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H r l c f A/ A s tc t t s r s l c r r t r s l f r t s

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Brain and spinal arteriovenous malformations are congenital lesions causing intracranial haemorrhage or permanent disability especially in young people. We investigated whether the vast majority or all brain and spinal arteriovenous malformations are associated with detectable tumour-related somatic mutations. In a cohort of 31 patients (21 with brain and 10 with spinal arteriovenous malformations), tissue and paired blood samples were analysed with ultradeep next generation sequencing of a panel of 422 common tumour genes to identify the somatic mutations. We used droplet digital polymerase chain reaction to confirm the panel sequenced mutations and identify the additional low variant frequency mutations. The association of mutation variant frequencies and clinical features were analysed. The average sequencing depth was 1077 ± 298×. High prevalence (87.1%) of ***KRAS*/*BRAF*** somatic mutations was found in brain and spinal arteriovenous malformations with no other replicated tumour-related mutations. The prevalence of ***KRAS*/*BRAF*** mutation was 81.0% (17 of 21) in brain and 100% (10 of 10) in spinal arteriovenous malformations. We detected activating ***BRAF*** mutations and two novel mutations in ***KRAS*** (p.G12A and p.S65_A66insDS) in CNS arteriovenous malformations for the first time. The mutation variant frequencies were negatively correlated with nidus volumes of brain (***P*** = 0.038) and spinal (***P*** = 0.028) arteriovenous malformations but not ages. Our findings support a causative role of somatic tumour-related mutations of ***KRAS*/*BRAF*** in the overwhelming majority of brain and spinal arteriovenous malformations. This pathway homogeneity and high prevalence implies the development of targeted therapies with RAS/RAF pathway inhibitors without the necessity of tissue genetic diagnosis.

1 D a e f Ne e , X a H a , Ca a Med ca U e , Be , C a
2 S a e Ke Lab a f Ca d a c a D ea e, F a H a , Na a Ce e f Ca d a c a D ea e , C e e Acade f Med ca Sc e ce a d Pe U Med ca C e e, Be , C a
3 D a e f Ne e , T We e H a , U e Hea Ne , T , Ca ada
4 T a a a Med c e Re ea c I e, Ge e ee Tec I c., T , Ca ada
5 D a e f P b c Hea , Na Med ca U e , Na , C a

C e de ce : Y b Wa , P D
F a H a , C e e Acade f Med ca Sc e ce a d Pe U Med ca C e e
167 Be Rd, Be , 100037, C a
E- a : b a @ a .c

C e de ce a a be add e ed : H Z a , MD, P D
D a e f Ne e , X a H a , Ca a Med ca U e , 45 C a c S , Be 100053, C a
E- a : a @163.c

w r s -ea ed ac a ; KRAS/BRAF; a e e af a

A r t s BAVM = b a a e e af a ; ddPCR = d e d a e a e c a eac ; NGS = e e e a e e c ; SAVM = a a e e af a

tr ct

A e e af a a e fa - ac a af a c a ac e ed b c ec be ee feed- a e e a d d a e , a d a a e, a e 20 e e c e CNS, c d e b a a d a c d (G e a d Be a , 1970; M *et al.*, 2012). B a a e e af a (BAVM) cc 1.3 e 100 000 a e ea a d a e e a d b ed ac a , e e e a e ce f a a e e af a (SAVM) 1/10 f BAVM a d acc f ~20 30% a a a c a af a (C e a d S e , 1983). Ge e a- ca be a c a ed e ed a d e a- a ed b a e e af a , c a a e TGF-β/SMAD a a (Ga e *et al.*, 2004) e ed a ae a c e a ec a a (HHT) e RAS 21 e ac a 1 (RASA1) e ca - a af a -a e e af a d e (CM-AVM) (Ee a *et al.*, 2003; La *et al.*, 2018). H e e, a d c a c a af a a e c e c a d ee be a c a ed a c a d e e a . T e e c de a d c a e - e af a , ca e af a (C *et al.*, 2017; A -O ab *et al.*, 2018; N ae *et al.*, 2018), ac a a a e f d S e-Webe d e (S e *et al.*, 2013; Na a a *et al.*, 2014), a c a d e af a (L a e *et al.*, 2009, 2015; Ca e *et al.*, 2016; Ca *et al.*, 2016) a e a a c a c a ae a a . F e e d e, e e e c e a f e e e a e a c a ed a c f d ca ce, a e PI3K-AKT- TOR a c a af a c d e a d a c af a (Ka a *et al.*, 2017) a d RAS-MAPK a a e c d BAVM (A -O ab *et al.*, 2018; N ae *et al.*, 2018). S ec ca , ac a a *KRAS*, c a .G12V a d .G12D, c a e a ca ce d e , a e a c a ed BAVM (N ae *et al.*, 2018). H e e, ab 60% f BAVM a b ed *KRAS* a a ca be f BAVM e a de ec ed a a d a c a a e bee ed SAVM . He e, a dee e e e a e e c (NGS) a a e f 422 e e, e e a ed e e e a a a a BAVM a d SAVM a e a c a ed de ec ab e - e a ed - a c a .

