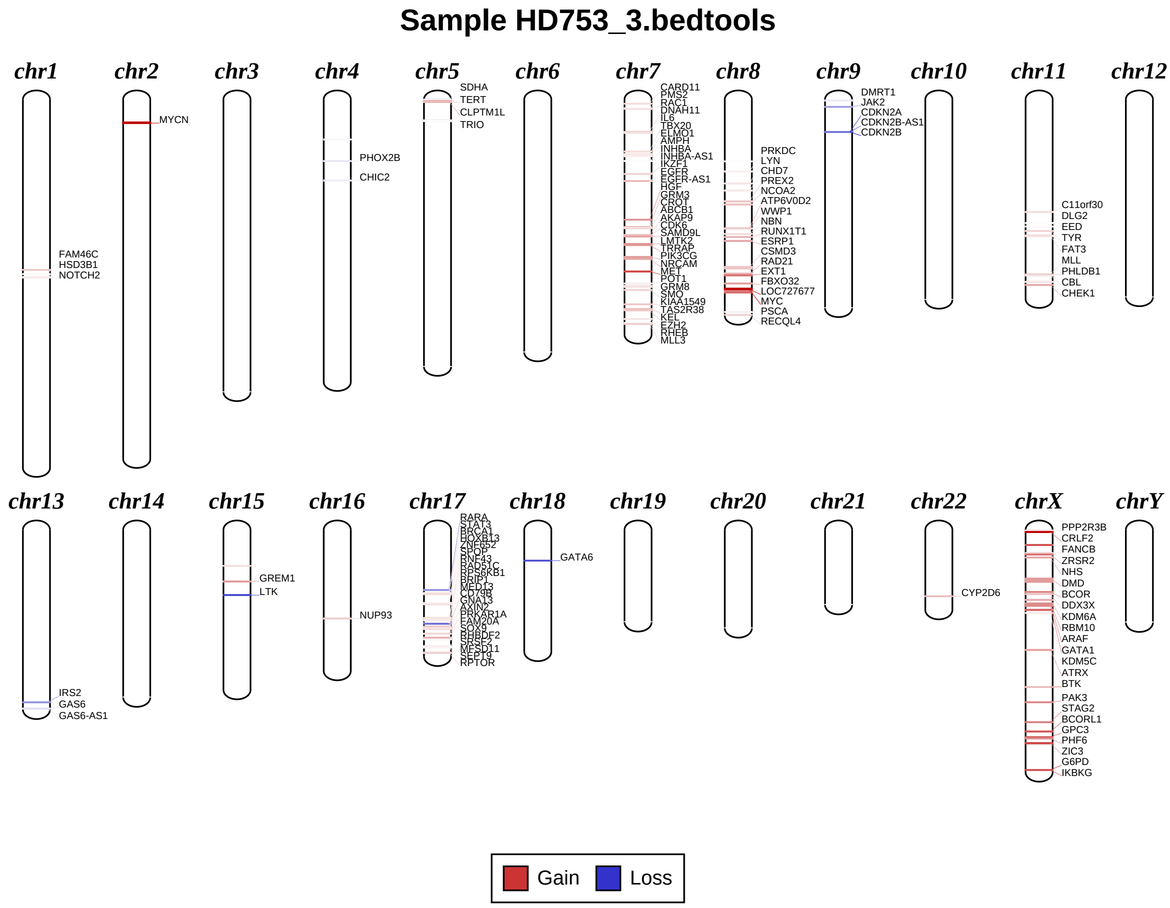

Figure 1: Ideogram representing chromosome wise copy number events observed in sample HD753_3. Copy gain events are drawn in red and copy loss events are drawn in blue.

Table 6: Duplication events detected in sample HD753_3. Gene column lists the name of genes (HGNC convention), CN column contains copy number observed and Depth column displays the coverage depth at the location (Loci column).

Gene	CN	Depth	Loci
MYCNOS, MYCN	9	3407.48	chr2:15729629-16086340
LOC727677, MYC	9	4076.32	chr8:128093106-129192460
MET	4	5155.89	chr7:116312530-116339669
MET	4	2222.36	chr7:116339669-116436309
TAS2R38, KEL, EZH2, RHEB, MLL3	3	1453.71	chr7:141672348-151879671
STAT3, BRCA1	3	1440.28	chr17:40469026-41248090
RNF43, RAD51C, RPS6KB1, BRIP1, MED13, CD79B, GNA13, AXIN2, PRKAR1A, FAM20A, SOX9, RHBDF2, SRSF2, SRSF2, MIR636, SRSF2, MIR636, MFSD11, SRSF2, MFSD11, SEPT9, RPTOR	3	1046.06	chr17:56432135-78938285
PSCA, RECQL4	3	699.78	chr8:129543758-145743186
PREX2, NCOA2, ATP6V0D2, WWP1, NBN, RUNX1T1, ESRP1	3	1219.44	chr8:68864809-95718352
POT1, GRM8, SMO, KIAA1549	3	1291.67	chr7:124503268-138604337

Gene	CN	Depth	Loci
NUP93	3	1229.2	chr16:56782028-56878711
NRAS, FAM46C, HSD3B1, NOTCH2	3	1236.54	chr1:115258835-120572569
NIPA2, GREM1	3	1016.07	chr15:23021376-33023568
MLL, PHLDB1, CBL, CHEK1	3	1552.92	chr11:118318180-125497553
KAT6A, PRKDC, LYN, CHD7, PREX2	3	1130.77	chr8:41906529-68864809
HOXB13, ZNF652, SPOP	3	1150.96	chr17:46804028-47700323
HGF, GRM3, CROT, ABCB1, AKAP9	3	1282.82	chr7:81399053-91719132
EXT1, FBXO32	3	1330.89	chr8:118811823-124553306
CYP2D6	3	702.1	chr22:42522943-42525265
CSMD3, RAD21	3	1136.85	chr8:113236859-117879116
CCDC127, SDHA, SDHA, TERT, CLPTM1L, TRIO	3	941.97	chr5:218285-14532057
CARD11, PMS2, RAC1, DNAH11, IL6, TBX20, ELMO1, AMPH, INHBA, INHBA, INHBA-AS1, IKZF1, EGFR, EGFR, EGFR-AS1	3	1072.63	chr7:2946153-55273441
C11orf30, DLG2, EED, TYR, FAT3	3	1487.38	chr11:76157827-92624397
AKAP9, CDK6, SAMD9L, LMTK2, TRRAP, PIK3CG, NRCAM	3	1483.3	chr7:91722300-107880675

Table 7: Deletion events detected in sample HD753_3. Gene column lists the name of genes (HGNC convention), CN column contains copy number observed and Depth column displays the coverage depth at the location (Loci column).

