UCSF Clinical Cancer Genomics Laboratory

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UCSF 500 Cancer Panel Final Report

CCGL No: 796

Tumor
Source: B1: Brain, right frontal
Diagnosis: Oligodendroglioma, IDH-mutant and 1p/19q-codeleted, WHO grade II
Collected:

Normal
Source: Peripheral blood
Collected:

Pathogenic or Likely Pathogenic SOMATIC ALTERATIONS

VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS	MUTANT ALLELE FREQUENCY
IDH1 p.R132H	NM_001282387	Pathogenic	1048	16%
TERT upstream chr5: g.1,295,228G>A	N/A	Pathogenic	751	12%
Chromosomes 1p and 19q co-deletion	N/A	Pathogenic	N/A	N/A
PIK3CA p.P124L, subclonal	NM_006218	Likely pathogenic	827	4%

'Reads' indicate 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.

Pathogenic or Likely Pathogenic GERMLINE ALTERATIONS*

VARIANT	TRANSCRIPT ID	CLASSIFICATION	READS (Normal/Tumor)	MUTANT ALLELE FREQUENCY (Normal/Tumor)
No pathogenic or likely pathogenic germline alterations identified.				

***Germline variants are reported if classified as pathogenic or likely pathogenic in ClinVar and confirmed by a CCGL molecular pathologist. For variants not classified in ClinVar, truncating variants in well-established tumor suppressor genes are reported if present in <1% of 1000g or esp6500 datasets. Missense variants present in <1% of 1000g or esp6500 datasets are reviewed only if loss of heterozygosity is present in the tumor sample. Germline variants are limited to single nucleotide variants and small indels in gene coding regions.**

INTERPRETATION

This diffuse glioma demonstrates the p.R132H activating hotspot mutation in IDH1 and a hotspot mutation in the promoter region of the TERT gene. The only chromosomal copy number changes seen in this tumor are losses of 1p and 19q. Together, this combination of genetic alterations (IDH1 and TERT promoter mutation plus 1p/19q co-deletion) defines the vast majority of oligodendrogliomas arising in the cerebral hemispheres in adults [refs. 1-3].

Also seen in this tumor is a missense mutation in PIK3CA that is present at subclonal variant allele frequency (4% relative to the 16% seen for the IDH1 p.R132H mutation), suggesting that it is present in only a subset of the tumor cells. This specific variant (p.P124L) has not been previously identified in gliomas, but this variant and other substitutions at this same codon have been identified as confirmed somatic mutations in a few human cancers [COSMIC database]. Together with the fact that PIK3CA mutations are recurrently found in a subset of oligodendrogliomas [refs. 1-2], this PIKC3A variant has been classified as likely pathogenic.

There are no pathogenic germline alterations identified by this assay in genes that are known to increase risk of diffuse gliomas including TP53, POT1, and CDKN2A. The clinical history of autism spectrum disorder is noted in this patient. The UCSF500 Cancer Gene Panel is designed to assess a spectrum of cancer-related genes only, and is not intended as a diagnostic test for any of the genetic alterations that have been associated with autism spectrum disorder.

References:
1. The Cancer Genome Atlas Research Network. Comprehensive, integrative genomic analysis of diffuse lower-grade gliomas. *New England Journal of Medicine* 372: 2481-2498, 2015.
2. Suzuki H, et al. Mutational landscape and clonal architecture in grade II and III gliomas. *Nature Genetics* 47: 458-468, 2015.
3. Eckel-Passow JE, et al. Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. *New England Journal of Medicine* 372: 2499-2508, 2015.

SOMATIC ALTERATIONS OF UNKNOWN SIGNIFICANCE*				
VARIANT	**TRANSCRIPT ID**	**CLASSIFICATION**	**READS**	**MUTANT ALLELE FREQUENCY**
None identified.				

***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 479 cancer genes, as well as select introns of 47 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. The analysis uses open source or licensed software for alignment to the human reference sequence UCSC build hg19 (NCBI build 37) and variant calling.

TEST LIMITATIONS:

This assay is designed to detect single nucleotide variants, small to medium insertion/deletions (indels), and copy number changes. Large insertions/deletions and gene rearrangements may also be detected by the assay; however, the sensitivity of detection of structural rearrangements is variable for different genes. If the pre-test probability of a structural rearrangement is high and the test is negative, an orthogonal testing method should be considered.

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 and small indels is >98% and the positive predictive value for fully clonal SNVs and small indels is >99%. Sensitivity for detection of copy number changes

is >98% for samples with high tumor content. Sensitivity for detection of NPM1, FLT3, and EGFR exons 19 and 20 insertions and deletions is 95%.