t r ls t s

t t r l t s l r r t

T e - e BAVM a e a d 10 SAVM a e de e ca e ec f e d a e Be X a H a C a e e ec ed d . T e d a a ed b e e c ee f Be X a H a (NO.2016032) a d e f ed c - e f a a e e a d a a b a ed bef e e . A f e a e e af a d a e e e ade a a d a ca e a a b e d ea . Pa e de a adc f ca BAVM /SAVM de ed d c e e e c ded. Pa e fa f a e e af a d c e ed e e c ac a d ea e e e e c ded. Af e ca e e c , e d a d ec ed f e e a d a c e a a e . T e e ac ed e b d a e, e f e e a e a e e e e c fac f Na Ge e ee B ec I c. (Na , C a) f NGS a d d e d a e a e a ca eac (ddPCR) a a e .

l r c ss l r r r t

Ge c DNA a e ac ed f e a e a d ac ed e b d a e DNea ® B d a d T e K (Q a e) f e a fac e ' ec e ded c . F eac a e, 1 2μ e c DNA a f a e ed e C a M220 ca e (C a) 300 350 . F a e ed DNA a ce ed e d- a , A- a - , a d ada a KAPA H e P K (KAPA B e , KK8504), f ed b e e ec a d ca- A e c AMP e XP bead (Bec a C e) a ed a fac e ' c . F a , b a e e e a ed b PCR a d ed A e c AMP e XP bead . Sa e a c a e f ed Na D ™ 2000 (T e 604.1(()-5.8(T)-18(e)-18(604.1(()-5.8(T)-18(e)-18(

