Gene-Drug Predictive Associations

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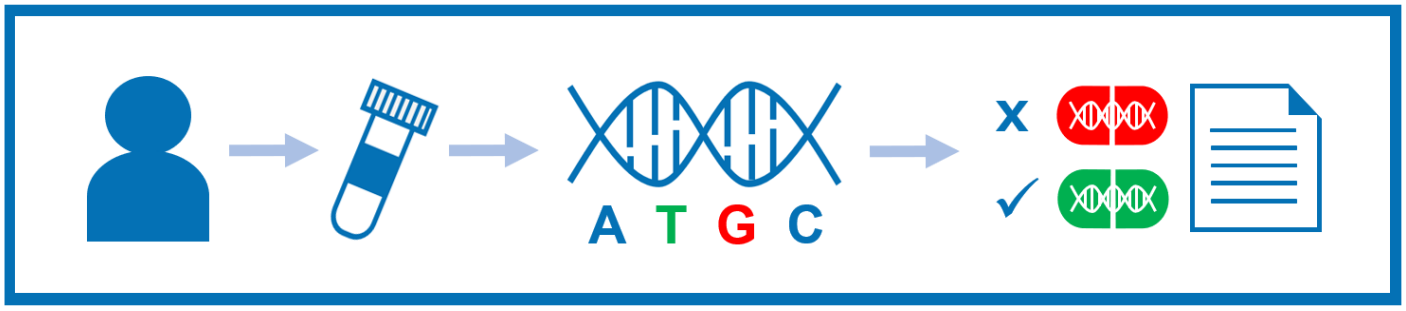
Genome Enhancer release 3.3 (GKDB version 20.0, CIViC version 01 October 2022)

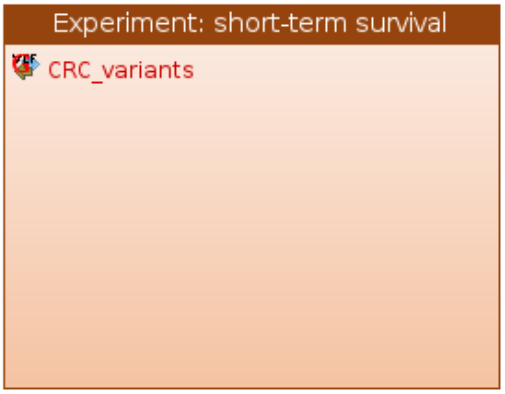


MTB Report - From somatic variants to treatment options

GENE-DRUG PREDICTIVE ASSOCIATIONS

This report is based on the following genomics data, which was submitted for the current study in the Genome Enhancer pipeline:

Experiment: short-term survival
CRC_variants



Annotation diagram of experimental data used in the study.

The studied pathology, which was selected during the Genome Enhancer analysis launch, was *Colorectal Neoplasms*. This disease matches the following pathology, which was used as the input parameter for the Molecular Tumor Board (MTB) method to produce this report: *Colorectal Cancer*.

The Variant Effect Predictor analysis was applied to the input vcf track, which was submitted for the analysis in the *Experiment: short-term survival* condition. All mutations, which were found in the studied data in comparison to the reference genome, were annotated with the predicted effects. The gene-drug predictive associations were further retrieved with the use of the MTB method.

Gene-drug predictive associations method used in the MTB report: somatic variants of the studied input data (mutations, amplifications, deletions, rearrangements) were searched in curated databases of predictive biomarkers (GKDB, CIViC) and reported according to their clinical evidence (Levels of Evidence).

Levels of Evidence: Findings are classified into six levels of evidence combining the axis A-B and the axis 1-2-3. Level A means evidence was found in the same cancer type as the one being studied. Level B means evidence was found in any other cancer type. On the 1-2-3 axis, level 1 means the evidence is supported by drug approval organizations or clinical guidelines, level 2 contains a clinical evidence (clinical trials, case reports) and level 3 consists of a preclinical evidence.

The report summarizes all predictive associations in a detailed table. The results are sorted by the level of evidence (A1-B1-A2-B2-A3-B3). To allow a quick interpretation, the type of the association (response, resistance) is colored (green, red) and new variants are displayed in gray.

