
Supplementary information

**A prognostic human brain network for
diffuse midline glioma**

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	Whole cohort (n=288)	Discovery cohort	External validation cohort					P (discovery vs. external validation cohort)	PNOC trial cohort (n=38)	P (discovery vs. PNOC trial cohort)
		GOSH (n=125)	Whole cohort (n=125)	CHCO (n=81)	HERBY (n=23)	AA (n=11)	USP (n=10)			
Age at diagnosis, median (IQR), years	6.8 (4.9 – 11.1)	6.6 (5.2 – 9.6)	7.0 (4.8 – 11.8)	6.3 (4.4 – 11.2)	13.0 (9.9 – 14.7)	6.1 (4.0 – 7.1)	6.2 (5.4 – 7.4)	0.593	6.3 (4.8 – 9.2)	0.615
Sex, n (%)										
Female	158 (54.9)	71 (56.8)	70 (56.0)	44 (54.3)	13 (56.5)	6 (54.5)	7 (70.0)	1.000	17 (44.7)	0.120
Male	130 (45.1)	54 (43.2)	55 (44.0)	37 (45.7)	10 (43.5)	5 (45.5)	3 (30.0)		21 (55.3)	
Tumour location, n (%)										
Pons	229 (79.5)	106 (84.8)	85 (68.0)	66 (81.5)	0 (0.0)	11 (100.0)	8 (80.0)	0.003*	38 (100.0)	0.008*
Thalamus	59 (20.5)	19 (15.2)	40 (32.0)	15 (18.5)	23 (100.0)	0 (0.0)	2 (20.0)		0 (0.0)	
Tumour volume, median (IQR), mm ³	27635.0 (21215.0 – 37020.0)	25640.0 (20350.0 – 33340.0)	28980.0 (21980.0 – 40660.0)	27940.0 (21500.0 – 35720.0)	43820.0 (23735.0 – 68745.0)	27830.0 (23630.0 – 32390.0)	27210.0 (22597.5 – 40612.5)	0.016*	32974.5 (26040.5 – 41050.0)	0.003*
Extent of resection										
Gross-total	2 (0.7)	1 (0.8)	1 (0.8)	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0.075	0 (0.0)	<0.001*
Subtotal	24 (8.3)	10 (8.0)	13 (10.4)	4 (4.9)	9 (39.1)	0 (0.0)	0 (0.0)		1 (2.6)	
Biopsy only	157 (54.5)	52 (41.6)	68 (54.4)	44 (54.3)	14 (60.9)	1 (9.1)	9 (90.0)		37 (97.4)	
None	105 (36.5)	62 (49.6)	43 (34.4)	32 (39.5)	0 (0.0)	10 (90.9)	1 (10.0)		0 (0.0)	
Adjuvant radiotherapy										
Yes	265 (92.0)	116 (92.8)	112 (89.6)	75 (92.6)	22 (95.7)	9 (81.8)	6 (60.0)	0.504	37 (97.4)	0.455
No	23 (8.0)	9 (7.2)	13 (10.4)	6 (7.4)	1 (4.3)	2 (18.2)	4 (40.0)		1 (2.6)	
Other adjuvant therapy										
Yes	134 (46.5)	45 (36.0)	51 (40.8)	23 (28.4)	22 (95.7)	0 (0.0)	6 (60.0)	0.516	38 (100.0)	<0.001*
No	154 (53.5)	80 (64.0)	74 (59.2)	58 (71.6)	1 (4.3)	11 (100.0)	4 (40.0)		0 (0.0)	

Supplementary Table 1. DMG patient cohort clinical characteristics and between-cohort comparisons.

GOSH: Great Ormond Street Hospital for Children NHS Foundation Trust; CHCO: Children's Hospital Colorado; HERBY: Phase II, Open-Label, Randomised, Multicentre Trial of Bevacizumab in Paediatric Patients with Newly Diagnosed High-Grade Glioma (NCT01390948); AA: Institute of Neurosurgery Dr. Alfonso Asenjo; USP: University of São Paulo; PNOC: Pediatric Neuro-Oncology Consortium; IQR: interquartile range; SD: standard deviation. Asterisks denote significant values.

