ATRX mutation in Pineal Parenchymal Tumor of Intermediate Differentiation

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BACKGROUND

- Pineal parenchymal tumors (pineocytomas, pineal parenchymal tumors of intermediate differentiation (PPTID) and pineoblastomas) are rare tumors (<0.5% of intracranial neoplasms) ranging from WHO Grade I to IV
- Tumors in this class can cause major morbidity and death
- Distinguishing between WHO Grade II and III PPTID and between PPTID and pineoblastomas can be challenging
- Few studies on molecular profiles of pineal parenchymal tumors have been done
- Recent identification of an isolated ATRX (α-thalassemia/mental retardation syndrome X-linked gene) mutation using Next Generation Sequencing in a PPTID raises the possibility of ATRX involvement in pineal parenchymal tumor biology

OBJECTIVES

Based on our identification of an ATRX mutation in a PPTID of a 22 year old female, we analyzed the frequency of ATRX loss in pineal parenchymal tumors using ATRX immunohistochemical staining.

STUDY METHODS

- Next Generation Sequencing panel of 41 CNS-related genes were analyzed in a recent PPTID
- The TJUH Co-Path Database was searched from 1995 to 2016 with the following terms: pineal cyst, pineocytoma, pineal parenchymal tumor of intermediate differentiation, and pineoblastoma
- Pineal cysts served as the non-neoplastic control
- Samples deemed to have adequate tissue size were subsequently stained for ATRX using validated immunohistochemical staining methods routinely performed by our lab
- The following data was obtained for each case (Table 1):
  - Patient age and gender
  - Pathology diagnosis, including tumor classification and grade
  - ATRX IHC result (positive = ≥90% nuclear staining; negative = ≤ 5% nuclear staining)

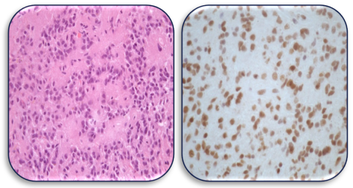
	Pineal Cyst	Pineocytoma	PPTID	Pineoblastoma
Number	2	3	5	2
Age (Mean)	36	44.7	36	30.5
Female/ Male	0/2	3/0	4/1	1/1
Grade I	N/A	3	0	0
Grade II	N/A	0	2	0
Grade II/ III	N/A	0	2	0
Grade III	N/A	0	1	0
Grade IV	N/A	0	0	2

Table 1: Demographics and WHO grade of pineal lesions studied.

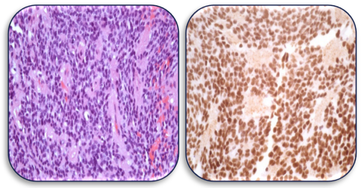
RESULTS

Brain Tumor Gene Sequencing Panel					
ACVR1	EGFR	IDH1	NF1	POLE	SMARCB1
AKT1	FGFR1	IDH2	NF2	POLR2A	SMO
ATRX	FUBP1	KLF4	NRAS	PTEN	TERT prom
BCOR	H3F3A	KRAS	PDGFRA	PTPN11	TP53
BRAF	HIST1H3B	LTBP4	PIK3CA	RB1	TRAF7
CIC	HIST1H3C	LZTR1	PIK3R1	SMAD4	ZBTB20
CTNND2	HRAS	MSH6	PLCG1	SMARCA4	

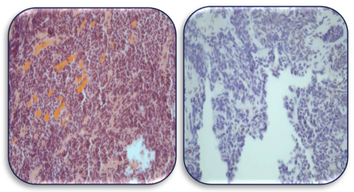
Table 2: The Brain Tumor Panel performed on DNA extracted from FFPE tumor tissue using Illumina's TruSeq Amplicon Cancer Panel kit. A mutation in the ATRX gene (4 nucleotide deletion variant resulting in a frameshift mutation) was detected. **No mutations were identified in any of the other 40 genes analyzed.**



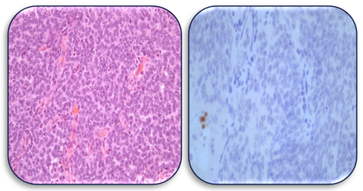
Pineal Cyst in a 36 year old male, ATRX retained



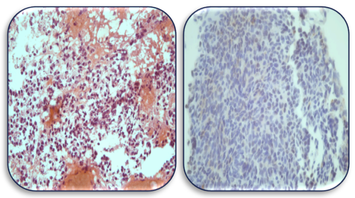
Pineocytoma in a 51 year old female, WHO Grade I, ATRX retained



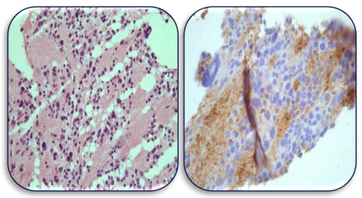
Pineoblastoma in a 31 year old female, WHO Grade IV, Loss of ATRX IHC staining



PPTID* in a 22 year old female, (*index case) WHO Grade III, Loss of ATRX IHC staining



PPTID in a 28 year old female, WHO Grade II-III, Loss of ATRX IHC staining



PPTID in a 49 year old female, WHO Grade II, Loss of ATRX IHC staining

Figure 1: Representative images of the 12 pineal lesion cases (pineal cysts, pineocytomas, PPTIDs, and pineoblastomas) are shown. The images on the left are H&E (hematoxylin and eosin) stains, and the images on the right are ATRX immunohistochemical stains.

RESULTS (CONTINUED)

	Pineal Cyst	Pineocytoma	PPTID	Pineoblastoma
Number of cases	2	3	5	2
Loss of IHC staining for ATRX	0	0	**3**	**1**

Table 3: ATRX was maintained in all pineal cysts and pineocytomas analyzed. 3 of 5 PPTIDs and 1 of 2 pineoblastomas showed loss of ATRX (no staining in ≥95 % cells) by immunohistochemistry. In this limited sample, **4 of 10 pineal parenchymal neoplasms demonstrated loss of expression of ATRX: 3 PPTIDs and 1 pineoblastoma.**

- ATRX loss was identified in PPTIDs and pineoblastomas, but not pineocytomas
- No grade-related association (grade II vs grade III) of ATRX loss was observed in PPTIDs
- No significant age-related differences in ATRX status were observed in our analyzed cases: 42.8 ± 11.2 years (ATRX retained) vs 32.5 ± 11.6 years (ATRX loss)

DISCUSSION

- Previous molecular analysis of a PPTID and a pineoblastoma by two different groups identified mutations in TSC1 and IKZF3 (PPTID) and in DICER1, ARID1 and KDM5C (pineoblastoma); Neither group reported the presence of an ATRX mutation
- The alternative lengthening of telomeres (ALT) pathway is a telomerase-independent mechanisms of telomere length maintenance allowing improved survival of a variety of tumor cell types
- ALT activation in many tumors is related to loss of function of the ATP-dependent helicase ATRX (tumors with ATRX loss show ALT phenotype)
- Loss of ATRX has been proposed as a potential strong prognostic marker in both pancreatic neuroendocrine tumors and neuroblastomas

CONCLUSIONS

- **Our study suggests that ATRX loss may occur with some frequency in pineal parenchymal tumors**
- **ATRX loss may play a role in the biological behavior of pineal parenchymal tumors**
- **Collaborative studies may help determine the relationship between ATRX loss in pineal parenchymal tumors and tumor behavior, leading to more predictive grading for these neoplasms**