Gene	CN	Depth	Loci
RARA	1	2956.98	chr17:38497282-38499676
PPP2R3B, CRLF2, FANCB, ZRSR2, NHS, DMD, BCOR, DDX3X, KDM6A, RBM10, ARAF, GATA1, KDM5C	1	665.76	chrX:320389-53222482
PHOX2B, CHIC2	1	598.86	chr4:27162572-54930627
LTK	1	113.2	chr15:41803307-41804311
IRS2, GAS6-AS1, GAS6, GAS6	1	322.92	chr13:110434353-114566778
GATA6	1	109.41	chr18:19751090-19757211
DMRT1, JAK2	1	648.78	chr9:845380-5126957
CDKN2A, CDKN2B-AS1, CDKN2B, CDKN2B-AS1	1	357.65	chr9:21968129-22062228
BTK, PAK3, STAG2, BCORL1, GPC3, PHF6, ZIC3, G6PD, G6PD, IKBKG	1	733.32	chrX:100604718-153775209
ATRX	1	764.09	chrX:76776109-77041667

1.3.2 HD753_4 Results

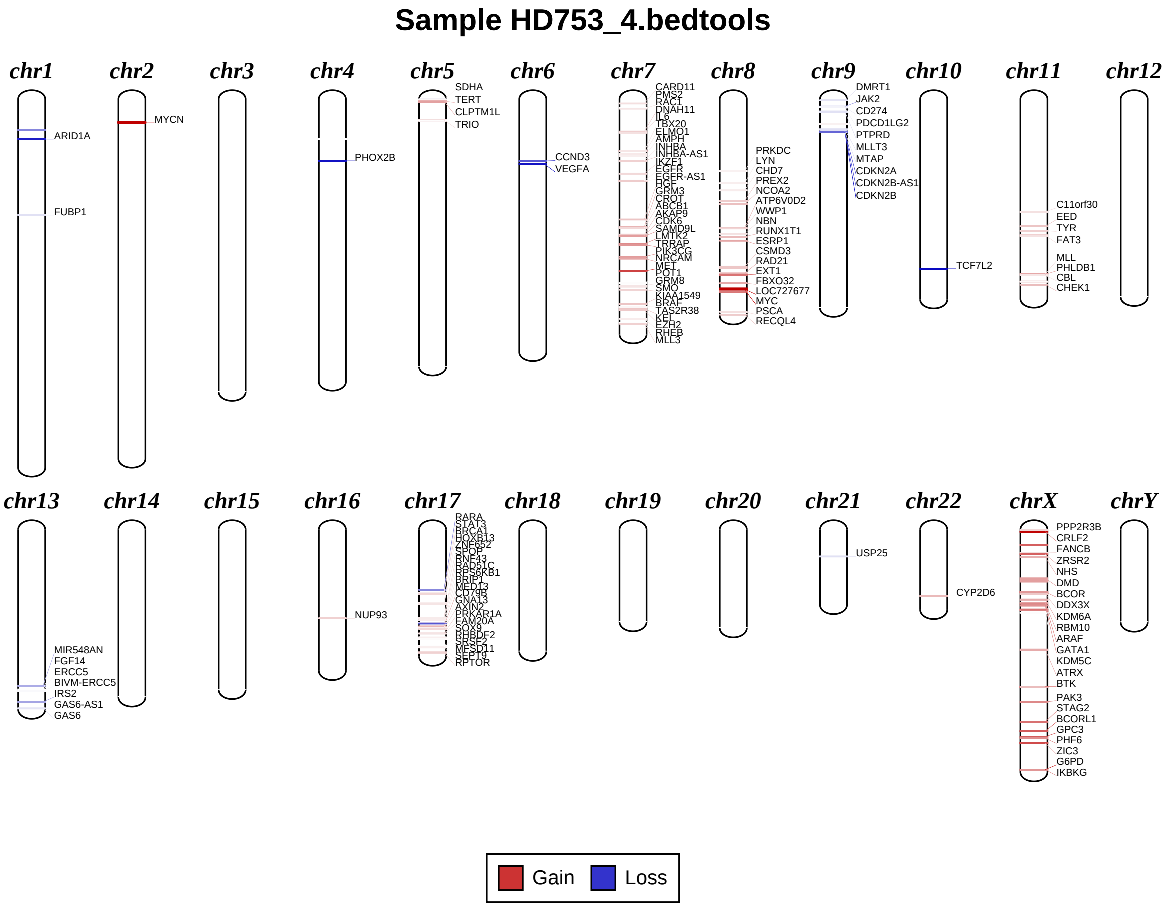

Figure 2: Ideogram representing chromosome wise copy number events observed in sample HD753_4. Copy gain events are drawn in red and copy loss events are drawn in blue.

Table 8: Duplication events detected in sample HD753_4. Gene column lists the name of genes (HGNC convention), CN column contains copy number observed and Depth column displays the coverage depth at the location (Loci column).

Gene	CN	Depth	Loci
MYCNOS, MYCN	9	3210.06	chr2:15729629-16086340
LOC727677, MYC	9	3808.59	chr8:128093106-129192460
NRCAM, MET	4	4735.58	chr7:107880235-116335700
MET	4	3046.81	chr7:116335700-116436309
STAT3, BRCA1	3	1354.15	chr17:40468930-41248090
SAMD9L, LMTK2, TRRAP, PIK3CG, NRCAM	3	1436.99	chr7:92760906-107878400
RNF43, RAD51C, RPS6KB1, BRIP1, MED13, CD79B, GNA13, AXIN2, PRKAR1A, FAM20A, SOX9, RHBDF2, SRSF2, SRSF2, MIR636, SRSF2, MIR636, MFSD11, SRSF2, MFSD11, SEPT9, RPTOR	3	985.26	chr17:56432135-78938285
PSCA, RECQL4	3	683.55	chr8:129543758-145743186
PRKDC, LYN, CHD7, PREX2	3	1057.83	chr8:48686615-68864809
PREX2, NCOA2, ATP6V0D2, WWP1, NBN, RUNX1T1, ESRP1	3	1134.78	chr8:68864809-95718352