Table 1. Report for Colorectal Cancer

Gene	Variant	Disease	Known Variant	Association	Drugs	Evidence	PMID	Level
BRCA1	S370I S1512I S408I S1533I S283I S1465I S362I S3I S308I F304L F88L F170L F278L F257L F8L F263L	Epithelial Ovarian Cancer	any variant (LoF)	response	olaparib	FDA-approved	FDA	B1
BRCA1	S370I S1512I S408I S1533I S283I S1465I S362I S3I S308I F304L F88L F170L F278L F257L F8L F263L	Epithelial Ovarian Cancer	any variant (LoF)	response	rucaparib	FDA-approved	FDA	B1
BRCA2	V2466A	Epithelial Ovarian Cancer	any variant (LoF)	response	olaparib	FDA-approved	FDA	B1
BRCA2	V2466A	Epithelial Ovarian Cancer	any variant (LoF)	response	rucaparib	FDA-approved	FDA	B1
POLE	V411L V384L	Colon Cancer	any variant (LoF)	response	PD1 blockade	case report	28188185	A2
RNF43	L418M L291M L377M P231L R343H R216H R302H P104L I47V P190L	Colon Cancer	any variant (GoF)	response	porcupine inhibitors	case report	ENA 2015 (abstract C45)	A2
GSTP1	I105V	Colorectal Cancer	I105V	sensitivity/response	FOLFOX Regimen	clin. trials	19922504	A2
PTEN	R130Q	Colon Cancer	any variant (LoF)	resistance	anti-EGFR mAbs	late trials	21163703, 19398573	A2
PTEN	R130Q	Pancreas Adenocarcinoma	any variant (LoF)	response	AKT inhibitors	case report	22025163	B2
TSC1	M322T M271T M201T	angiosarcoma	any variant (LoF)	response	everolimus	case report	26859683	B2
TSC1	M322T M271T M201T	Renal Cell Carcinoma	any variant (LoF)	response	everolimus	case report	24622468, 26859683, ASCO 2015 (abstr	B2

							11010), ASCO 2015 (abstr 4519)	
PTPRD	R995C	angiosarcoma	any mut. (GoF)	response	IGF-1R antibodies	case report	23800680	B2
PTEN	R130Q	Endometrial Cancer	any variant (LoF)	response	PARP inhibitors	case report	21468130, 20944090	B2
BRCA1	S370I S1512I S408I S1533I S283I S1465I S362I S3I S308I F304L F88L F170L F278L F257L F8L F263L	Pancreas Adenocarcinoma	any variant (LoF)	response	PARP inhibitors	case report	25366685, 25719666	B2
B2M	L41W C45G F64V F82V F34V	Melanoma	any variant (LoF)	resistance	PD1 blockade	case report	27433843	B2
BRCA2	V2466A	Melanoma	any variant (LoF)	response	PD1 blockade	case report	26997480	B2
PTEN	R130Q	Prostate Cancer	any variant (LoF)	response	PI3K beta inhibitor	case report	ASCO 2014 (abstr 2514)	B2
BRCA2	V2466A	Pancreas Adenocarcinoma	any variant (LoF)	response	platinum	case report	25719666	B2
TSC1	M322T M271T M201T	Endometrial Cancer	any variant (GoF)	response	tensirolimus	case report	27016228	B2
BRCA1	S370I S1512I S408I S1533I S283I S1465I S362I S3I S308I F304L F88L F170L F278L F257L F8L F263L	Cancer	any variant (LoF)	response	WEE1 inhibitors	case report	25964244	B2
XRCC1	Q399R	Cervical Cancer	Q399R	sensitivity/response	Carboplatin	clin. trials	16875718	B2
XRCC1	Q399R	Cervical Cancer	Q399R	sensitivity/response	Cisplatin	clin. trials	16875718	B2
PTEN	R130Q	Melanoma	any variant (LoF)	resistance	BRAF inhibitors in BRAF mutant tumor	early trials	10.1200/PO.16.00054	B2
TP53	V157A V25A V64A V118A P72R P33R	Inflammatory Breast Carcinoma	any mut. (LoF)	resistance	CDK4/CDK6 inhibitor abemaciclib	early trials	27217383	B2

