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Supplemental material

Somatic mosaicism in the MAPK pathway in sporadic brain arteriovenous malformation and association with phenotype

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Supplemental Table 1.

Clinical phenotype and allelic burden of somatic *KRAS* mutations for sporadic BAVM subjects.

Subject	Sex	Race	BAVM size (mm)	Age at DX (y)	Age at resection (y)	First TX	Age at first TX (y)	Age at first ICH (y)	Venous drainage (type)	Associated aneurysm (number)	G12V Allelic Freq (%)	G12D Allelic Freq (%)
D1	F	1	28.5	8.2	8.2	S	8.2	8.2	DS	0	F	F
D2	M	1	15	5.9	6.5	S	5.9	5.9	D	unknown	0	0.98
D3	F	1	29	30.9	31.5	S	31.4		S	1	4.99	0
D4	F	1	20	63.6	63.6	S	63.6	63.6	D	0	0	0
D5	M	1	25	47.4	47.6	S	47.6	47.4	S	0	N/A	N/A
D6	F	1	10	54.1	54.9	S	54.9	54.1	S	unknown	0	0.08
D7	F	1	10	67.4	67.5	S	67.4	67.4	S	unknown	0	0
D8	M	1	10	9.1	9.1	S	9.1	9.1	D	1	3.5	0
D9	F	1	10	15.4	15.4	S	15.4	15.4	unknown	unknown	0.24	0
D10	F	1	29.2	29.9	30.2	S	30.2		S	0	0.46	0
D11	M	1	15	38.7	38.7	S	38.7		S	0	0	2.56
D12	M	1	10	47.0	47.2	S	47.2	47.0	S	unknown	0	2.52
D13	M	1	3	45.3	45.5	S	45.5		S	0	0	0.19
D14	F	1	20	40.7	40.7	E	40.7		S	0	0	3
R1	M	1	14	62.8	63.3	S	63.3		S	0	0	1.18
R2	F	1	25	25.3	26.7	RS	26.1	25.3	S	0	0	1.81
R3	M	1	20	13.7	13.7	S	13.7	13.7	D	0	0	0.14
R4	F	1	10.8	28.3	28.4	E	28.3	28.3	S	0	F	F
R5	M	1	15	13.6	13.6	S	13.6	13.6	D	0	0	0.11
R6	F	9	17	14.7	14.8	S	14.8	14.7	D	0	0	0
R7	F	1	42	13.2	13.2	S	13.2	13.2	S	0	0	0
R8	M	1	14	11.6	12.2	E	11.6	11.6	S	1	0	0
R9	F	9	11	16.5	16.5	S	16.5	16.5	S	0	0.11	F
R10	M	1	25	16.8	17.4	S	17.4		S	0	0	0
R11	M	1	18.8	0.1	0.5	S	0.5	0.1	S	0	0	F
R12	F	9	18.1	13.1	13.1	S	13.1	13.1	S	0	0	F
R13	F	1	17.5	14.3	14.4	E	14.3	14.3	D	0	0	0
R14	F	4	56.3	14.1	14.1	E	14.1	14.1	DS	0	0	0