Gene	CN	Depth	Loci
POT1, GRM8, SMO, KIAA1549, BRAF, TAS2R38, KEL, EZH2, RHEB, MLL3	3	1383.66	chr7:124462349-151879671
NUP93	3	1156.22	chr16:56782028-56878711
MLL, PHLDB1, CBL, CHEK1	3	1443.7	chr11:118307674-125497553
HOXB13, ZNF652, SPOP	3	1078.12	chr17:46804028-47700323
HGF, GRM3, CROT, ABCB1, AKAP9, CDK6, SAMD9L	3	1198.66	chr7:81399053-92760906
FBXO32	3	1051.59	chr8:124526431-124553306
EXT1, FBXO32	3	1301.2	chr8:118811823-124526431
EED, TYR, FAT3	3	1636.83	chr11:85989283-92624397
CYP2D6	3	680.21	chr22:42522943-42525369
CSMD3, RAD21	3	1062.6	chr8:113236859-117879116
CCDC127, SDHA, SDHA, TERT, CLPTM1L, TRIO	3	896.26	chr5:218285-14532057
CARD11, PMS2, RAC1, DNAH11, IL6, TBX20, ELMO1, AMPH, INHBA, INHBA, INHBA-AS1, IKZF1, EGFR, EGFR, EGFR-AS1	3	1010.54	chr7:2946153-55273441
C11orf30	3	1191.31	chr11:76157827-76261312

Table 9: Deletion events detected in sample HD753_4. Gene column lists the name of genes (HGNC convention), CN column contains copy number observed and Depth column displays the coverage depth at the location (Loci column).

Gene	CN	Depth	Loci
USP25	1	682.48	chr21:17135058-17250927
RARA	1	2787.03	chr17:38497482-38499177
PPP2R3B, CRLF2, FANCB, ZRSR2, NHS, DMD, BCOR, DDX3X, KDM6A, RBM10, ARAF, GATA1, KDM5C	1	620.9	chrX:320389-53222482
PHOX2B	1	399.86	chr4:27162287-41748357
MIR548AN, FGF14, BIVM-ERCC5, ERCC5, IRS2, GAS6-AS1, GAS6, GAS6	1	634.49	chr13:100041547-114566778
FUBP1	1	704.69	chr1:78414264-78435748
DMRT1, JAK2	1	602.78	chr9:845380-5126957
CDKN2A, CDKN2B-AS1, CDKN2B, CDKN2B-AS1	1	347.12	chr9:21968129-22062228
CDA, ARID1A	1	155.91	chr1:20945002-27023944
CD274, PDCD1LG2, PTPRD, MLLT3, MTAP, CDKN2A	1	786.59	chr9:5455949-21968129
CCND3, VEGFA	1	172.01	chr6:41909068-43739196
BTK, PAK3, STAG2, BCORL1, GPC3, PHF6, ZIC3, G6PD, G6PD, IKBKG	1	693.44	chrX:100604718-153775209
ATRX	1	705.82	chrX:76763817-77041667
TCF7L2	0	139.28	chr10:114710993-114711498

1.4 Fusion gene discovery

Fusion events are detected using the software DELLY2[5]. From the genome alignments, DELLY discovers fusion events (translocations and inversions) by integrating insert distances determined by the paired-end reads and split-read alignments to accurately detect genomic rearrangements at single nucleotide resolution. Fusion events are tagged as "Known fusions" if they match the entry in ChimerDB[6] (collection of known fusion events). Known fusion events are reported in the following sections (if any).

Table 10: Summary of fusion events detected in each sample.

Sample	Known events	Unknown events
HD753_3	1	2
HD753_4	1	2

1.4.1 HD753_3 Results

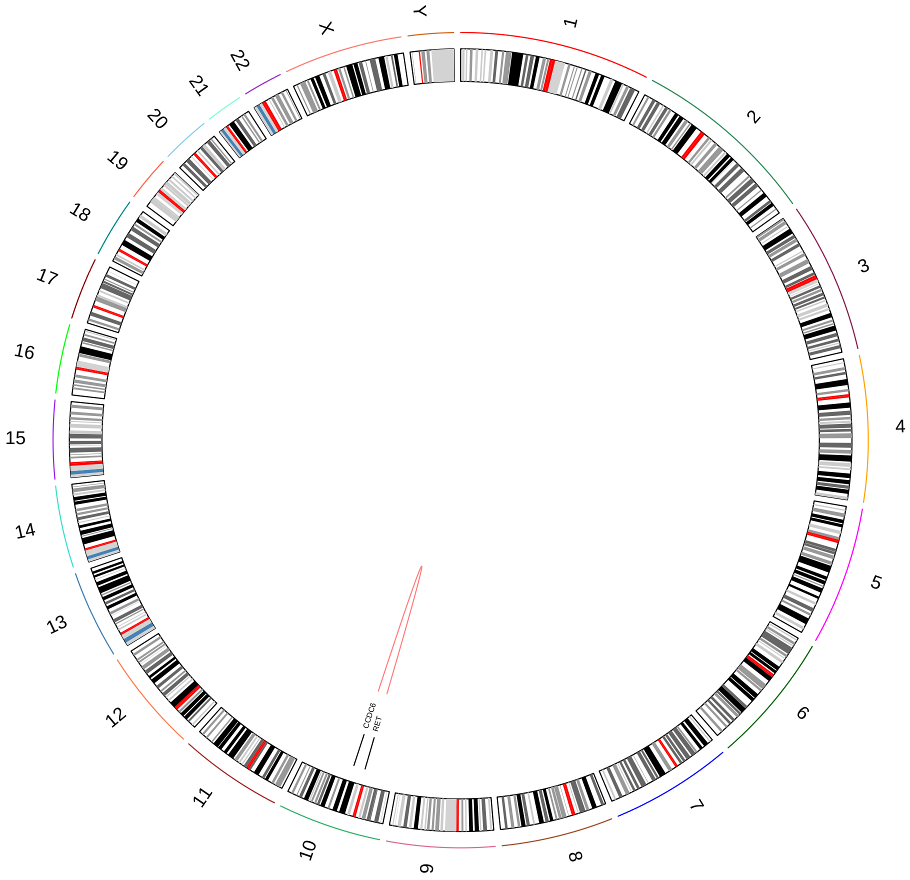

Figure 3: Circos plot displaying fusion events in relation to chromosome location for sample HD753_3. Fusion events observed on the same chromosome are drawn in red whereas fusion events that are on different chromosomes are drawn in blue. Gene annotations are drawn at the tip of the arcs.