Table 1 Clinical characteristics of patients with AVM

Patient	AVM type	Age	Gender	Ruptured	Location	Nidus size (mm)	High risk structure[a]	Deep venous drainage	Spetzler-Martin grade	Pathology (AVM)
1	SAVM	34	M	Y	Cervical spinal cord (C5)	20.31 × 12.38 × 10.07	Y	-	-	Glomus
2	BAVM	28	M	N	Right frontal lobe of brain	23.69 × 19.46 × 17.86	N	N	I	-
3	BAVM	17	M	Y	Right parietal lobe of brain	45.99 × 37.01 × 29.93	N	N	III	-
4	BAVM	54	F	Y	Right frontal lobe of brain	32.35 × 29.71 × 28.02	N	N	I	-
5	BAVM	44	M	N	Right temporal lobe of brain	25.38 × 25.36 × 17.68	N	N	I	-
6	SAVM	21	F	N	Thoracic spinal cord (T12)	20.08 × 10.89 × 8.63	Y	-	-	Glomus
7	BAVM	48	M	Y	Left cerebellum	44.18 × 34.71 × 27.00	Y	Y	III	-
8	SAVM	45	F	Y	Cervical spinal cord (C7)	22.21 × 9.31 × 10.43	Y	-	-	Juvenile
9	SAVM	45	M	N	Thoracic spinal cord (T6)	13.17 × 7.78 × 9.01	N	-	-	Juvenile
10	SAVM	25	M	Y	Cervical spinal cord (C3)	16.99 × 11.75 × 10.19	N	-	-	Glomus
11	BAVM	10	M	Y	Left parietal lobe of brain	27.32 × 22.80 × 19.49	Y	Y	III	-
12	BAVM	36	F	Y	Left cerebellum	25.01 × 20.02 × 13.08	N	N	I	-
13	BAVM	52	M	Y	Left occipital lobe of brain	37.49 × 36.33 × 21.12	N	N	II	-
14	BAVM	29	F	N	Left frontal lobe of brain	40.81 × 30.16 × 27.90	N	N	II	-
15	BAVM	31	M	N	Right temporal lobe of brain	44.05 × 41.32 × 33.37	Y	N	IV	-
16	BAVM	11	M	Y	Left temporal lobe of brain	38.31 × 25.83 × 19.00	Y	Y	II	-
17	BAVM	13	M	Y	Right occipital lobe of brain	37.21 × 29.57 × 29.52	Y	N	III	-
18	BAVM	5	M	N	Left occipital lobe of brain	27.56 × 22.26 × 18.45	N	Y	I	-
19	BAVM	15	M	Y	Right cerebellum	40.01 × 28.16 × 24.60	Y	N	III	-
20	BAVM	43	F	Y	Right parietal lobe of brain	38.63 × 38.41 × 24.13	Y	N	III	-
21	SAVM	28	M	Y	Cervical spinal cord (C2)	13.54 × 9.90 × 6.89	N	-	-	Juvenile
22	SAVM	28	M	N	Thoracic spinal cord (T12)	24.21 × 12.21 × 8.09	Y	-	-	Juvenile
23	SAVM	16	M	N	Thoracic spinal cord (T7)	7.37 × 4.32 × 4.02	N	-	-	Juvenile
24	BAVM	48	M	Y	Left parietal lobe of brain	32.58 × 31.45 × 31.45	Y	N	III	-
25	BAVM	11	F	Y	Right parietal lobe of brain	NA[b]	N	N	II	-
26	BAVM	43	M	N	Left temporal lobe of brain	40.71 × 25.34 × 40.31	Y	N	II	-
27	SAVM	14	M	Y	Thoracic spinal cord (T12)	20.38 × 9.90 × 9.26	Y	-	-	Juvenile
28	BAVM	22	F	Y	Left temporal lobe of brain	33.91 × 28.40 × 15.45	Y	Y	III	-
29	SAVM	11	M	Y	Cervical spinal cord (C4–5)	14.77 × 10.05 × 8.26	Y	-	-	Glomus
30	BAVM	42	F	Y	Right temporal lobe of brain	26.79 × 25.71 × 23.95	Y	Y	II	-
31	BAVM	18	M	N	Left parietal lobe of brain	49.61 × 49.45 × 46.23	N	N	III	-

[a]High risk structure includes aneurysm, pseudoaneurysm, venectasia and high-flow fistula.
[b]Nidus volume and largest diameter were not detected in Patient 25 due to emergency surgery.

r rs tt w t, tls trct r (D A) tr rt s f A s/ A s d t sst (**A**) Patient 2, right frontal lobe BAVM, KRAS p.G12D, ddPCR variant frequencies = 5.61%. ( ) Patient 16, left temporal lobe BAVM, BRAF p.V600E, ddPCR variant frequencies = 2.99%. ( ) Patient 17, occipital lobe BAVM, negative. (**D**) Patient 1, cervical SAVM, KRAS p.G12D, ddPCR variant frequencies = 4.40%. ( ) Patient 21, cervical SAVM, BRAF p.V600E, ddPCR variant frequencies = 7.29%. Typical dark flow void signal on the MRI T_2-weighted images (left) indicate the niduses (white arrowhead) of arteriovenous malformation, which are surrounded by feeding arteries and draining veins. Feeding arteries (white arrow), nidus (white arrowhead), draining veins (black arrow) and high risk structure (white hollow arrowhead) can be identified clearly on the DSA (middle). Intraoperative images (right) demonstrate the tortuous dilated vessels on the surface of brain/spinal cord, of which the feeding arteries, nidus (white arrowhead), high risk structure (white hollow arrowhead), and the draining veins (black arrow) can be recognized easily.

t c t f s tc tc r ts s c

O ae c ded 422 -ea ed e e, e dea f c ca be f d S e e a Tab e 1. A Tab e 2, e a e a e e c de a 1077 ± 298×. A e 31 a e , 21 ca ed ac a *KRAS* a- a d ca ed *BRAF* a e a e.

N e f a e e e de ec ed c e d a- a ed b d a e. E c f a e e f e RAS/RAF a a a, e e e a e e f d d a e f e a a e (S e e a Tab e 1).