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 Version 2 Gene List										
ABL1	ABL2	ACVR1	ACVR1B	AJUBA	AKT1	AKT2	AKT3	ALK	APC	APOBEC3G
AR	ARAF	ARFRP1	ARHGAP35	ARID1A	ARID1B	ARID2	ARID5B	ASH2L	ASXL1	ASXL2
ATF1	ATM	ATR	ATRX	AURKA	AURKB	AXIN1	AXIN2	AXL	BAP1	BARD1
BCL2	BCL2A1	BCL2L1	BCL2L12	BCL2L2	BCL6	BCOR	BCORL1	BLM	BRAF	BRCA1
BRCA2	BRD4	BRIP1	BTG1	BTK	CALR	CARD11	CBFB	CBL	CBLB	CCND1
CCND2	CCND3	CCNE1	CD79A	CD79B	CD274	CDC42	CDC73	CDH1	CDK12	CDK4
CDK6	CDK8	CDKN1A	CDKN1B	CDKN2A	CDKN2B	CDKN2C	CEBPA	CHD1	CHD2	CHD4
CHD5	CHEK1	CHEK2	CIC	CLDN18	CNOT3	COL1A1	COL2A1	CRCT1	CREB1	CREBBP
CRKL	CSF1R	CSF3R	CTCF	CTNNA1	CTNNB1	CUL3	CUX1	CYLD	CXCR4	DCC
DDIT3	DDR2	DDX3X	DDX41	DGKH	DICER1	DIS3	DNAJB1	DNMT3A	DOT1L	DUSP2
DUSP4	DUSP6	DYNC1I1	EBF1	EDNRB	EGFR	EGR1	EIF1AX	ELF3	EMSY (C11orf30)	EP300
EPCAM	EPHA2	EPHA3	EPHA5	EPHA7	EPHB1	EPOR	ERBB2	ERBB3	ERBB4	ERCC1
ERCC2	ERG	ERRFI1	ESPL1	ESR1	ESR2	ETS1	ETV6	EWSR1	EZH1	EZH2
FAM123B (WTX)	FAM46C	FANCA	FANCC	FANCE	FANCF	FANCG	FANCL	FAT1	FAT3	FBXW7
FGF10	FGF14	FGF19	FGF23	FGF3	FGF4	FGF6	FGFR1	FGFR2	FGFR3	FGFR4
FH	FLCN	FLT1	FLT3	FLT4	FOXA1	FOXL2	FOXO1	FOXP1	FRS2	FUBP1
FUS	FYN	GAB2	GATA1	GATA2	GATA3	GLI1	GLI2	GNA11	GNA13	GNAQ
GNAS	GPC3	GPR124 (ADGRA2)	GRIN2A	GRM3	GSK3B	H3F3A	H3F3B	HDAC4	HDAC9	HEY1
HGF	HIF1A	HIST1H3B	HMGA2	HNF1A	HOXB13	HRAS	HSPA2	HSPA5	HSP90AB1	ID3
IDH1	IDH2	IGF1R	IGF2	IGF2R	IKBKE	IKZF1	IKZF2	IKZF3	IL2RB	IL7R
INHBA	INPP4B	IPMK	IRF4	IRS2	JAK1	JAK2	JAK3	JAZF1	KAT6A (MYST3)	KDM5A
KDM5C	KDM6A	KDR	KEAP1	KIT	KLF4	KLHL6	KMT2A	KMT2B	KMT2D	KNSTRN
KRAS	LEF1	LIFR	LRP1B	LZTR1	MALAT1	MAML2	MAP2K1	MAP2K2	MAP2K4	
MAP3K1	MAP3K2	MAP3K5	MAP3K7	MAP3K9	MAPK1	MCL1	MDM2	MDM4	MED12	MEF2B
MEN1	MET	MGA	MGMT	MITF	MLH1	MLH3	MPL	MRE11A	MSH2	MSH3
MSH6	MTOR	MUTYH	MYB	MYBL1	MYC	MYCL1	MYCN	MYD88	MYH9	NAV3
NBN	NCKAP5	NCOA2	NCOA3	NCOR1	NF1	NF2	NFE2L2	NFKBIA	NFKBIE	NIPBL
NKX2-1	NOTCH1	NOTCH3	NPM1	NRAS	NSD1	NSD2	NT5C2	NTRK1	NTRK2	NTRK3
NUP93	NUTM1	OR5L1	PAK1	PAK3	PALB2	PARK2	PAX3	PAX5	PAX7	PAX8
PBRM1	PDCD1LG2	PDGFB	PDGFRA	PDGFRB	PDK1	PHF6	PHOX2B	PIK3CA	PIK3CG	PIK3R1
PIK3R2	PLAG1	PLCB4	PMS1	POLD1	POLE	POLQ	POT1	POU3F2	PPM1D	PPP2R1A
PPP6C	PRDM1	PREX2	PRKACA	PRKAG2	PRKAR1A	PRKCA	PRKCH	PRKDC	PTCH1	PTCH2
PTEN	PTK2B	PTPN1	PTPN11	PTPRB	PTPRD	PTPRK	PTPRT	RAC1	RAD21	RAD50
RAD51	RAD51C	RAD51D	RAF1	RARA	RASA1	RASA2	RB1	RBM10	REL	RELA
RET	RHEB	RHOA	RICTOR	RIT1	RNF43	ROBO1	ROS1	RPL10	RPTOR	RRAGC
RRAS	RRAS2	RSPO2	RSPO3	RUNX1	RUNX1T1	SDHB	SDHD	SETBP1	SETD2	SF3B1
SH2B3	SHH	SIN3A	SLIT2	SLITRK6	SMAD2	SMAD3	SMAD4	SMARCA2	SMARCA4	SMARCB1
SMC1A	SMC3	SMO	SNCAIP	SOCS1	SOS1	SOS2	SOX9	SOX10	SOX2	SPEN
SPOP	SPRED1	SPRY1	SPRY2	SPRY4	SPTA1	SRC	SRSF2	SS18	STAG2	STAT3
STAT4	STAT6	STK11	SUFU	SYK	SYNE1	TADA1	TBX3	TCEB1	TCF7L2	TERT
TET2	TFE3	TFEB	TGFBR2	TLR4	TNFAIP3	TNFRSF14	TOP1	TOP2A	TMPRSS2	TP53
TRAF3	TRAF7	TRIM28	TSC1	TSC2	TSHR	TSHZ2	TSHZ3	TSLP	TTYH1	TYK2
U2AF1	USP7	VEGFA	VHL	WISP3	WRN	WT1	XBP1	XPO1	YAP1	YWHAE
ZBTB20	ZFHX3	ZMYM3	ZNF217	ZNF703	ZNFHX4	ZRSR2				