TP53	V157A V25A V64A V118A P72R P33R	Acute Promyelocytic Leukemia	any mut. (LoF)	response	decitabine	early trials	27959731	B2
TP53	V157A V25A V64A V118A P72R P33R	myelodisplastic syndrome	any mut. (LoF)	response	decitabine	early trials	27959731	B2
TSC1	M322T M271T M201T	Urothelial Carcinoma	any variant (LoF)	response	everolimus	early trials	22923433	B2
PTEN	R130Q	Prostate Cancer	any variant (LoF)	response	everolimus	early trials	23582881	B2
FGFR2	D101N D84N	Bile Duct Adenocarcinoma	multiple, any mut. (GoF)	resistance	FGFR inhibitors	early trials	28034880, ASCO 2017 (abstr 2500)	B2
PTEN	R130Q	Endometrial Cancer	any variant (LoF)	no response	mTOR inhibitors	early trials	21788564, 23238879	B2
FANCA	L63V G809D G37D G501S T266A T234A H209R T92A	Prostate Cancer	any variant (LoF)	response	PARP inhibitors	early trials	26510020	B2
BRCA1	S370I S1512I S408I S1533I S283I S1465I S362I S3I S308I F304L F88L F170L F278L F257L F8L F263L	Inflammatory Breast Carcinoma	any variant (LoF)	response	PARP inhibitors	early trials	20609467, 25366685	B2
BRCA1	S370I S1512I S408I S1533I S283I S1465I S362I S3I S308I F304L F88L F170L F278L F257L F8L F263L	Prostate Cancer	any variant (LoF)	response	PARP inhibitors	early trials	19553641, 25366685, 26510020	B2
BRCA2	V2466A	Inflammatory Breast Carcinoma	any variant (LoF)	response	PARP inhibitors	early trials	20609467	B2

BRCA2	V2466A	Prostate Cancer	any variant (LoF)	response	PARP inhibitors	early trials	26510020	B2
BRCA1	S370I S1512I S408I S1533I S283I S1465I S362I S3I S308I F304L F88L F170L F278L F257L F8L F263L	Epithelial Ovarian Cancer	any variant (LoF)	response	PARP inhibitors + chemotherapy	early trials	22307137, ASCO 2012 (abstr 1009)	B2
BRCA2	V2466A	Epithelial Ovarian Cancer	any variant (LoF)	response	PARP inhibitors + chemotherapy	early trials	22307137, ASCO 2012 (abstr 1009)	B2
PTEN	R130Q	Melanoma	any variant (LoF)	resistance	PD1 inhibitors	early trials	26645196	B2
BRCA1	S370I S1512I S408I S1533I S283I S1465I S362I S3I S308I F304L F88L F170L F278L F257L F8L F263L	Inflammatory Breast Carcinoma	any variant (LoF)	response	platinum agents	early trials	25847936	B2
BRCA2	V2466A	Inflammatory Breast Carcinoma	any variant (LoF)	response	platinum agents	early trials	25847936	B2
PTEN	R130Q	Cancer	any variant (LoF)	response	sirolimus	early trials	ASCO 2013 (abstr 2532)	B2
BRCA1	S370I S1512I S408I S1533I S283I S1465I S362I S3I S308I F304L F88L F170L F278L F257L F8L F263L	Inflammatory Breast Carcinoma	any variant (LoF)	response	veliparib + cisplatin	early trials	26801247	B2
BRCA2	V2466A	Inflammatory Breast Carcinoma	any variant (LoF)	response	veliparib + cisplatin	early trials	26801247	B2

TP53	V157A V25A V64A V118A P72R P33R	Epithelial Ovarian Cancer	any variant (GoF)	response	WEE1 inhibitors + carboplatin	early trials	ASCO2015 (abstr 2507)	B2
PTEN	R130Q	Inflammatory Breast Carcinoma	any variant (LoF)	response	everolimus + trastuzumab + chemotherapy (HER2 ampl)	late trials	27091708	B2
BRCA1	S370I S1512I S408I S1533I S283I S1465I S362I S3I S308I F304L F88L F170L F278L F257L F8L F263L	Epithelial Ovarian Cancer	any variant (LoF)	response	platinum agents	late trials	22406760, 22711857	B2
BRCA2	V2466A	Epithelial Ovarian Cancer	any variant (LoF)	response	platinum agents	late trials	22406760, 22711857	B2
FBXW7	D591Y D473Y D511Y	B-cell Adult Acute Lymphocytic Leukemia	any variant (LoF)	response	steroids in early setting	late trials	20861909	B2
APC	V1822D	Colon Cancer	any variant (LoF)	sensitivity	tankyrase inhibitors	preclinical	22440753, 23539443	A3
PIK3CB	R321Q	Head And Neck Carcinoma	any variant (GoF)	sensitivity	AKT inhibitor	preclinical	23619167	B3
PIK3CB	R321Q	Head And Neck Carcinoma	any variant (GoF)	sensitivity	mTORC1/2 inhibitors	preclinical	23619167	B3
FBXW7	D591Y D473Y D511Y	Cancer	any variant (LoF)	resistance	anti-tubulin agents	preclinical	21368834	B3
PTEN	R130Q	Inflammatory Breast Carcinoma	any variant (LoF)	sensitivity	ATM inhibitor	preclinical	27397505	B3
SUZ12	E347K E324K	Cancer	any variant (LoF)	sensitivity	BET inhibitors	preclinical	25119042	B3
FAT1	E4156G S89G E4158G K4059N K4061N D2309N D2311N V862L V482I S404R	Head And Neck Carcinoma	any mut. (LoF)	sensitivity	BET inhibitors	preclinical	27397505	B3
ERCC6	Q1413R Q1360R M1097V M1044V	Epithelial Ovarian Cancer	any variant (LoF)	sensitivity	cisplatin	preclinical	25634215	B3
MSH3	I79V A1045T	Cancer	any variant (LoF)	sensitivity	DNA-PKcs inhibitors	preclinical	24556366	B3