We f d e e ce de e e a a a d e e a a e *KRAS* e e, a a f e ece a f 0.13% 8.82%. *KRAS* (NM_004985.3)

l r s l ts f

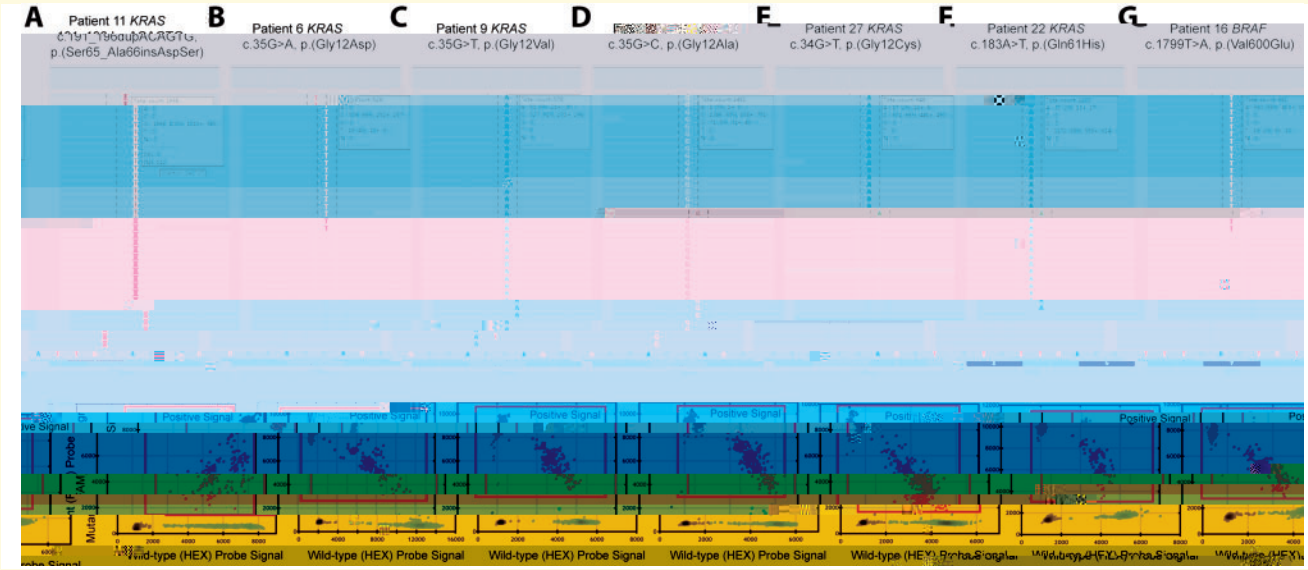
t t		r l w t s					
		D t t s		*KRAS/BRAF* t t s	, %	*KRAS/BRAF* t t s	% ,
1	SAVM	1570.71	KRAS	KRAS c.35G>A	4.65	KRAS p.G12D	4.40
2	BAVM	1535.78	KRAS	KRAS c.35G>A	6.57	KRAS p.G12D	5.61
3	BAVM	1640.67	KRAS	KRAS c.35G>A	0.60	KRAS p.G12D	0.45
4	BAVM	1163.57	KRAS/TET2	KRAS c.35G>A	2.01	KRAS p.G12D	1.39
5	BAVM	775.55	KRAS	KRAS c.35G>A	2.50	KRAS p.G12D	2.95
6	SAVM	412.07	KRAS	KRAS c.35G>A	3.60	KRAS p.G12D	5.16
7	BAVM	1263.04	KRAS	KRAS c.35G>T	0.81	KRAS p.G12V	0.53
8	SAVM	1293.91	KRAS	KRAS c.35G>T	2.85	KRAS p.G12V	2.33
9	SAVM	443.22	KRAS	KRAS c.35G>T	8.82	KRAS p.G12V	7.10
10	SAVM	1187.50	KRAS	KRAS c.35G>C	4.86	KRAS p.G12A	4.85
11	BAVM	1469.84	KRAS	KRAS c.191_196dupACAGTG	5.56	KRAS p.S65_A66insDS	7.09
12	BAVM	1289.46	None	-	-	KRAS p.G12D	0.27
13	BAVM	1346.49	None	-	-	KRAS p.G12D	0.14
14	BAVM	1125.61	None	-	-	KRAS p.G12V	0.03
15	BAVM	1123.18	KRAS/FLT4	KRAS c.35G>A	1.52	KRAS p.G12D	1.47
16	BAVM	1296.57	BRAF/KMT2C	BRAF c.1799T>A	1.93	BRAF p.V600E	2.99
17	BAVM	1033.87	None	-	-	Negative	-
18	BAVM	1116.77	None	-	-	Negative	-
19	BAVM	994.44	KRAS/CYP2D6	KRAS c.35G>A	3.64	KRAS p.G12D	2.28
20	BAVM	978.54	None	-	-	KRAS p.G12V	1.20
21	SAVM	784.63	BRAF	BRAF c.1799T>A	6.54	BRAF p.V600E	7.29
22	SAVM	951.59	KRAS	KRAS c.183A>T	2.50	KRAS p.Q61H	2.22
23	SAVM	1269.42	KRAS	KRAS c.35G>A	5.58	KRAS p.G12D	5.72
24	BAVM	1154.37	KRAS/DNMT3A/WAS	KRAS c.35G>T	2.02	KRAS p.G12V	1.77
25	BAVM	898.58	KRAS	KRAS c.35G>A	0.72	KRAS p.G12D	0.44
26	BAVM	807.56	None	-	-	Negative	-
27	SAVM	1098.06	KRAS	KRAS c.34G>T	1.79	KRAS p.G12C	2.01
28	BAVM	946.65	KRAS/FRG1	KRAS c.35G>A	2.86	KRAS p.G12D	3.19
29	SAVM	950.56	KRAS	KRAS c.35G>T	7.23	KRAS p.G12V	7.13
30	BAVM	703.56	KRAS	KRAS c.35G>A	1.11	KRAS p.G12D	1.48
31	BAVM	776.58	None	-	-	Negative	-

