Acta Neuropathologica (2020) 140:89–93
https://doi.org/10.1007/s00401-020-02161-7

CORRESPONDENCE

Frequent inactivating mutations of the PBAF complex gene *PBRM1* in meningioma with papillary features

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Received: 5 February 2020 / Revised: 13 April 2020 / Accepted: 4 May 2020 / Published online: 13 May 2020

Papillary meningioma (PM) is a World Health Organization (WHO) grade III tumor defined histologically by a perivascular pseudopapillary growth pattern across most of the tumor (> 50%) [10]. A papillary growth pattern in meningiomas has been associated with brain invasion and aggressive clinical behavior [2, 8, 9, 12]. The standard treatment of PM is surgical resection followed by radiation. However, most patients develop recurrences, and metastatic disease is common, particularly to the lung [9, 19]. Another WHO grade III meningioma is the rhabdoid subtype which often harbors mutations in *BAP1* [14, 15]. Interestingly, some meningiomas have cells with rhabdoid cytomorphology arranged in a papillary architecture suggesting a potential molecular and genetic link between the papillary and rhabdoid histologic subtypes of meningioma [8, 14]. The genetic alterations associated with PM remain unclear. Major obstacles to molecular characterization include low incidence of tumor, scarcity of tumor tissues available for genomic analyses, and the presence of artifactual pseudo-papillary features in some meningiomas which thereby confound cohorts [2]. To overcome these challenges and identify potentially recurrent somatic alterations in PM subtype of meningiomas, we mined data collected as part of our clinical comprehensive genomic profiling (CGP) initiative which has to date analyzed 8 PM (> 50% papillary morphology) and 22 meningiomas with focal papillary features (10–50%) amongst over 500 additional meningiomas of other subtypes.

The samples were analyzed in a CAP/CLIA-accredited laboratory (Foundation Medicine, Cambridge, MA). Approval for this study, including a waiver of informed consent and a HIPAA waiver of authorization, was obtained from the Western Institutional Review Board (Protocol no. 20152817). Three board-certified neuropathologists (E.A.W., S.H.R., and S.S.) confirmed the pathologic diagnosis of each case on routine hematoxylin and eosin-stained slides. DNA was extracted from 40-µm-thick paraffin-embedded sections, and CGP was performed on hybridization-captured, adaptor ligation-based libraries to a mean coverage depth of > 650 × for 236 or 315 genes plus the introns from 19 or 28 genes frequently involved in cancer. TMB (tumor mutational burden) was determined on up to

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Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00401-020-02161-7) contains supplementary material, which is available to authorized users.

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1.14 Mb of sequenced DNA using an estimation algorithm that extrapolates to the genome as a whole [5–7].

In our cohort of eight PMs, we identified three cases with inactivation of *PBRM1*: two cases with a truncating mutation in *PBRM1* and one with homozygous deletion of *PBRM1* (Table 1). Of the 22 meningiomas with only focal papillary features, 8 cases were *PBRM1*-mutant. Thus, 11 of 30 cases with at least focal papillary morphology (10–50% of papillary features in the H&E sections) had inactivation of *PBRM1* (Supplementary Table 1). In the entire cohort of 562 available meningiomas that represents a general population of all WHO grades, we identified five additional cases with inactivating alterations in *PBRM1* that did not display overt papillary morphology in the H&E sections available for analysis. Thus, 11 of 16 *PBRM1*-mutant cases (69%) occurred in meningioma with papillary histologic features, supporting a significant association between papillary features and *PBRM1* mutation ($p < 0.0001$). Among the 16 *PBRM1*-mutant cases (2.8% of cohort), the detected *PBRM1* alterations included six intragenic deletions, four frame-shifting insertions, four frame-shifting deletions, and two truncating mutations (Fig. 1). All showed biallelic inactivation by SNP array analysis and mutant allele read count data analysis. Median TMB was 2.1 mutations/Mb and all cases were microsatellite stable. Representative histopathology of *PBRM1*-mutant meningiomas is included in Fig. 2. The majority of *PBRM1*-mutant meningiomas occurred in female patients ($n = 10/16$, 62.5%), and median age was 51 years. Most cases were located supratentorially ($n = 10$). Additional characteristics of *PBRM1*-mutant meningiomas are shown in Table 1. A notable feature of our cohort was the frequent overlap of *PBRM1* mutation with mutations in *BAP1* ($n = 5$). Three of these five cases displayed papillary features while two displayed rhabdoid features. An association between *BAP1* mutation and rhabdoid histology has been previously described [14]. This association was confirmed in our cohort of 562 meningiomas, in which 13 of 17 cases that were *BAP1*-mutant/*PBRM1*-wt had rhabdoid features. Among the 19 *PBRM1*-wt meningiomas with papillary histology, two had mutations in *BAP1,* consistent with prior reports of rare *BAP1*-mutant cases with papillary morphology [14, 18]. Notably, meningiomas that were

Table 1 Location, histology, and molecular characteristics of *PBRM1*-mutant meningioma

