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Authors

Chau, Lianne Q
Levy, Michael L
Crawford, John Ross

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Unusual KRAS missense mutation (p.E63K) in patient with juvenile pilocytic astrocytoma of the tectum

Lianne Q Chau,[1] Michael L Levy,[2] John Ross Crawford[3]

[1]Tumor Initiation and Maintenance Program, Sanford Burnham Prebys Medical Discovery Institute, La Jolla, California, USA
[2]Neurosurgery, University of California San Diego, San Diego, California, USA
[3]Neurosciences and Pediatrics, University of California San Diego, San Diego, California, USA

Correspondence to
Dr John Ross Crawford, jrcrawford@ucsd.edu

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DESCRIPTION

A 24-year-old woman with a history of tectal glioma initially diagnosed at 7 years of age presented following cyst fenestration and biopsy for progression on neuroimaging. Contrast enhanced MRI of the brain revealed a relatively well-defined mass with progression of solid and cystic components in the tectal region of the brainstem (figure 1). At initial presentation at 7 years of age, the patient underwent an endoscopic third ventriculostomy followed by ventriculoperitoneal shunt placement for treatment of persistent hydrocephalus. Due to the location and slow growing nature of the tumour, the patient did not undergo surgical resection, radiation, or chemotherapy, but was monitored with serial MRI. Histologically, the tumour was classified as a juvenile pilocytic astrocytoma (JPA). A next generation sequencing panel consisting of 397 cancer-related genes (table 1) performed on paraffin-embedded formalin fixed tumour of the previously untreated tumour revealed a clinically significant KRAS missense mutation (c.187G>A p.E63K). Variants in JAK1 (c.6+1G>T, splice site exon 2), RAF1 (c.1423T>C p.F475L) and NOTCH3 (c.1505C>T p.S502F) were also detected. However, following review of Catalogue of Somatic Mutations in Cancer (COSMIC) database (https://cancer.sanger.ac.uk/cosmic), these specific mutations have not been reported and are considered variants of unknown significance.

JPAs are slow growing WHO grade I tumours that account for approximately 20% of paediatric brain tumours.[1] JPAs can arise sporadically, as with this particular patient, or in association with neurofibromatosis type 1 (NF1), a familial tumour syndrome that increases the risk of developing gliomas.[1 2] These tumours often develop in the cerebellum, brainstem, hypothalamus and optic tract and rarely become anaplastic or malignant.[2] The majority of JPAs are associated with increased activation of the mitogen-activated protein kinase (MAPK) signalling pathway.[1 2] The most common genetic alteration, found in over 70% of cases, is the KIAA1549-BRAF fusion, a 2 Mb tandem duplication of 7q34 that leads to loss of the N-terminus regulatory domain of BRAF and thus constitutive activation of MAPK.[2] Several other gene fusions such as FAM131B-BRAF, SRGAP3-RAFand FGFR1-TACC1 have also been reported, but are much less common.[1 2] These gene fusions are primarily found in cerebellar JPAs and less frequently in non-cerebellar JPAs.[1 2] Non-fusion mutations in genes along the MAPK pathway are found more frequently in non-cerebellar JPAs, and include somatic BRAF, KRAS, FGFR1, PTPN11 mutations as well as the germline NF1 mutation.[1 2]

KRAS is an oncogene that encodes for the KRAS protein, a GTPase involved in signal transduction.[3] KRAS is involved in several signalling cascades, including MAPK, PI3K/AKT, RAL-GDS, JAK/STAT3 and NORE1/RASFF1 pathways and thus plays a role in a variety of cellular processes including cell proliferation, apoptosis, growth arrest, differentiation, transcription and translation.[3] Activating mutations in KRAS decrease GTP hydrolysis activity and most notably lead to increased cell proliferation through the MAPK and PI3K/AKT pathways.[3] KRAS mutations have been implicated in numerous cancers and are associated with a less favourable outcome.[3] They have the highest incidence rates in pancreatic, colon and lung carcinomas, but are rare in JPAs, occurring in 2% or less of cases.[2 3] The KRAS p.E63K mutation detected in our patient comprises approximately 0.025% (11 of 43 817) of all KRAS mutations reported (COSMIC, October 2018), and has been