[a]Average depth of the 422 tumour-related genes.
[b]Negative indicates that no positive mutations were found with KRAS p.G12A, p.G12D, p.G12V, p.Q61H, p.Q61K, p.A66delinsDSA, or BRAF p.V600E primers and probes.
VF = variant frequencies.

a e e f d a c d 12: c.35G>A .G 12A , c.35G>T .G 12Va , c.34G>T .G 12C , a d c.35G>C .G 12A a ; a c d 61 c.183A>T .G 61H a ; a d a c d 66 c.191_196d ACAGTG .S65_A a66 A Se a . Ac a a *BRAF* (NM_004333.4) c.1799T>A .Va 600G a a b e ed e SAVM a e a d e BAVM a e . F c , e e .G12D, .G12V, .G12C, .G12A, .Q61H, .S65_A66 DS, a d .V600E a c e efe e e a , e ec e . R e e a e NGS e f e e a a e e F . 2. N e f e e a e e a a ed e 1000 Ge e da aba e. *KRAS* .G12V, .G12A a d .Q61H e e a a ed e E AC B e da aba e. *KRAS* .G12D, .G12C a d *BRAF* .V600E ad E AC a e e c f 2/101 204, 2/101 218 a d 2/121 220, e ec e . T e e a *KRAS* .G12A, a d .S65_A66 DS a e e e . bee e ed SAVM a d BAVM.

r t f t t s t c t f t l l w r t f r c t t s w t r l t t l

T e 21 *KRAS* a d *BRAF* a de ec ed b a e e e c f 422 a e e e e c ed ddPCR. R e e a e ddPCR e f e e a a e F . 2. A Tab e 2, f add a *KRAS* a e e de ec ed e e e e c - e a e a a e . T e a a e a e ce f *KRAS/BRAF* - a a e ef e 87.1% (27 f 31) c . T e a a f e e ce f a e ed b ddPCR a ed f 0.03% 7.29%. T e a a f e e ce f e - a de e ed b ddPCR ed c e a e a a f e e ce de e ed b NGS-ba ed e d (= 0.950, $P < 0.001$) (S e e a F . 1).



r rs t t t r t cs w r s t f t r s l t s f t s *KRAS/BRAF* t t s t t s s t Top: IGV snapshot. Each grey bar represents a sequencing read with base pairs matching the reference genome. Base cells deviating from the reference genome are considered as variants and are labelled. Bottom: 2D scatterplot of ddPCR results. Each dot represents a droplet. Blue: the droplet encloses at least one copy of mutant template. Green: the droplet encloses at least one copy of wild-type template. Orange: the droplet encloses at least one copy of wild-type and mutant template. Black: the droplet encloses no target molecular.

