UCSF Clinical Cancer Genomics Laboratory

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UCSF 500 Cancer Panel Final Report

CCGL No: 155
Date:

Tumor

Source: Brain, anterior boundary resection

Diagnosis: Oligodendroglioma, IDH mutant, WHO grade II

Normal

Source: Peripheral Blood

GENOMIC ALTERATIONS IN THE TUMOR SAMPLE

VARIANT	TRANSCRIPT ID	CLASSIFICATION	COVERAGE	MUTANT ALLELE FREQUENCY
IDH1 p.R132H	NM_001282387	Pathogenic	443	26%
TP53 p.R209fs	NM_000546	Pathogenic	521	48%

'Coverage' indicates the number of unique DNA molecules sequenced. 'Mutant Allele Frequency' indicates the percentage of the reads with the respective 'Variant' and is affected by the degree of normal cell contamination of the sample and whether the variant is fully clonal or subclonal.

GENOMIC ALTERATIONS IN THE NORMAL SAMPLE*

VARIANT	TRANSCRIPT ID	CLASSIFICATION	COVERAGE	MUTANT ALLELE FREQUENCY
No pathogenic or likely pathogenic germline alterations identified.				

***Germline variants are only reported if classified as pathogenic or likely pathogenic in ClinVar and confirmed by a CCGL molecular pathologist.**

INTERPRETATION

This recurrent low-grade infiltrative glioma contains two pathogenic mutations: the R132H hotspot mutation in IDH1 and a frameshift mutation in TP53 with copy neutral loss of heterozygosity. The only copy number changes are losses of chromosome 19p and a small portion of 19q. Also present in this tumor is a subclonal missense variant of unknown significance in NOTCH3.

Together, the genetic findings in this case are consistent with those of an adult-type diffuse astrocytoma. The absence of p53 overexpression in the tumor cells by immunohistochemistry is likely due to the presence of a frameshift mutation in TP53 rather than the more common missense mutations.

References:

1. Suzuki H et al. Mutational landscape and clonal architecture in grade II and III gliomas. *Nature Genet.* 47: 458-468, 2015.

2. The Cancer Genome Atlas Research Network. Comprehensive integrative genomic analysis of diffuse lower-grade gliomas. *N. Engl. J. Med.* 372: 2481-2498, 2015.

3. Bai H, et al. Integrated genomic characterization of IDH1-mutant glioma malignant progression. *Nature Genet.* Epub 30 Nov 2015

SOMATIC ALTERATIONS OF UNKNOWN SIGNFICANCE*				
VARIANT	**TRANSCRIPT ID**	**CLASSIFICATION**	**COVERAGE**	**MUTANT ALLELE FREQUENCY**
NOTCH3 p.C1428Y	NM_000435	VUS	43	7%

***The above variants have not yet been adequately characterized and are therefore classified as variants of unknown significance.**

TEST METHODOLOGY:

The UCSF 500 Cancer Gene Test uses capture-based next-generation sequencing to target and analyze the coding regions of greater than 500 cancer genes, as well as select introns of 40 genes (gene list on last page of this report). Genomic DNA was extracted from both tumor and normal tissue for library preparation. Target enrichment was performed by hybrid capture using custom oligonucleotides. Sequencing of captured libraries was performed on an Illumina HiSeq 2500. Sequence reads are de-duplicated to allow for accurate allele frequency determination and copy number calling. All analysis was based on the human reference sequence UCSC build hg19 (NCBI build 37). Data analysis is performed using the following software packages:

- BWA: 0.7.10-r789
- Samtools: 1.1 (using htslib 1.1)
- Picard tools: 1.97 (1504)
- GATK: 2014.4-3.3.0-0-ga3711
- SATK: 2013.1-10-gd6fa6c3
- Annovar: v2015Mar22
- CNVkit: 0.3.3
- Pindel
- IGV
- Nexus Copy Number
- Freebayes
- Delly

TEST LIMITATIONS:

This assay is designed to detect single nucleotide variants, small (<10bp) insertion/deletions (indels), and copy number changes. Large insertions or deletions and gene rearrangements may be detected by the assay but have not been validated.