	A989T A980T							
RNF43	L418M L291M L377M P231L R343H R216H R302H P104L I47V P190L	Pancreas Adenocarcinoma	any variant (GoF)	sensitivity	FZD5 antibodies	preclinical	27869803	B3
SMARCB1	P6R P190R P245R	ovarian rhabdoid Cancer	any mut. (LoF)	sensitivity	HDAC inhibitors	preclinical	26920892	B3
PTEN	R130Q	Melanoma	any variant (LoF)	resistance	MEK inhibitors in BRAF mutant tumors	preclinical	23039341	B3
TP53	V157A V25A V64A V118A P72R P33R	Urothelial Carcinoma	any mut. (LoF)	sensitivity	mitomycin C	preclinical	27397505	B3
TP53	V157A V25A V64A V118A P72R P33R	Urothelial Carcinoma	any mut. (LoF)	sensitivity	gemcitabine	preclinical	27397505	B3
TP53	V157A V25A V64A V118A P72R P33R	Urothelial Carcinoma	any mut. (LoF)	sensitivity	doxorubicin	preclinical	27397505	B3
STAG2	I1257L I1220L	Glioma	any variant (LoF)	sensitivity	PARP inhibitors	preclinical	24356817	B3
ATR	R2425Q R2022Q R2361Q M211T	Cancer	any variant (LoF)	sensitivity	PARP inhibitors	preclinical	23548269	B3
PTEN	R130Q	Cancer	any variant (LoF)	sensitivity	PI3K pathway inhibitors	preclinical	21673091, 23287563, 21998291	B3
PTEN	R130Q	Endometrial Cancer	any variant (LoF)	sensitivity	PI3K pathway inhibitors	preclinical	22662154	B3
PTEN	R130Q	Epithelial Ovarian Cancer	any variant (LoF)	sensitivity	PI3K pathway inhibitors	preclinical	21632463	B3
PTEN	R130Q	Inflammatory Breast Carcinoma	any variant (LoF)	sensitivity	PI3K pathway inhibitors	preclinical	23085766, 22932669	B3
PTEN	R130Q	Thyroid Gland Papillary Carcinoma	any variant (LoF)	sensitivity	PI3K pathway inhibitors	preclinical	21289267	B3
INPP4B	R838C R653C	Inflammatory Breast Carcinoma	any variant (LoF)	sensitivity	PI3K pathway inhibitors	preclinical	23551093	B3
PTEN	R130Q	Glioma	any variant (LoF)	sensitivity	PI3K pathway inhibitors (alone or in combination)	preclinical	21325073, 21191045, 17804702	B3

PTEN	R130Q	Lung Acinar Adenocarcinoma	any variant (LoF)	sensitivity	PI3K pathway inhibitors (alone or in combination)	preclinical	23136191	B3
PTEN	R130Q	Prostate Cancer	any variant (LoF)	sensitivity	PI3K pathway inhibitors + AR antagonists	preclinical	21575859	B3
PTEN	R130Q	Epithelial Ovarian Cancer	any variant (LoF)	sensitivity	PI3K pathway inhibitors + MEK inhibitors	preclinical	21632463	B3
ATR	R2425Q R2022Q R2361Q M211T	Glioma	any variant (LoF)	sensitivity	temozolomide	preclinical	23960094	B3
SETD2	R2077Q A1958T A1592T A508T	Cancer	any variant (LoF)	sensitivity	WEE1 inhibitors	preclinical	ENA 2014 (abstr 211)	B3

The MTB method and the corresponding report structure were developed by Julia Perera-Bel in the research group of Prof. Dr. Tim Beißbarth at the University Medical Center Göttingen (UMG). Perera-Bel J, Hutter B, Heining C, et al. From somatic variants towards precision oncology: Evidence-driven reporting of treatment options in molecular tumor boards. Genome Med. 2018;10(1):18. Published 2018 Mar 15. doi:10.1186/s13073-018-0529-2).

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