l r rtr s lf r t ss r t t s *KRAS* *BRAF*

T e e a e ce f *KRAS/BRAF* a a 81.0% (17 f 21) BAVM a d 100% (10 f 10) SAVM. B a e e ec a d ddPCR e e ed a SAVM a d BAVM a ed e a a e *KRAS* a d *BRAF*, c a abe e a e ce. F e a e, *KRAS* .G12D a d .G12V e e a b SAVM a d BAVM, a e a e ce f 30.0% a d 30.0% SAVM, a d 52.4% a d 19.0% BAVM, e- ec e, e ea *BRAF* .V600E a a e a d f d e BAVM a d e SAVM a e (F . 3).

t t r tfr c s r t l c rr l t w t s l s l r st trs, t t t t s

Beca e f ca d ffe e ce d e be ee SAVM a d BAVM, e a a e a a ed e c e- a a a a f e e ce 10 a e SAVM. T e a a a f e e c a e a e c - e a ed d e a d a e d a e e (= −0.686, *P* = 0.028 d e, a d = −0.764, *P* = 0.010 d a e d a e e, e ec e). S a, 20 a e BAVM (d e a d a e d a e e e e a a abe Pa e 25 d e e e ec e), e a a a f e e ce e e a e a e c e a ed e dce (= −0.522, *P* = 0.038 d e, a d = −0.524, *P* = 0.037 d a e d a e e, e ec e). F e e, - ca c e a a f d be ee a a a f e e ce a d a e (= −0.338, *P* = 0.085) (F . 4). F e e, a e e e d ded e a e be f a e acc d a a f e - ce. S ca d ffe e ce d e a d e e e b e ed be ee e b a d a a f e e ce. A Tab e 3, a e a a f e e ce ed ca a e e a d e b SAVM a d BAVM. I e e a a e, e ed ddPCR a a f e e ce a e a a f e e ce.