R15	M	9	35	17.2	17.3	E	17.3		DS	0	0	0.96
R16	F	9	40	13.4	13.4	S	13.4		S	0	0	F
R17	M	1	25.4	17.0	17.3	E	17.3		DS	0	0	0.47
R18	M	9	30	15.2	15.6	E	15.6		DS	0	0	0.41
R19	M	9	40	53.0	53.3	S	53.2		DS	0	3.65	0
R20	M	1	40	27.9	28.3	S	28.3		S	0	0.05	0
R21	F	4	30	24.7	24.8	S	24.7	24.7	S	unknown	0	0.41
R22	M	1	30	41.3	41.5	S	41.4		S	0	0	0
R23	F	1	29	24.2	61.6	S	61.6	61.5	S	0	0	3.76
R24	M	9	29	28.1	28.7	S	28.7	28.1	DS	0	0	2.29
R25	F	4	29	24.3	24.3	S	24.3	24.3	S	unknown	0	1.08
R26	F	4	25.6	26.1	38.4	S	38.4		S	1	0	0
R27	M	9	25.3	47.9	48.0	S	47.9	47.9	DS	0	0	3.23
R28	F	1	25	37.3	39.5	S	39.5		D	0	4.32	0
R29	M	1	20.2	24.2	24.3	S	24.2	24.2	S	0	0	F
R30	F	1	20	54.1	54.4	S	54.4		S	0	0	1.06
R31	M	9	19.2	21.7	22.1	S	22.1	21.7	D	0	0	0
R32	F	9	18	58.8	58.9	S	58.9		S	2	0	0
R33	M	2	17.9	54.3	54.3	S	54.3	54.3	DS	0	0	0
R34	F	1	17	47.1	47.5	S	47.5		S	1	0	0
R35	F	1	13.3	59.1	59.5	S	59.5	59.1	S	0	2.55	0
R36	M	1	10	58.9	59.0	S	58.9	58.9	S	0	0	F
R37	M	9	10	58.5	58.5	S	58.5	58.5	S	unknown	0	0.34
R38	M	1	10	39.5	40.3	S	40.3	39.5	D	0	0	0
R39	F	9	10	49.1	49.3	S	49.2		S	4	0	0
R40	M	1	9	61.2	61.3	S	61.3	61.2	S	0	0	0
R41	F	1	7.8	57.8	57.8	S	57.8	57.8	S	0	0.3	0
R42	F	1	7	51.3	51.4	S	51.3	51.3	D	1	0	0
R43	M	1	7	28.3	28.3	S	28.3	28.3	S	0	0	0.77
R44	M	9	6.7	20.0	20.0	S	20.0	20.0	D	1	0	0
R45	F	2	6.5	58.7	58.7	S	58.7	58.7	S	0	0	0.04
R46	M	9	6	32.2	32.2	S	32.2	32.2	S	0	0	0
R47	F	1	5	40.9	41.3	S	41.2	40.9	S	0	0	0
R48	M	1	2	41.6	42.0	S	41.9	41.6	S	0	0	0

R49	M	1	28	35.8	35.8	S	35.8		D	0	F	0
R50	M	1	28	27.6	27.9	S	27.9		DS	0	F	F
R51	F	1	19	63.9	63.9	S	63.9	63.9	S	0	0	F
R52	F	1	17.3	53.8	54.1	S	54.1		S	0	0	F
R53	F	1	13.3	47.9	48.1	S	48.0		D	0	0	0
R54	M	1	13	43.5	43.6	S	43.6		S	3	0	0
R55	F	4	12	54.0	54.0	S	54.0	54.0	D	0	0	0
R56	M	1	10	55.5	55.7	S	55.7		S	0	0	F

Legend:

Subject: D, discovery, R, replication.

Race: 1-White, 2-African American, 4-Asian, 9-More than one race.

DX, BAVM diagnosis.

TX: first treatment: S, surgery, RS, radiosurgery, E, embolization.

Venous drainage: D, deep, S, superficial, DS, both deep and superficial.

Associated aneurysms: number of BAVM-associated aneurysms.

Allelic Freq: somatic mutation allelic frequency by ddPCR. F: failed QC. N/A: not available, or not enough DNA.

Supplemental Table 2.

Variant filtering results for whole exome sequencing in 14 sporadic BAVM subjects.

Subject	Original Mutect2 variants	PASS Mutect2 variants	Variants with 0 counts in blood	Variants with ≥3 counts in BAVM	Variants with allelic freq ≥ 2%	NS variants	Probably damaging variants
D1	3,628	2,031	1,903	1,414	1,207	899	339
D2	2,653	1,301	1,242	814	643	485	187
D3	2,536	1,246	1,177	691	544	398	164
D4	6,541	4,271	4,064	3,428	3,256	2,343	955
D5	3,498	1,952	1,830	1,546	1,107	797	315
D6	2,459	1,220	1,161	734	640	464	189
D7	4,472	2,595	2,446	2,097	1,489	1,101	498
D8	2,225	760	708	362	230	164	63
D9	1,742	725	681	308	221	165	65
D10	1,801	824	760	347	249	180	70
D11	2,848	1,501	1,412	848	652	479	202
D12	1,726	665	632	262	197	142	39
D13	4,447	2,662	2,483	2,113	1,701	1,234	503
D14	2,218	848	785	454	217	153	63
Total variants	37,591	22,367	21,098	15,238	12,272	8,946	3,624

Legend:

Subject: D, discovery.