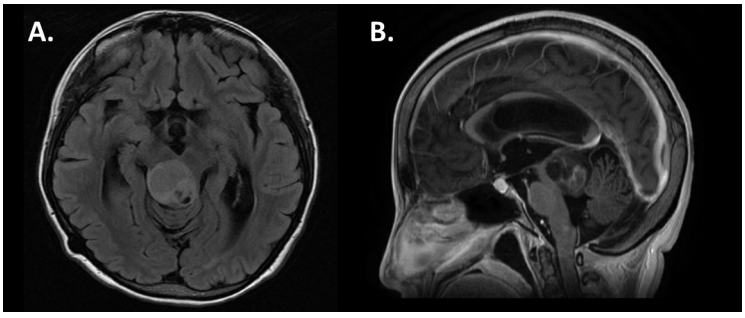

Figure 1 MRI demonstrates a cystic and solid hyperintense mass of the dorsal tectum (A) with associated minimal contrast enhancement and hydrocephalus (B).

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Table 1 Next generation cancer gene panel

Genes for which entire coding panel is interrogated											
ABL1	ABL2	ACVR1B	AKAP9	AKT1	AKT2	AKT3	ALK	AMER1	APC	AR	ARAF
ARFRP1	ARID1A	ARID1B	ARID2	ASPSCR1	ASXL1	ATF6	ATM	ATP1A1	ATP2B3	ATR	ATRX
AURKA	AURKB	AXIN1	AXL	BAP1	BARD1	BCL11A	BCL11B	BCL2	BCL2L1	BCL2L2	BCL6
BCOR	BCORL1	BLM	BMPR1A	BRAF	BRCA1	BRCA2	BRD4	BRIP1	BTG1	BTK	C11orf30
CACNA1D	CAMTA1	CARD11	CASP8	CBFB	CBL	CBLB	CCND1	CCND2	CCND3	CCNE1	CD274
CD79A	CD79B	CDC73	CDH1	CDH11	CDK12	CDK4	CDK6	CDK8	CDKN1A	CDKN1B	CDKN2A
CDKN2B	CDKN2C	CEBPA	CHD2	CHD4	CHEK1	CHEK2	CIC	CLTCL1	COL1A1	CREBBP	CRKL
CRLF2	CSF1R	CSF3R	CTCF	CTNNA1	CTNNB1	CUL3	CYLD	DAXX	DDIT3	DDR2	DICER1
DNM2	DNMT3A	DOT1L	EBF1	EGFR	EIF1AX	EP300	EPHA3	EPHA5	EPHA7	EPHB1	ERBB2
ERBB3	ERBB4	ERCC3	ERCC4	ERCC5	ERG	ERRFI1	ESR1	ETV1	ETV4	ETV5	ETV6
EWSR1	EXT1	EZH2	FAM46C	FANCA	FANCC	FANCD2	FANCE	FANCF	FANCG	FANCL	FAS
FAT1	FBXO11	FBXW7	FGF10	FGF14	FGF19	FGF23	FGF3	FGF4	FGF6	FGFR1	FGFR2
FGFR3	FGFR4	FH	FLCN	FLT1	FLT3	FLT4	FOXA1	FOXL2	FOXO1	FOXP1	FRS2
FUBP1	FUS	GABRA6	GATA1	GATA2	GATA3	GATA4	GATA6	GID4	GLI1	GMPS	GNA11
GNA13	GNAQ	GNAS	GPR124	GRIN2A	GRM3	GSK3B	H3F3A	HGF	HIP1	HNF1A	HRAS
HSD3B1	HSP90AA1	IDH1	IDH2	IGF1R	IGF2	IKBKE	IKZF1	IL7R	INHBA	INPP4B	IRF2
IRF4	IRS2	ITK	JAK1	JAK2	JAK3	JUN	KAT6A	KAT6B	KDM5A	KDM5C	KDM6A
KDR	KEAP1	KEL	KIF5B	KIT	KLHL6	KMT2A	KMT2D	KRAS	LCP1	LIFR	LMO1
LRIG3	LRP1B	LYN	LZTR1	MAGI2	MAML2	MAP2K1	MAP2K2	MAP2K4	MAP3K1	MCL1	MDM2
MDM4	MED12	MEF2B	MEN1	MET	MITF	MLH1	MLLT3	MLLT4	MN1	MPL	MRE11A
MSH2	MSH6	MTOR	MUTYH	MYB	MYC	MYCL	MYCN	MYD88	MYH11	MYH9	NCOA1
NCOA2	NF1	NF2	NFE2L2	NFKBIA	NIN	NKX2-1	NOTCH1	NOTCH2	NOTCH3	NPM1	NR4A3
NRAS	NSD1	NTRK1	NTRK2	NTRK3	NUMA1	NUP214	NUP93	NUP98	PAK3	PALB2	PARK2