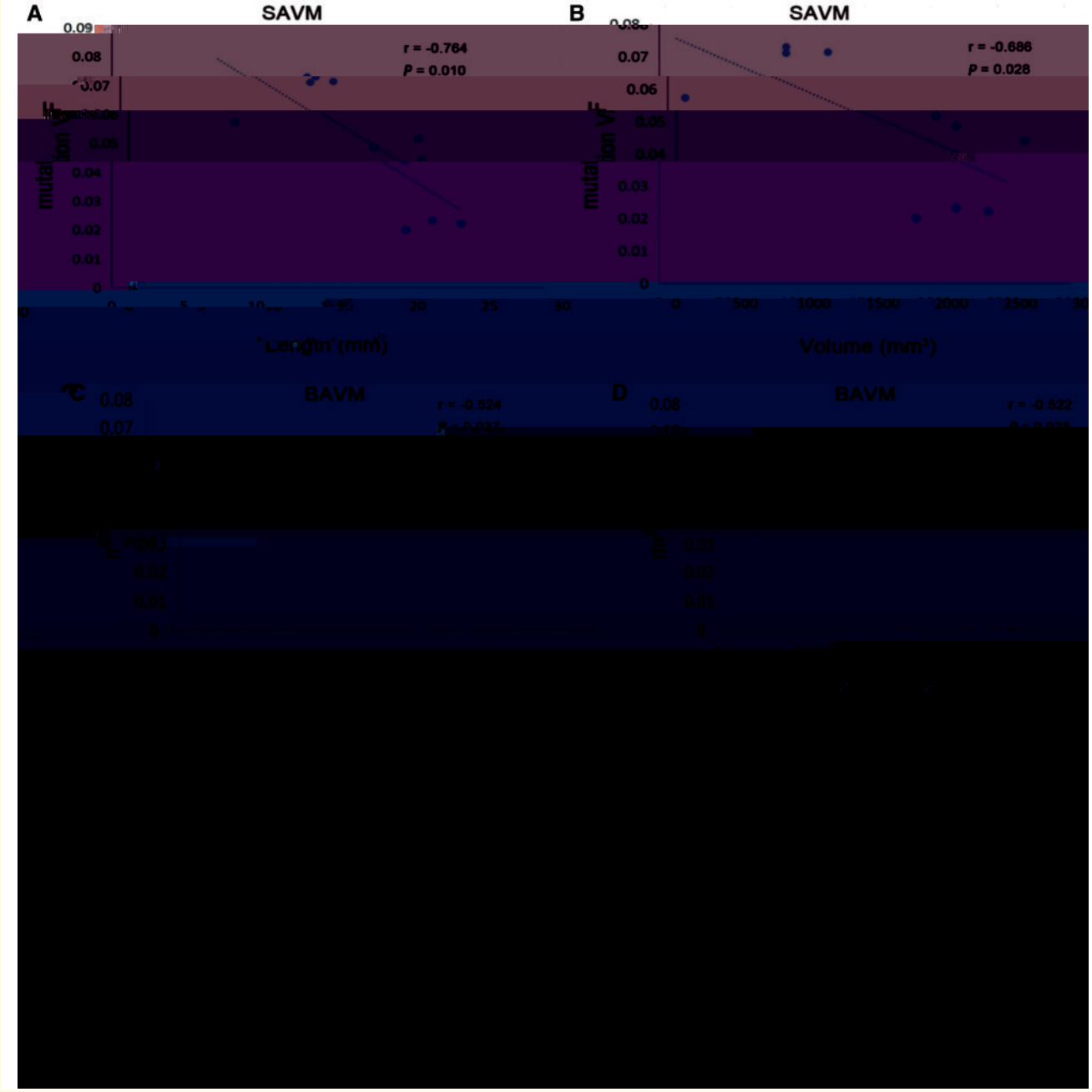
D sc ss

I d, e ed 31 CNS a e e a f a- , c d BAVM a d SAVM, f a c a- a a e f 422 -e a e d e e. T e d f d a e () e a e ce (ea 90%) f *KRAS/BRAF* a c a BAVM a d SAVM e e e e a a e ca ed adde a e e c ; () e e de ce f ac a- *BRAF* a BAVM a d SAVM; a d () e - de ce a SAVM, a d ea e e c a ace ed a e e e c e e, a e e a e e a e a *KRAS* a d *BRAF* BAVM. M e e, e a be e d e a *KRAS* .G12A a d .S65_A66 DS) CNS a e e a f a . F a, e f d a a a a f e e ce e a- e c ea e d d e a d a e d a e e.

b a e, a d a a a e ca f e de a d f e a e e f a e e a f a .

H r l c f s tc *KRAS/BRAF* t t

Rece , ac a a c *KRAS* a e e b e ed a e a e e a e ce f 64% BAVM , a d a c a ed e ac a f e MAPK/ERK a a , e f e a ace a a a a d ea f KRAS (N ae *et al.*, 2018). C e , ac a ed a c a f MAPK a a e e , .e. *KRAS*, *NRAS*, *BRAF* a d *MAP2K1* e e de c bed ac a a a d e ac a a a c a a f a c d a e e a f - a (C *et al.*, 2017; A -O ab *et al.*, 2018), e f - c e e f e RAS/RAF/MAPK/ERK a a a e e a f a . I e e , BAVM - de ec ab e *KRAS* a a a ad e e f a ed ERK1/2, e a e RAS/RAF/



r t t r tfr c s w r t l c rr l t w t s l s l r st trs t A s A s t tw t t t (**A**) The mutation variant frequencies (VF) were negatively correlated with SAVM largest diameters, r = −0.764, P = 0.010. ( ) The mutation variant frequencies were negatively correlated with SAVM nidus volumes, r = −0.686, P = 0.028. ( ) The mutation variant frequencies were negatively correlated with BAVM largest diameters, r = −0.524, P = 0.037. (**D**) The mutation variant frequencies were negatively correlated with BAVM nidus volumes, r = −0.522, P = 0.038. ( ) The mutation variant frequencies were not associated with patient ages, r = −0.338, P = 0.085.

l c t ff r c sl t l tw l w r tfr c r s

	A			A		
	n	t	l	*n*	t	l
Low VF[a]	5	20.8 ± 2.7	2196.5 ± 267.5	8	38.6 ± 7.0	35 684.4 ± 16 337.7
High VF	5	13.8 ± 4.5	1017.6 ± 634.2	8	31.0 ± 6.1	17 733.9 ± 8301.3
P		0.017	0.005		0.038	0.015

[a]Patients were divided into two groups with the same number of patients according to variant frequencies (VF).

e e c a e, e de d f *KRAS/BRAF* a ea 90% f BAVM a d SAVM, e de b f e RAS/RAF/MAPK/ERK a ec e MEK b a a a ac e f f e a e d e a e f BAVM. BRAF a d MEK-b a e a ead ed c ca ac ce f *BRAF* .V600E a ed e a a (L *et al.*, 2014). K a ea a BAVM a d SAVM a e a-e e *KRAS BRAF*, e e f a e e a c ca a e-e a a d e e c c a, c fea b e BAVM SAVM de f a e ec.