	Centre of gravity coordinates			P_{FWE}	Voxels (n)	Cluster location(s)
	x	y	z			
Cluster 1	-2.55	-41.20	-40.60	$P \leq 0.0005$	6639	Brainstem, cerebellum
Cluster 2	-2.27	-55.70	-12.60	$P \leq 0.0005$	324	Cerebellar vermis
Cluster 3	-63.50	-0.60	2.54	$P \leq 0.0005$	122	Left superior temporal gyrus
Cluster 4	23.30	34.20	-11.00	$P \leq 0.0005$	102	Right orbitofrontal cortex
Cluster 5	33.00	-5.98	-35.60	$P \leq 0.0005$	93	Right hippocampus
Cluster 6	35.50	1.21	-15.80	$P \leq 0.0005$	77	Right amygdala, right insular cortex
Cluster 7	-36.40	36.20	8.01	$P \leq 0.0005$	65	Left orbitofrontal cortex
Cluster 8	-39.20	0.15	-14.60	$P \leq 0.0005$	60	Left amygdala, left insular cortex
Cluster 9	-19.40	-12.20	-1.02	$P \leq 0.0005$	75	Left pallidum
Cluster 10	-42.00	-18.10	39.30	$P \leq 0.0005$	173	Left precentral gyrus
Cluster 11	8.70	-24.00	5.79	$P \leq 0.0005$	109	Right thalamus
Cluster 12	18.20	-8.84	0.01	$P \leq 0.0005$	35	Right pallidum
Cluster 13	18.40	-28.50	59.70	$P \leq 0.0005$	21	Right precentral gyrus
Cluster 14	-1.03	-7.79	59.60	$P \leq 0.0005$	93	Right and left supplementary motor area
Cluster 15	6.79	-1.08	42.30	$P \leq 0.0005$	37	Right cingulate cortex
Cluster 16	-26.60	-36.40	-3.43	$P \leq 0.0005$	29	Left hippocampus
Cluster 17	-10.30	27.80	17.50	$P \leq 0.0005$	21	Left cingulate cortex
Cluster 18	-10.80	-25.20	4.26	$P \leq 0.0005$	20	Left thalamus

Supplementary Table 2. Significant clusters in the DMG network.

Clusters are illustrated spatially in **Main Text Fig. 1d**. Coordinates are reported in MNI space (mm) with cluster sizes in voxels (1.0 x 1.0 x 1.0mm). Several clusters included more than one neuroanatomic location, listed under cluster location(s).

	Whole cohort (n=520)	UCSF-PDGM (n=248)	NHNN (n=272)	P
Age at diagnosis, median (IQR), years	62.0 (54.0 – 69.7)	62.0 (54.0 – 70.0)	62.0 (53.8 – 69.6)	P=0.786
Sex, n (%)				
Female	197 (37.9)	102 (39.7)	95 (34.9)	P=0.149
Male	323 (62.1)	146 (56.8)	177 (65.1)	
Tumour volume, median (IQR), mm ³	24594.5 (10724.5 – 45888.5)	16555.0 (7558.5 – 32030.0)	30699.5 (15375.0 – 53634.0)	P<0.001*
Extent of resection				
Gross-total	196 (37.7)	152 (61.3)	44 (16.2)	P<0.001*
Subtotal	203 (39.0)	74 (29.8)	129 (47.4)	
Biopsy	121 (23.3)	22 (8.9)	99 (36.4)	
MGMT promoter methylation				
Yes	289 (55.6)	168 (67.7)	120 (44.1)	P<0.001*
No	221 (42.5)	70 (28.2)	152 (55.9)	
Indeterminate or not tested	10 (1.9)	10 (4.0)	0 (0.0)	
RT + TMZ				
Yes	457 (87.9)	248 (100.0)	209 (76.8)	P<0.001*
No	63 (12.1)	0 (0.0)	63 (23.2)	

Supplementary Table 3. GBM patient cohort characteristics and between-cohort comparison.

UCSF: University of California, San Francisco; NHNN: National Hospital for Neurology and Neurosurgery; IQR: interquartile range; SD: standard deviation. Asterisks denote significant values.