Table 11: Fusion events detected in sample HD753_3. Associated disease and source of annotation are mentioned in Disease and Source column, respectively.

Fusion genes	Fusion location	Supporting fusion reads	Supporting paired reads	Disease	Source
RET–CCDC6	chr10:43609952-chr10:61638611	33	36	adenocarcinoma	Mitelman,OMIM,GenBank

1.4.2 HD753_4 Results

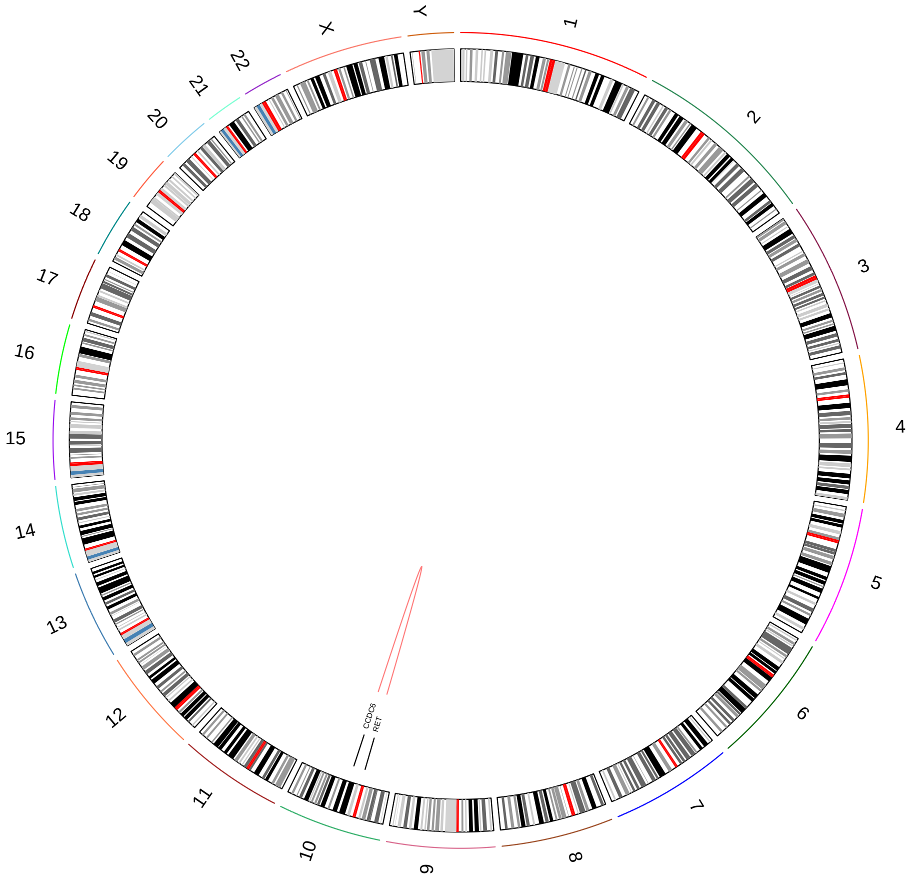

Figure 4: Circos plot displaying fusion events in relation to chromosome location for sample HD753_4. Fusion events observed on the same chromosome are drawn in red whereas fusion events that are on different chromosomes are drawn in blue. Gene annotations are drawn at the tip of the arcs.

Table 12: Fusion events detected in sample HD753_4. Associated disease and source of annotation are mentioned in Disease and Source column, respectively.

Fusion genes	Fusion location	Supporting fusion reads	Supporting paired reads	Disease	Source
RET–CCDC6	chr10:43609952-chr10:61638611	22	21	adenocarcinoma	Mitel-man,OMIM,GenBank

2 Quality Metrics

2.1 Sequence Quality Metrics

The base quality of each sequence read is inspected. Low quality calls are removed before proceeding with further processing. Using a sliding window approach, bases with low quality are removed from the 3' and 5' ends. Bases are removed if the average phred quality is below 15. Finally only mate pairs (forward and reverse read) were used for the next analysis step. The total amount of raw sequence data and the results of the quality filtering is collected and reported in the following table.

Table 13: Sequence quality metrics per sample

Sample	Total Reads	LQ Reads	Single Reads	HQ Reads
HD753_3	83,483,850	1,900,592 (2.3%)	1,791,324 (2.1%)	79,791,934 (95.6%)
HD753_4	77,279,854	1,821,082 (2.4%)	1,720,580 (2.2%)	73,738,192 (95.4%)

Total Reads: Total number of sequence reads analysed for each sample.

LQ Reads: Number of low quality reads.

Single Reads: Number of high quality reads without mates (2nd read).

HQ Reads: Number of high quality reads used for further analysis.

2.2 Alignment Metrics

Mapping to the reference sequence/database is done using BWA[7] with default parameters. The following table contains the number of reads mapped to the reference for each sample. Please note that the mapping efficiency depends on the accuracy of the reference and the quality of sequence reads.

Table 14: Mapped read metrics observed per sample

Sample Name	HQ Reads	Mapped Reads
HD753_3	79,791,934	79,692,755 (99.88%)
HD753_4	73,738,192	73,635,493 (99.86%)

2.3 Alignment Classification

The alignment classification table includes the following read categories:

- Mapped: Reads mapped to reference.
- Unique: Reads mapped to exactly one site on the reference.
- Non-unique: Reads mapped to more than one site on the reference.
- Singletons: Mapped reads without mates (read not paired).
- Cross-Contig: Read pairs with the mate mapped to a different contig.

- On target: Reads mapped to target +/- 100 bp extension.

Percentage of reads in categories **Non-unique, Unique, Singletons, Cross-Contig** are calculated based on the number of reads mapping to entire reference.
Percentage of reads in category **On target** is calculated based on the number of reads mapped uniquely (excluding **Singletons** and **Cross-Contig** - if any).