Patient no.	Gender	Age (years)	Tumor location	Histologic subtype/WHO grade	*PBRM1* mutation	*PBRM1* allele frequency (%)	Concurrent *BAP1* Alterations	TMB (mutations/Mb)
1	Male	55	Temporal	Papillary/III	p.F732fs*13	60	None	6.1
2	Female	50	Adrenal gland	Papillary/III	Two copy number loss		Two copy loss of *BAP1*	1.7
3	Female	42	Cavernous sinus	Papillary /III	p.R146*	50.9	*BAP1* p.Q260*	3.5
4	Female	60	Left frontal	Papillary features/I	p.A482fs*18	53.4	None	2.6
5	Male	69	Left frontoparietal	Papillary features/II	p.Q949fs*59	65	None	0.9
6	Female	37	Left supraorbital	Papillary features/II	p.E1029fs*100	34	None	< 0.1
7	Male	42	Right supratentorial	Papillary features/II	p.K1372*	13.9	None	< 0.1
8	Male	46	Frontoparietal	Papillary features/II	Two copy number loss		Two copy loss of *BAP1*	3.5
9	Female	45	Right cerebellopontine angle	Papillary features/I	Two copy number loss		Two copy loss of *BAP1*	3.8
10	Female	67	Right infratentorial	Papillary features/II	Two copy number loss		Two copy loss of *BAP1*	1.7
11	Female	51	Right frontoparietal	Papillary & rhabdoid features/II	Two copy number loss		None	2.6
12	Female	71	Parasagittal	Anaplastic/III	p.S39fs*14	41	None	0.9
13	Male	70	Left frontal	Rhabdoid/III	p.S652fs*13	18	None	2.4
14	Female	58	Left neck	Rhabdoid/III	Two copy number loss		Two copy loss of *BAP1*	4.8
15	Female	51	Right parietooccipital	Rhabdoid features/II	p.L1565fs*31	55.5	Two copy loss of *BAP1*	< 0.1
16	Male	52	Left cavernous sinus	Chordoid/II	p.V964fs*18	7	None	1.2

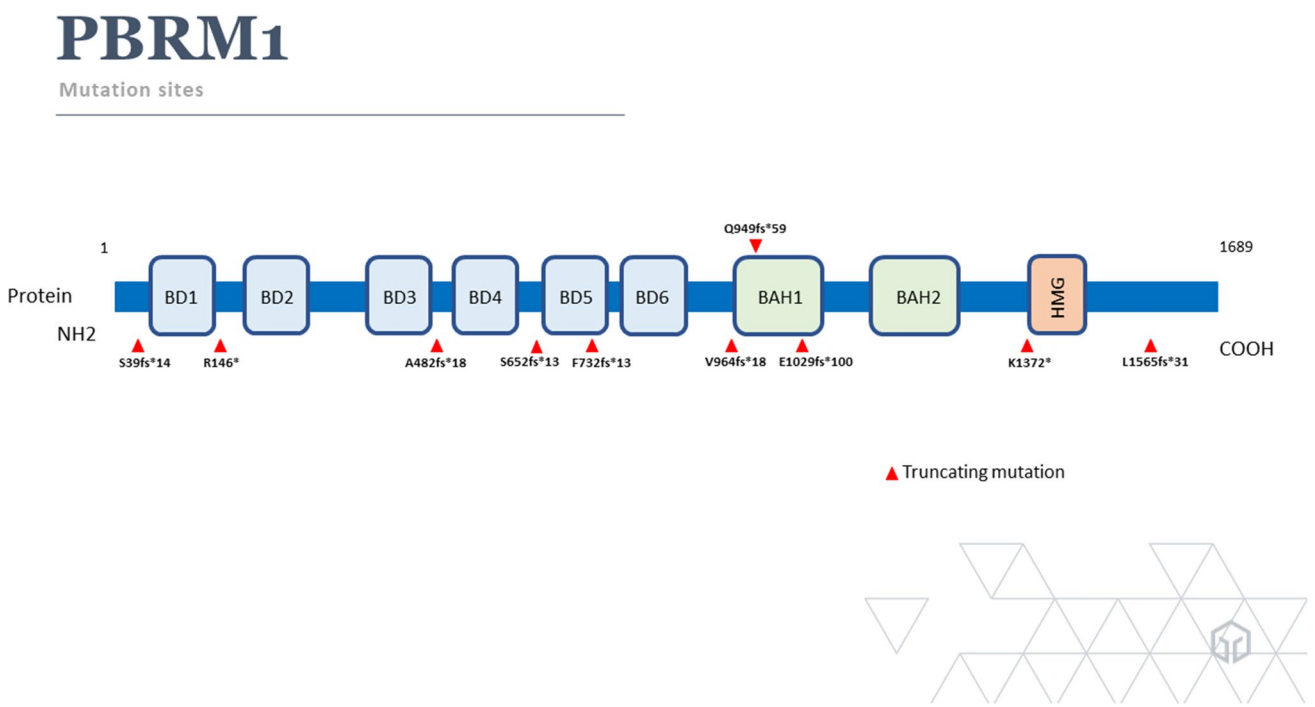

Fig. 1 Schematic diagram of *PBRM1* truncating mutations identified in meningioma cases. Six additional cases were identified with two copy-number loss of *PBRM1*