tc t A s A s

BAVM a d SAVM be CNS ac a af a-a d a e e f e a e a a a e e, df-fe b e d ffe e ca a e e a. C c a BAVM a d SAVM a e a e bee e-ed e a e, c a be e e de ce f e e-b ca (Ha e a a *et al.*, 1999; Wa *et al.*, 2009; S a a *et al.*, 2012). I a cc a a d ffe e e f e a be ee e f a d e ee f e b c de e e, e d e e a d f e d a d ffe e a f e CNS. B, add a a ac ec a fea e f a e e a-f a, a e c a ac e ed b abe a a e e a d ac a e de (A ff a d L e, 1974; K a d S e e, 2006; Ka a a d L d, 2008; Ra e-Ca a *et al.*, 2014). I e d, e de-a ed a b BAVM a d SAVM a e a-c e fea e (Ga *et al.*, 2010, 2011). Be de, e d e a ce, a e a e e d e a e a e ce, ed a e a ca ac a e de a d a ac e c ca c e f b BAVM a d SAVM. H e e, e e e c ba f SAVM e a e e ed. He e, e e-c da e e e e c ba f a a f SAVM, a be a a c f 10 a e, a d a e a b e a e a c a *BRAF* a d *KRAS* c-a ab e e a e ce a BAVM. O d, e e e de b a a de ac a a a e e af a (C *et al.*, 2017; A-O ab *et al.*, 2018; N ae *et al.*, 2018), a e a ea e e e c e e f a a e e af a, c a cc d ffe e e e f e a e a a a.

KRAS/BRAF t t r t fr c rtr s lf r t s

T e d f ec e e a e *KRAS/BRAF*-a b BAVM a d SAVM, e a e c a e f e a, e ab e ce f *KRAS/BRAF* a b a a c a af a e a BAVM (N ae *et al.*, 2018), a d e d ec d c f a e-e af a-e e b a a a a de (A-O ab *et al.*, 2018), c e e a *KRAS/BRAF* a a e ca a e a d b-a de e e d e d e a fea, a e c a a c a e de a e e af-a. M e e, e ab e ce f c ea f a a a f e e ce a e a e a d e e a e c-ea a e e af a e d, c e a a e a e e e *KRAS/BRAF* a d a d acc a e e a d e. O e c a, a e a e c e-a be ee a a f e e ce a d a e e a-f a e a e e a a e e af a e f ec a e f a e d-e a ec ac a a c a a d a-e a e e f ea e e af a. I ce a, e a d e d e a e, d-e e d e a ce d a be c a e d e a e e af a, e ef e d e a a e e af a ce. H e e, e ce e e e f a e e af a e a be a a e a e e a a f d. F e a e, a e a d ffe e ce a be ee e d-e a a d a ce a a d a e a e e af a a a e a d f a a a f e e ce a e e. F e a a f e d e a ce a e d f BAVM a d SAVM d e e e.

Rece, *EPHB4* a e e de ed e f Ga e a e a af a (V a *et al.*, 2018), a d a c ac a *RASA1* a a de ed ca a af a e e a a e e e *RASA1* a (La *et al.*, 2018). T e e e ed a c a af a e de c d be e a a c a e d e e a e e af a e, c a *RASA1*, *EPHB4*, *ENG*, *ACVRL1*, *GDF2*, *NF1* e c. (Ma ba a *et al.*, 2000; Ee a *et al.*, 2003; Ma d *et al.*, 2010; C da *et al.*, 2013; T ac a *et al.*, 2014; La *et al.*, 2018; V a *et al.*, 2018). Bef e a e e d a de 422-e e e e e c, e e e e c a a e f ed 12 f c a d a c a e e de-ec ed e e e e. De e a, e ad ca e d e dea f e e e e a a e bee e a c a e d a c a af a e a c c c ca a a e e f a c a af a-. A a e e d e NGS a e de a e d f a e-e af a c d b -e a e d a c a e e a d a c a af a a-e e d be de e e ed e f e.

A e e a e d e d e e e *KRAS/BRAF* a a e e a d f c e ca a e e e BAVM a d SAVM f a e e e c e e e d, e e a a e c e d e a c a-a e e c d. T e ec f *BRAF*^{V600E} e-ce eb a e b e e a e - c

e e , e ed 10 20% a c a a f a
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M, M, S a ( )-299.3(H,)-313.8I a: YH,K a , M, T d a
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