Table 15: Read metrics for HD753_3, HD753_4.

Read category	HD753_3	HD753_4
Mapped	79,692,755	73,635,493
Unique	78,148,831 (98.06%)	72,185,992 (98.03%)
Non-unique	1,543,924 (1.94%)	1,449,501 (1.97%)
Singletons	16,467 (0.02%)	15,256 (0.02%)
Cross-Contig	185,612 (0.23%)	167,679 (0.23%)
On target	60,223,567 (77.26%)	53,068,587 (73.70%)

Reads in categorie(s) **Non-unique** , **Singletons** and **Cross-Contig** are excluded from analysis.

2.4 Alignment Refinement Metrics

The removal of PCR duplicates is done using Picard[8] in order to remove the artificial coverage brought on by the PCR amplification step during the library preparation. If a read maps to the same genomic location and has same orientation as the read already mapped it is considered as duplicated. For paired-end, both reads should fulfill the criteria in order to designate as PCR duplicate. One copy of the duplicate read pair is kept in the alignment.

Local realignment serves to transform regions with misalignments due to indels into clean reads containing a consensus indel suitable for standard variant discovery approaches. GATK is used for this purpose.

The goal of Base Quality Recalibration is to improve the base quality score of reads for downstream processing and also correct for error covariates like machine cycle and dinucleotide context. A base quality score represents the probability of a particular base mismatching the reference genome. After recalibration quality scores are more accurate in that they are closer to the true probability of mismatch. This process is achieved by analyzing the covariation among several different features of a base. The reported quality score, sequencing cycle, and sequencing context are considered for this step. GATK modules are used for achieving this.

The following table contains the number of high-quality reads after read mapping, alignment and refinement.

Table 16: HQAligned reads per sample

Sample Name	Input Reads	Duplicate Reads	HQ Reads
HD753_3	60,223,567	25,157,050 (41.77%)	35,066,517 (58.23%)
HD753_4	53,068,587	20,017,660 (37.72%)	33,050,927 (62.28%)

2.5 Coverage Report

The coverage plot showing the base coverage distribution from the HQ aligned data. Depth of coverage is plotted on X-axis and the percentage of the respective reference covered is plotted on Y-axis. The coverage plot is restricted to the target region without extension. The shape of the curve defines the uniformity of the reference coverage in the samples analysed. Samples with high uniformity usually have >90% covered at 0.2x average coverage (e.g. 100x for 500x average coverage)

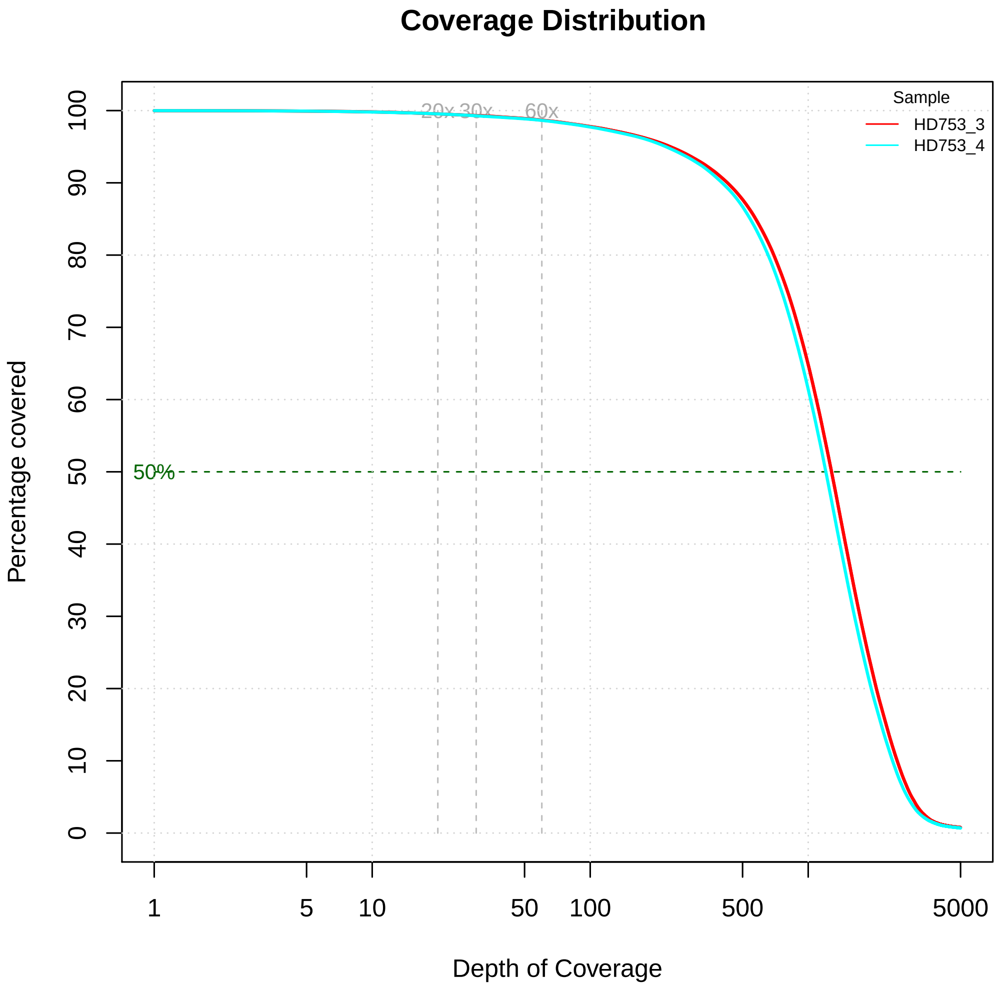

Figure 5: Coverage plot (excluding duplicated fragments).