	Whole cohort (n=288)	Final follow-up cohort (n=71)	P
Age at diagnosis, median (IQR), years	6.8 (4.9 – 11.1)	7.5 (5.2 – 10.8)	0.473
Sex, n (%)			
Female	158 (54.9)	36 (50.7)	0.595
Male	130 (45.1)	35 (49.3)	
Tumour location, n (%)			
Pons	229 (79.5)	58 (81.7)	0.743
Thalamus	59 (20.5)	13 (18.3)	
Tumour volume, median (IQR), mm ³	27635.0 (21215.0 – 37020.0)	26650.0 (19465.0 – 33295.0)	0.162
Extent of resection			
Gross-total	2 (0.7)	1 (1.4)	0.605
Subtotal	24 (8.3)	8 (11.3)	
Biopsy only	157 (54.5)	36 (50.7)	
None	105 (36.5)	26 (36.6)	
Adjuvant radiotherapy			
Yes	265 (92.0)	68 (95.8)	0.441
No	23 (8.0)	3 (4.2)	
Adjuvant chemotherapy			
Yes	134 (46.5)	32 (45.1)	0.895
No	154 (53.5)	39 (54.9)	

Supplementary Table 4. Follow-up imaging cohort characteristics and comparison with whole study cohort.

IQR: interquartile range; SD: standard deviation.

	Label permutation test		Spin permutation test	
	p	P _{FDR}	p	P _{FDR}
0-1 years	-0.03	0.018	-0.13	0.436
1-2 years	-0.08	1.000	-0.14	0.366
2-3 years	-0.05	<0.001	-0.13	0.463
3-4 years	-0.07	1.000	-0.19	0.454
4-5 years	0.06	<0.001	0.12	0.461
5-6 years*	0.20	<0.001	0.51	0.001
6-7 years	-0.05	<0.001	-0.15	0.402
7-8 years	-0.05	<0.001	-0.14	0.420
8-9 years	0.04	<0.001	0.16	0.221
9-10 years	-0.02	1.000	-0.01	0.924
10-11 years*	0.12	<0.001	0.37	0.002
11-12 years	0.08	0.228	0.37	0.023
12-13 years	0.02	<0.001	0.01	0.980
13-14 years	0.04	1.000	0.13	0.258
14-15 years	0.02	<0.001	0.08	0.639
15-16 years	-0.03	<0.001	-0.08	0.440

Supplementary Table 5. Spatial comparison of age-wise changes in neurometabolic activity with DMG network topography.

Values represent label and spin permutation test results. Asterisks represent significant spatial similarity of peak, age-wise neurometabolic changes with DMG network topography. Red text indicates negative values.

	Whole cohort (n=288)	DNA methylation cohort (n=36)	P
Age at diagnosis, median (IQR), years	6.8 (4.9 – 11.1)	10.7 (6.9 – 13.7)	0.002*
Sex, n (%)			
Female	158 (54.9)	21 (58.3)	0.726
Male	130 (45.1)	15 (41.7)	
Tumour location, n (%)			
Pons	229 (79.5)	15 (41.7)	<0.001*
Thalamus	59 (20.5)	21 (58.3)	
Tumour volume, median (IQR), mm ³	27635.0 (21215.0 – 37020.0)	26580.0 (18825.0 – 41895.0)	1.000

Supplementary Table 6. DNA methylation cohort characteristics and comparison with whole study cohort.

IQR: interquartile range; SD: standard deviation. Asterisks denote significant values.

	All thalamic DMG (n=59)	Subtotal resection cohort (n=23)	P
Age at diagnosis, median (IQR), years	11.4 (7.3 – 14.6)	12.75 (7.5 – 14.5)	0.788
Sex, n (%)			
Female	32 (54.2)	12 (52.2)	0.782
Male	27 (45.8)	11 (47.8)	
Tumour volume, median (IQR), mm³	37200.0 (25260.0 – 58050.0)	32440.0 (23310.0 – 39870.0)	0.128
Extent of resection			
Gross-total	2 (3.4)	0 (0.0)	NA (cohort defining)
Subtotal	28 (47.5)	23 (100.0)	
Biopsy only	29 (49.2)	0 (0.0)	
None	0 (0.0)	0 (0.0)	
Adjuvant radiotherapy			
Yes	54 (91.5)	20 (87.0)	0.680
No	5 (8.5)	3 (13.0)	
Adjuvant chemotherapy			
Yes	45 (76.3)	21 (91.3)	0.213
No	14 (23.7)	2 (8.7)	

Supplementary Table 7. Thalamic DMG subtotal resection cohort characteristics and comparison with all included thalamic DMG across the study cohort.

IQR: interquartile range; SD: standard deviation. Asterisks denote significant values.