NS: non-synonymous.

Supplemental Table 3.

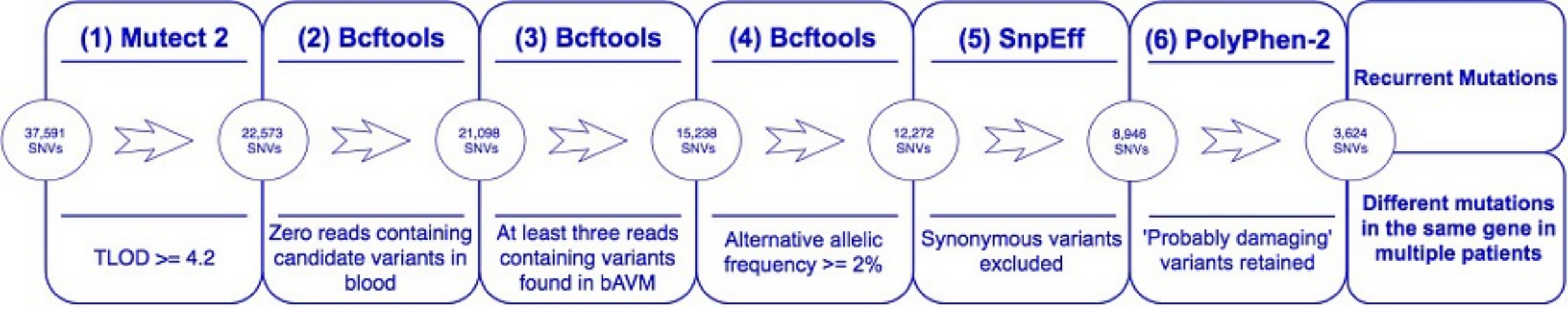
Sequencing statistics for whole exome sequencing in 14 sporadic BAVM subjects.

Subject	BAVM (X)	Blood (X)	BAVM Mapped Reads	BAVM Total Reads	BAVM % Mapped Reads	Blood Mapped Reads	Blood Total Reads	Blood % Mapped Reads
D1	107	91	115,801,697	116,997,270	99.0	110,124,635	111,665,824	98.6
D2	115	79	126,843,880	127,680,812	99.3	100,393,152	101,559,918	98.9
D3	114	96	119,421,472	120,511,892	99.1	109,920,415	111,055,036	99.0
D4	89	96	87,935,182	88,567,368	99.3	119,195,662	120,773,302	98.7
D5	111	101	128,713,822	129,711,958	99.2	126,106,540	127,777,516	98.7
D6	98	102	106,866,694	108,032,584	98.9	122,431,818	124,110,874	98.6
D7	120	96	145,199,625	146,542,102	99.1	121,005,707	122,311,954	98.9
D8	118	102	138,634,452	140,205,496	98.9	121,875,893	123,481,094	98.7
D9	100	102	113,736,471	114,816,400	99.1	127,330,009	129,206,910	98.5
D10	88	125	102,177,604	103,365,246	98.9	151,473,066	153,100,136	98.9
D11	106	91	122,079,141	123,143,012	99.1	109,569,801	110,574,906	99.1
D12	93	70	110,446,680	111,726,088	98.9	89,639,763	90,815,102	98.7
D13	106	99	119,865,499	121,087,366	99.0	119,211,511	120,451,626	99.0
D14	142	104	167,677,190	169,562,810	98.9	124,022,177	125,408,192	98.9