Table 17: Depth of coverage summary (excluding duplicated fragments).

	target coverage		% of target covered with at least				
sample	total bases	average (x)	2x	50x	100x	300x	500x
HD753_3	4.14 GB	1425.33	100	98.9	97.8	93.4	87.7
HD753_4	3.92 GB	1350.25	100	98.9	97.7	93.0	86.7

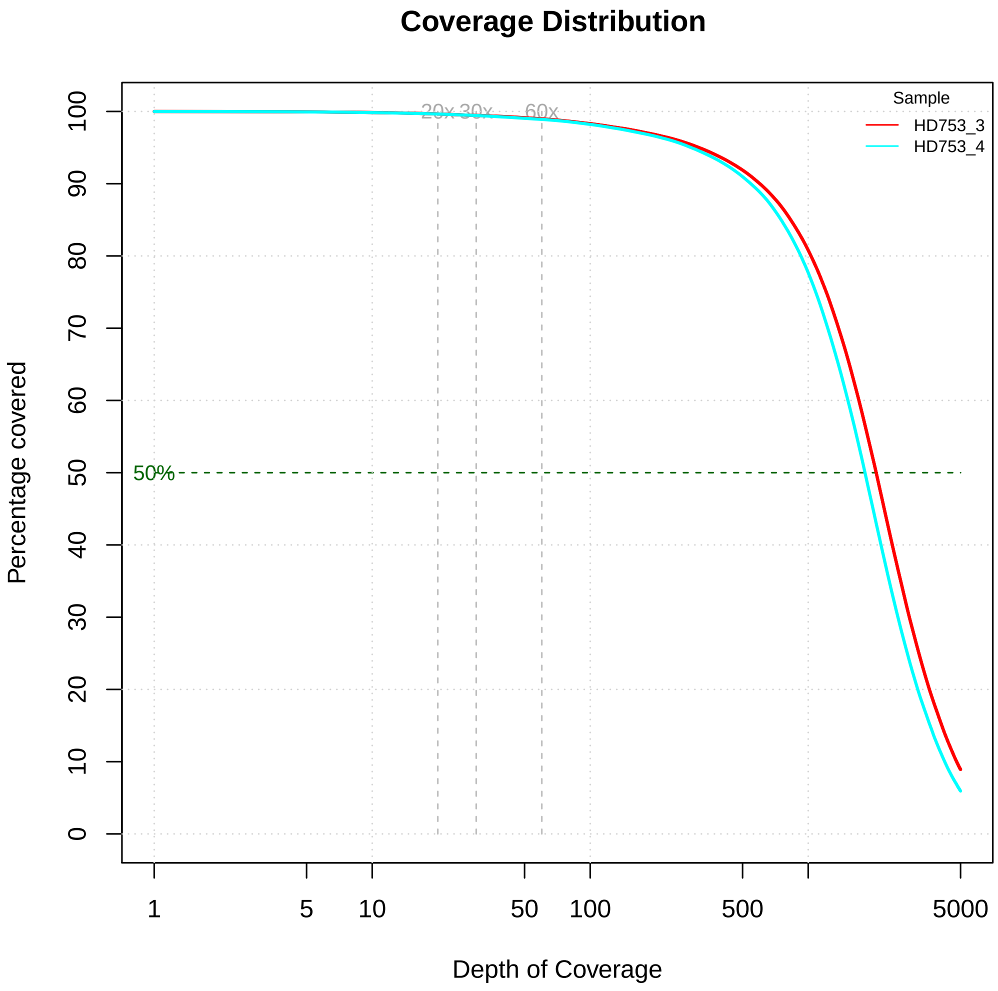

Figure 6: Coverage plot (including duplicated fragments).

Table 18: Depth of coverage summary (including duplicated fragments).

	target coverage		% of target covered with at least				
sample	total bases	average (x)	2x	50x	100x	300x	500x
HD753_3	7.23 GB	2486.13	100	99.1	98.3	95.3	91.9
HD753_4	6.40 GB	2200.72	100	99.0	98.2	94.8	91.0

2.6 Library Report

Fragment insert size histogram of the paired-end library observed from all the samples analysed. The insert size is determined by mapping individual read pairs on the reference sequence. The distance between 5'prime ends of both sequenced reads in a pair that are mapped to the reference is the observed length of the sequenced fragment. By performing this operation for all mapped reads the distribution can be generated. X-axis shows the insert size in bp and Y-axis shows the number of fragments with the observed fragment insert sizes.

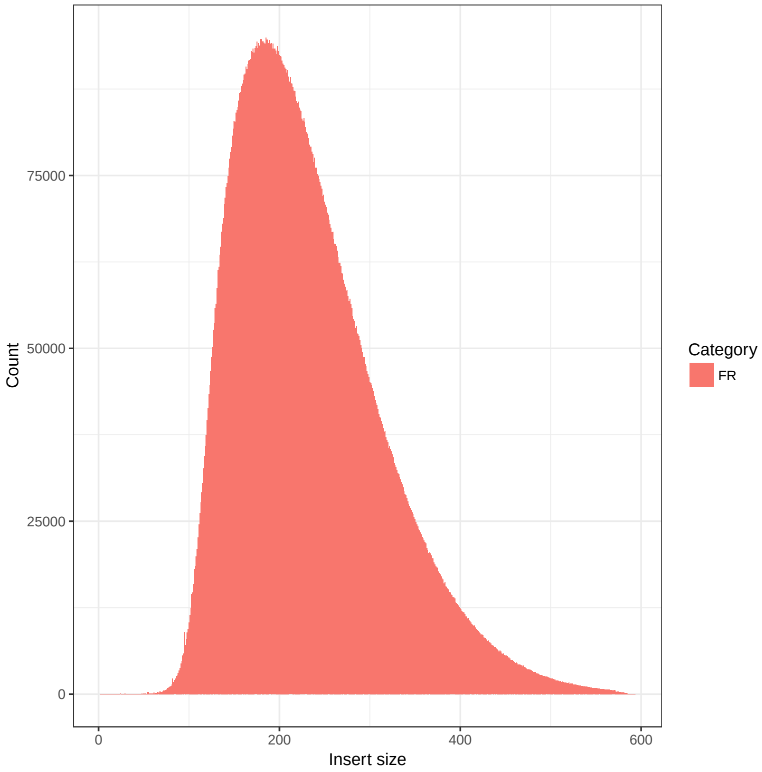

Figure 7: HD753_3 .

Table 19: Sample wise insert size metrics for HQ aligned reads. The mean insert size (Mean) and its standard deviation (Stddev) is given in base pairs.