PAX3	PAX5	PAX7	PBRM1	PCM1	PDCD1LG2	PDGFRA	PDGFRB	PDK1	PIK3C2B	PIK3CA	PIK3CB
PIK3CG	PIK3R1	PIK3R2	PLCG2	PMS1	PMS2	POLD1	POLE	PPARG	PPP2R1A	PRDM1	PRDM16
PREX2	PRKAR1A	PRKCI	PRKDC	PRSS8	PTCH1	PTEN	PTPN11	PTPRC	QKI	RAC1	RAD21
RAD50	RAD51	RAF1	RALGDS	RANBP17	RANBP2	RARA	RB1	RBM10	RET	RICTOR	RNF43
ROS1	RPTOR	RUNX1	RUNX1T1	SDHA	SDHB	SDHC	SDHD	SETBP1	SETD2	SF3B1	SLC34A2
SLIT2	SMAD2	SMAD3	SMAD4	SMARCA4	SMARCB1	SMO	SNCAIP	SOCS1	SOX10	SOX2	SOX9
SPEN	SPOP	SPTA1	SRC	SRGAP3	SS18	STAG2	STAT3	STAT4	STAT5B	STK11	SUFU
SYK	TAF1	TBX3	TCF7L2	TERC	TERT	TET2	TGFBR2	THRAP3	TMPRSS2	TNFAIP3	TNFRSF14
TOP1	TOP2A	TP53	TPR	TRIM24	TRIM33	TRIP11	TRRAP	TSC1	TSC2	TSHR	U2AF1
VEGFA	VHL	WHSC1	WISP3	WRN	WT1	XPO1	ZBTB2	ZMYM2	ZNF217	ZNF384	ZNF521
Subset of genes (28) for which potential rearrangements are evaluated											
ALK	ASPSCR1	BRAF	BRD4	DDIT3	EGFR	ETV1	ETV4	ETV5	ETV6	EWSR1	FGFR1
FGFR2	FGFR3	FOXO1	FUS	MYB	NOTCH2	NR4A3	NTRK1	NTRK2	PDGFRA	PPARG	RAF1
RET	ROS1	SS18	TMPRSS2								

reported once in a patient with a cerebellar JPA.[1] Our finding represents the first reported case of KRAS p.E63K mutation in a non-cerebellar JPA of the tectum. It is unclear what role if any the KRAS mutation or the unreported variants of JAK1, RAF1 and NOTCH3 may play in tumour growth. Further studies on phenotype/genotype correlations are required to understand the functional consequences of previously uncharacterised novel gene mutations in low grade glioma.

Learning points

- Juvenile pilocytic astrocytomas (JPAs) are relatively common low grade gliomas that are associated with mutations in genes that encode for proteins in the MAPK pathway.
- KRAS mutations are rare in JPAs and have been found in 2% or less of cases.
- The KRAS p.E63K missense mutation comprises about 0.025% of all reported KRAS mutations. We report the first case of this mutation in non-cerebellar pilocytic astrocytoma of the tectum.

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