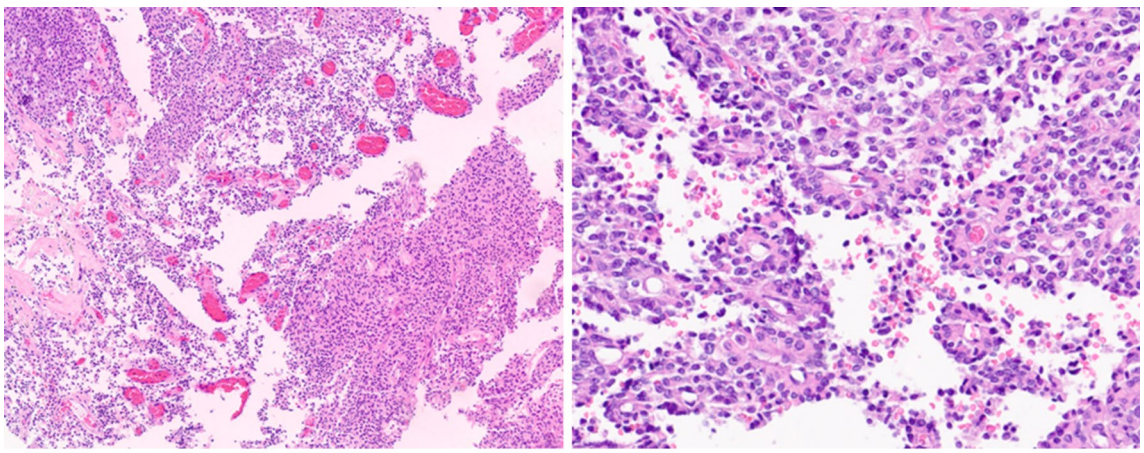

Fig. 2 *PBRM1*-mutant meningioma histopathologic features. **a** Examination reveals tumor cells arranged in a papillary pattern (H&E 100x). **b** Higher power image shows fragmentation of tissue architecture with the preservation of perivascular tumor cells with cytoplasm tapering towards a perivascular nuclear-free region (H&E 400x)

BAP1-wt/*PBRM1*-mutant frequently had papillary morphology (7 of 11). Our findings suggest that *BAP1* mutations tend to occur in rhabdoid meningiomas whereas *PBRM1* mutations tend to occur in papillary meningiomas, although genetic and histologic overlap is noted.

PBRM1 is a 37-exon gene residing on chromosome 3p21, adjacent to *BAP1*, separated by ~ 0.135 megabase pairs. *PBRM1* encodes the BAF180 protein, the chromatin targeting subunit of the PBAF chromatin remodeling complex [17]. *PBRM1* is a tumor suppressor gene, mutated in 40% of clear cell renal cell carcinoma (RCC), as well as a subset of papillary RCC and bladder carcinoma [3, 17]. Mutations in *PBRM1* are most often truncations and result in loss of protein expression. Previous studies have illustrated a significant increase in cell proliferation and cell migration after knockdown of *PBRM1* [20]. Recent work has also

demonstrated that BAF180 is required for centromeric cohesion, and DNA damage in cells lacking *PBRM1* results in dynamic chromosome instability [11]. It has been speculated that the latter results in the improved survival of a subset of patients with *PBRM1*-mutant clear cell RCC cohorts treated with programmed cell death 1 receptor (PD-1) inhibitor [11]. Although our findings suggest that *PBRM1* mutation is uncommon in meningioma, the inclusion of patients with this defined genetic subtype of meningioma in similar trials may reveal new therapeutic approaches. Mutations in other genes encoding components of the BAF complex, such as *SMARCB1, SMARCE1*, and *ARID1A*, have been previously reported in aggressive meningiomas [1, 4, 13, 16]. Dysregulation of chromatin remodeling is often identified in higher grade meningiomas, regardless of the molecular subgroup. It is postulated that the mutations resulting in disruption of SWI/SNF chromatin remodeling complexes are present in at least 20% of all human cancers [3].

In conclusion, we identify the tumor suppressor gene *PBRM1* as a recurrently altered gene in meningiomas with papillary histomorphology. Further investigational studies are needed to assess outcomes of *PBRM1*-mutant meningioma and to determine whether mutation is an independent negative prognostic biomarker.

Funding None.

Compliance with ethical standards

Conflict of interest EAW, ESS, DCP, NS, AR, JMV, BMA, JSR, and SHR are employees or consultants of Foundation Medicine, Inc., a wholly owned subsidiary of Roche Holdings, Inc. and Roche Finance Ltd, and these employees have equity interest in an affiliate of these Roche entities. SS is a consultant for RareCyte. PKB reports honoraria for consulting from Tesaro, Lilly, Angiochem, and Genentech-Roche; speaker's honoraria from Genentech-Roche and Merck; and research funding (to Massachusetts General Hospital) from BMS, Pfizer, Lilly and Merck. DPC reports receiving honoraria from Merck and Lilly outside the submitted work.

IRB approval status Reviewed and approved by Western IRB; Protocol no. 20152817.

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