Sample	Pair orientation	Mean	Stddev	# Read pairs
HD753_3	FR	232	81	17,495,031
HD753_4	FR	230	80	16,489,444

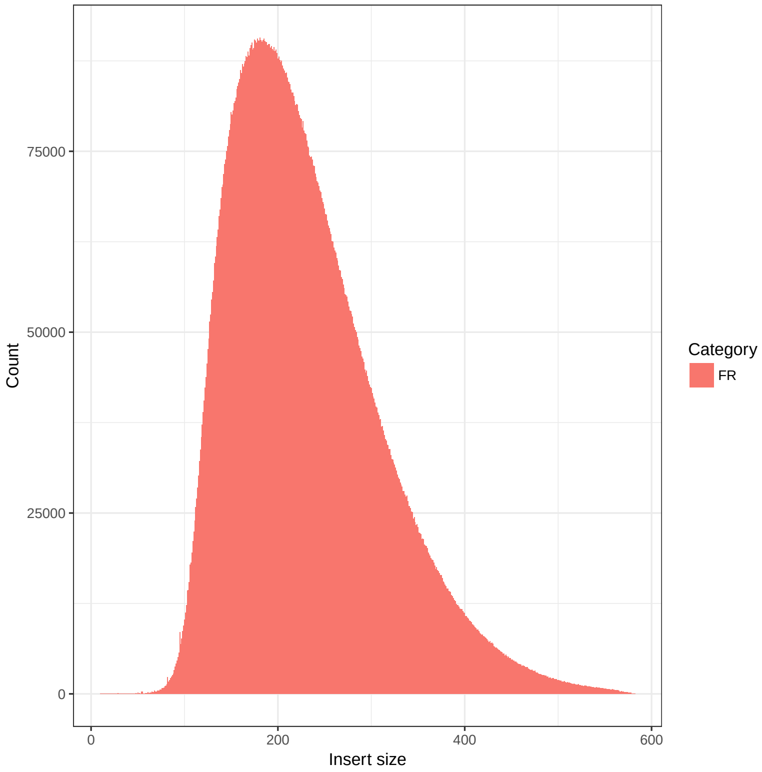

Figure 8: HD753_4 .

3 Deliverables

Table 20: List of delivered files, format and recommended programs to access the data.

File	Format	Program To Open File
PROJECT_supplementary_tables.tar.gz	GZ	Unzip tool
SAMPLE.CNV_deletion.tsv	TSV	Spreadsheet Editor
SAMPLE.CNV_duplication.tsv	TSV	Spreadsheet Editor
SAMPLE.fusion_events.tsv	TSV	Spreadsheet Editor
SAMPLE.hg19.HQ.alignment.bam	BAM	IGV, Tablet
SAMPLE.hg19.HQ.alignment.bam.bai	BAI	None
SAMPLE.hg19.alignment.bam	BAM	IGV, Tablet
SAMPLE.hg19.alignment.bam.bai	BAI	None
SAMPLE.indels.tsv	TSV	Spreadsheet Editor
SAMPLE.indels.vcf	VCF	Text Editor
SAMPLE.snps.tsv	TSV	Spreadsheet Editor
SAMPLE.snps.vcf	VCF	Text Editor

SAMPLE.hg19.alignment.bam was used for Fusion Gene discovery (see chapter 1.4)
SAMPLE.hg19.HQ.alignment.bam was used for Variant discovery (see chapter 1.1) and for Copy number analysis (see chapter 1.3)
PROJECT_supplementary_tables.tar.gz contains the variant calls (SNVs and InDels) that were observed in the sample(s) but filtered out due to QC checks.

4 Formats

Table 21: References and descriptions of file format.

Format	Description
TSV	Tab separated table style text file. This can be imported into spreadsheet processing software like MS OFFICE Excel.
FASTQ[9]	Text-based format for storing both a biological sequence (usually nucleotide sequence) and its corresponding quality scores. Both the sequence letter and quality score are encoded with a single ASCII character for brevity.
BAM[10]	Compressed binary version of the Sequence Alignment/Mapping (SAM) format, a compact and index-able representation of nucleotide sequence alignments.
VCF[11]	Variant Call Format (VCF) is a format to describe and report the variants.

5 FAQ

Q: How can I open a TSV file in Excel?
A: Start Excel and click File -> Open and select the TSV file you want to open. Next an assistant dialog should show up. Make sure that you select tab as separator. Set the format of all rows without numbers to text. The TSV files use the dot as decimal separator and comma as thousands separator. Make sure that you set both correctly.

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A Analysis Workflow

The schematic diagram of the data analysis steps that have been performed is shown in figure 1.