Specificity and sensitivity of this test to detect single nucleotide variants (SNVs) and small indels (≤ 5 bp) was determined by sequencing well characterized HapMap DNA samples from the Coriell Cell Repositories and comparing the genotypes produced by our assay with those from Illumina Platinum Genomes as the gold standard. For samples with at least 25% tumor, ≥ 200x coverage for the tumor sample, and ≥ 100x coverage for the normal sample, the sensitivity of the test for fully clonal SNVs is 99% and the sensitivity for small indels is 83%. For samples with at least 25% tumor, ≥ 200x coverage for the tumor sample, and ≥ 100x coverage for the normal sample, the specificity of the test for fully clonal SNVs is 98%, and the specificity for small indels is 71%. Sensitivity of detection of copy number changes is 100%.

CLIA NOTE:

This test was developed and its performance characteristics determined by the UCSF Clinical Cancer Genomics Laboratory. It has not been cleared or approved by the U.S. Food and Drug administration. The Clinical Cancer Genomics Laboratory is certified by the Clinical Laboratory Improvement Act of 1988 (CLIA certified) and as such is allowed to perform high complexity clinical testing.

UCSF 500 Gene List

ABCB1	ABL1	ABL2	ACVR1	ACVR1B	ACVR2A	AJUBA	AKT1	AKT2	AKT3	ALDH7A1
ALK	APC	APOBEC3G	AR	ARAF	ARFRP1	ARHGAP35	ARID1A	ARID1B	ARID2	ARID5B
ASH2L	ASXL1	ASXL2	ATF1	ATM	ATR	ATRX	ATXN1	AURKA	AURKB	AXIN1
AXIN2	AXL	BAP1	BARD1	BCL2	BCL2A1	BCL2L12	BCL2L2	BCL6	BCL10	BCL11B
BCOR	BCORL1	BIRC3	BLM	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTK	B4GALT3
CALR	CARD11	CBFB	CBL	CCND1	CCND2	CCND3	CCNE1	CD163L1	CD79A	CD79B
CD274	CDC42	CDC73	CDH1	CDH2	CDH4	CDH5	CDH20	CDK12	CDK4	CDK6
CDK8	CDKN1A	CDKN1B	CDKN2A	CDKN2B	CDKN2C	CEBPA	CHD4	CHEK1	CHEK2	CIC
CKS1B	CLDN18	COL1A1	COL2A1	CREBBP	CRKL	CSF1R	CSF3R	CTCF	CTNNA1	CTNNB1
CUL3	CUX1	CXCR4	CYLD	CYP2C8	CYP3A4	CYP3A5	DCC	DDIT3	DDR2	DDX3X
DICER1	DNMT3A	DOT1L	DPYD	DUSP2	DUSP4	DUSP6	DYNC1I1	EBF1	EDNRB	EGFR
EGR3	EIFA2	EIF1AX	ELF3	EMSY (C11orf30)	EP300	EPCAM	EPHA3	EPHA5	EPHA6	EPHA7
EPHB1	EPHB4	EPHB6	EPPK1	ERBB2	ERBB3	ERBB4	ERCC2	ERCC6L	ERG	ESPL1