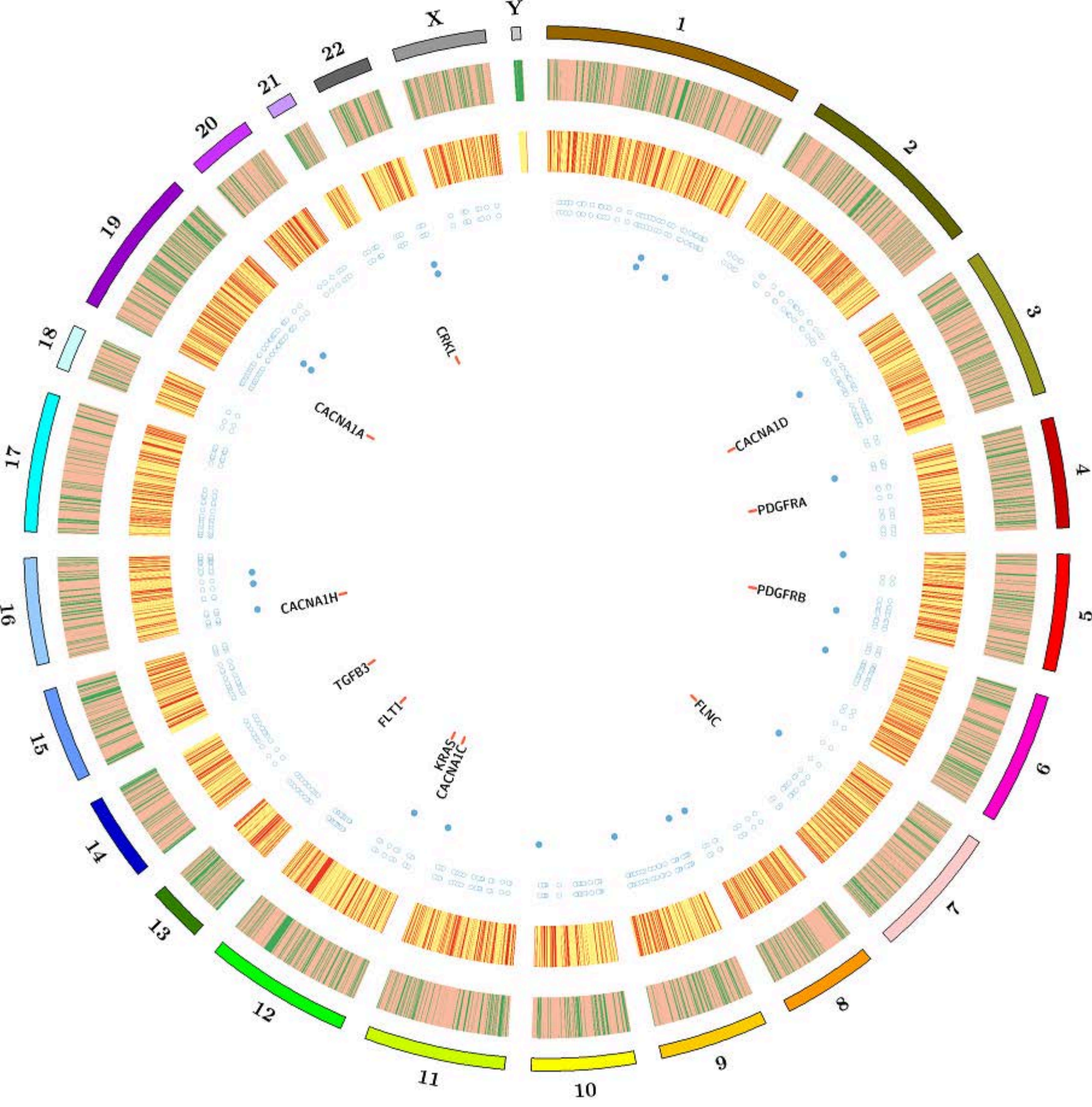
Legend:

Subject: D, discovery.

(X), average sequencing read coverage.



Supplemental Figure 1.
Workflow for identification of candidate somatic BAVM-associated variants.



Supplemental Figure 2.

Circos plot of sequencing coverage and distribution of candidate mutations. From outer to inner concentric layers: (A) Targeted exome regions on each chromosome concatenated sequentially. (B) Targeted region coverage: light red: regions with good coverage (CSS < 0.2), green: regions with low coverage (CSS > 0.2). (C) Sample coverage: yellow: regions with uniform coverage across samples (UE < 1.37), red: regions with non-uniform coverage across samples (UE > 1.37). (D) Different mutations in the same gene in multiple patients across the whole exome. (E) Recurrent mutations across the whole exome. (F) MAPK pathway genes with mutations in more than one patient.