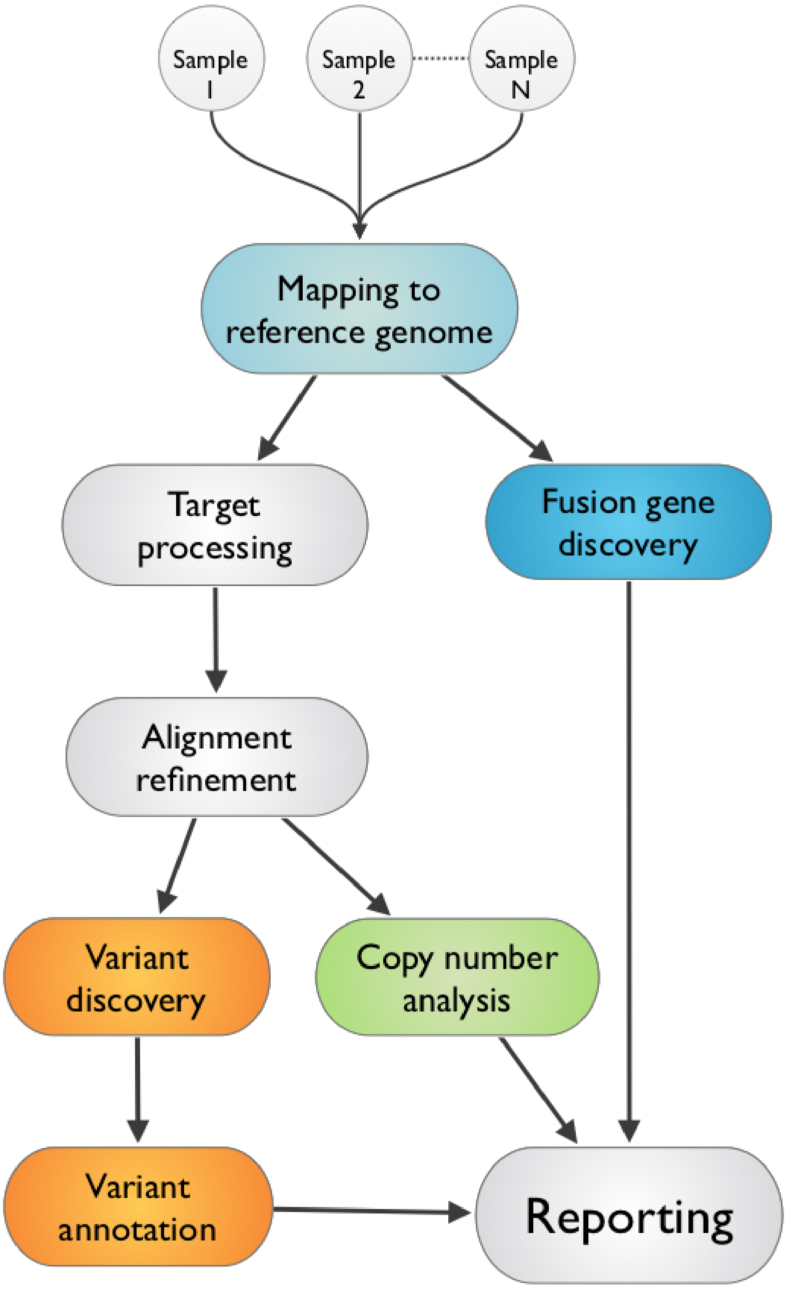

Figure 9: ONCOPANEL ALL-IN-ONE v1.4 Workflow

B Sequence Data Used

Table 22: Analysed samples (SE = single end, PE = paired end).

Sample	Read Type	File Name
HD753_3	PE	FE-0242_HD753_3_lib185570_5345_1_1.fastq FE-0242_HD753_3_lib185570_5345_1_2.fastq
HD753_4	PE	FE-0242_HD753_4_lib185571_5345_1_1.fastq FE-0242_HD753_4_lib185571_5345_1_2.fastq

C Reference Database

Table 23: Information about the Homo sapiens Reference Database.

Tag	Description
Name	Homo sapiens
Version	hg19.chronly
Source	UCSC
Size (bp)	3.095 GB
Sequences	23

Table 24: Information about additional reference data used.

Type	Version	Source
Annotation	19	GENCODE
dbSNP	150	NCBI
ClinVar[3]	02.10.17	NCBI
COSMIC[2]	71	Sanger Institute
ChimerDB[6]	2.0	ERCSB

Table 25: Information about the target region used.

Tag	Description
Name	GATC All in One
Size (bp)	2,908,369
Source	GATC Biotech AG

D Relevant Programs

Table 26: Name, version and description of relevant programs.

Program	Version	Description
bamtools[12]	2.3.0	BamTools provides a small, but powerful suite of command-line utility programs for manipulating and querying BAM files for data.
BamUtil[13]	1.0.10	BamUtil is a repository that contains several programs that perform operations on SAM/BAM files
bedtools[14]	2.26.0	Bedtools allows one to intersect, merge, count, complement, and shuffle genomic intervals from multiple files in widely-usedgenomic file formats such as BAM, BED, GFF/GTF, VCF
BWA[7]	0.7.15	BWA is a software package for mapping low-divergent sequences against a large reference genome
CNVkit[4]	0.9.1.dev0	CNVkit is a Python library and command-line software toolkit to infer and visualize copy number from targeted DNA sequencing data
Delly2[5]	0.7.6	DELLY2: Structural variant discovery by integrated paired-end and split-read analysis
GATK[15, 16]	3.7	GATK is a java-based command-line toolkit that process SAM / BAM / VCF files.
LoFreq[1]	2.1.2	Lofreq is a fast and sensitive variant caller for inferring SNVs and indels from next-generation sequencing data.
Picard[8]	1.131	Picard is a java-based command-line utilities for processing SAM / BAM files.
R[17]	3.2.4	R is a programming language and environment for statistical computing.
sambamba[18]	0.6.6	Sambamba is a high performance modern robust and fast tool (and library), for working with SAM and BAM files.
SAMTools[19]	0.1.18	SAMtools provide various utilities for manipulating alignments in the SAM format.
snpEff[20]	4.3	SnpEff is a genetic variant annotation and effect prediction toolbox.
SnpSift[20]	4.3	SnpSift helps filtering and manipulating genomic annotated files .
Trimmomatic[21]	0.33	Trimmomatic performs a variety of useful trimming tasks for Illumina paired-end and single-end data.

E Tables

Table 27: Definition of fields of the tab delimited variant report (Sample.indels.tsv and Sample.snps.tsv).

Name	Meaning
Ref ID	Name of chromosome or reference contig where the variant occurs.
Position	Position of reference contig or chromosome where the variant occurs.
Reference Base (s)	The reference base at the variant site.
Modified Base (s)	Alternative (observed) base in the samples in general [VARIANT].
Mutation Frequency (%)	The mutation frequency with which a particular mutation occurs in a population.
Coverage Depth (x)	The total depth of the reads that passed the internal quality control metrics from all reads present at this site.
dbID	Known variant indentifier.
FILTER	Variants passing the filters will be tagged as "PASS" and the variants failing the filters will be tagged by the respective filter names.
AF	Allele (Mutation) frequency.
DP	Counts for ref-forward bases, ref-reverse, alt-forward and alt-reverse bases.
CLNDSDBID	Variant disease database ID.
CLNSIG	Variant Clinical Significance, 0 - unknown, 1 - untested, 2 - non-pathogenic, 3 - probable-non-pathogenic, 4 - probable-pathogenic, 5 - pathogenic, 6 - drug-response, 7 - histocompatibility, 255 - other.

Table 28: Definition of genomic annotations as produced by snpEff (Sample.indels.tsv and Sample.snps.tsv).

Name	Meaning
EFFECT	Variant's effect on protein.
IMPACT	Predicted impact from variant's protein effect.
HGVS_C	Variant's codon change (DNA level).
HGVS_P	Variant's codon change (Protein level).
GENE	The gene entry associated with the location of the variant call.
BIOTYPE	Variant's coding status.
TRID	Associated transcript IDs.
CDS_POS	Variant's codon change position.
AA_POS	Variant's amino acid position.

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