ESR1	ESR2	ETS1	ETV6	EWSR1	EZH1	EZH2	FAM123B (WTX)	FAM46C	FAM58A	FANCA
FANCC	FANCE	FANCF	FANCG	FANCL	FBXO43	FBXW7	FGF10	FGF14	FGF19	FGF23
FGF3	FGF4	FGF6	FGFR1	FGFR2	FGFR3	FGFR4	FH	FHIT	FLCN	FLT1
FLT3	FLT4	FOXA1	FOXA2	FOXL2	FOXO1	FOXP1	FOXP4	FSIP1	FUBP1	FUS
FYN	GAB2	GAK	GATA1	GATA2	GATA3	GID4 (C17orf39)	GIGYF2	GIPC3	GLI1	GLI2
GNA11	GNA13	GNAQ	GNAS	GPR124	GPSM1	GRIN2A	GRM3	GSK3A	GSK3B	GSTP1
GUCY1A2	H3F3A	H3F3B	H3F3C	HDAC9	HGF	HIF1A	HIST1H1C	HIST1H3B	HNF1A	HOXA3
HOXB13	HRAS	HSPA2	HSPA5	HSP90AA1	ICK	ID3	IDH1	IDH2	IGF1R	IGF2R
IKBKE	IKZF1	IKZF2	IKZF3	IL36A	IL7R	INHBA	IRF4	IRS2	JAK1	JAK2
JAK3	JAZF1	JUN	KAT6A (MYST3)	KDM5A	KDM5C	KDM6A	KDR	KEAP1	KIT	KLF4
KLHL6	KMT2A	KMT2B	KMT2D	KRAS	LARS	LEF1	LIFR	LRP1B	LRP6	LRRK2
LTK	MAFB	MALAT1	MAP2K1	MAP2K2	MAP2K4	MAP3K1	MAP3K2	MAP3K5	MAP3K7	MAP3K9
MAPK1	MCL1	MCTP1	MDM2	MDM4	MECOM	MED12	MEF2B	MEN1	MET	MGA
MIR142	MITF	MLH1	MPL	MRAS	MRE11A	MSH2	MSH6	MTOR	MUTYH	MYB
MYBL1	MYC	MYCL	MYCN	MYD88	MYH9	NAV3	NBN	NCOR1	NF1	NF2
NFE2L3	NFE2L2	NFKBIA	NFKBIE	NIPBL	NKX2-1	NOTCH1	NOTCH3	NPM1	NRAS	NSD1
NT5C2	NTRK1	NTRK2	NTRK3	NUP93	NUP98	NUTM1	OR5L1	PAK3	PALB2	PAX3
PAX5	PAX8	PBRM1	PCBP1	PDCD1LG2	PDGFB	PDGFRA	PDGFRB	PDK1	PDS5B	PHF6
PHLPP2	PIK3CA	PIK3CG	PIK3R1	PIK3R2	PIM1	PKHD1	PLCG1	PLCH2	POLD1	POLE
POLQ	POT1	POU3F2	PPM1D	PPP2R1A	PPP6C	PRDM1	PRKACA	PRKAR1A	PRKCA	PRKDC
PRX	PTCH1	PTCH2	PTEN	PTK2B	PTPN1	PTPN11	PTPRD	PTPRK	PTPRT	PYDC2
RAC1	RAC2	RAD21	RAD50	RAD51	RAD51C	RAD51D	RAF1	RARA	RASA1	RB1
RBM10	REL	RELA	RET	RHEB	RHOA	RHOT1	RICTOR	RIT1	RNF43	ROS1
RPL5	RPTOR	RRAS	RRAS2	RUNX1	RUNX1T1	SDHB	SDHD	SETBP1	SETD2	SF3B1
SGK1	SH2B3	SHH	SHOC2	SIN3A	SLITRK6	SMAD2	SMAD3	SMAD4	SMARCA2	SMARCA4
SMARCB1	SMC1A	SMC3	SMG7	SMO	SNX31	SOCS1	SOS1	SOS2	SOX9	SOX10
SOX17	SOX2	SPEN	SPOP	SPRED1	SPRY1	SPRY2	SPRY4	SPTA1	SRC	SRSF2
SS18	STAG1	STAG2	STAT3	STAT4	STAT6	STK11	SUFU	TACC1	TADA1	TADA2B
TAS2R60	TBL1XR1	TBX3	TBX22	TCF3	TCF4	TCF7L2	TCL1A	TERT	TET2	TFE3
TFEB	TGFBR2	TLR4	TNC	TNFAIP3	TNFRSF14	TNKS	TNKS2	TOP1	TMPRSS2	TP53
TP63	TPMT	TRAF7	TRPM1	TRPM3	TRRAP	TSC1	TSC2	TSHR	TSHZ2	TSHZ3
U2AF1	UGT1A1	UGT1A7	USP7	USP9X	VAT1L	VEZF1	VHL	WAPAL	WHSC1	WISP3
WRN	WT1	XPO1	XRCC2	XRCC3	XRCC5	XRCC6	YAP1	YWHAE	ZFHX3	ZMYM3
ZNF217	ZNF668	ZNF703	ZRSR2							