CORRESPONDENCE

Reexamining the molecular findings in specialized stromal tumors of the prostate

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TO THE EDITOR:

We read with great interest the recent article "Reevaluating tumors of purported specialized prostatic stromal origin reveals molecular heterogeneity, including nonrecurring gene fusions characteristic of uterine and soft tissue sarcoma subtypes" [1]. Acosta et al. studied 11 prostatic stromal sarcoma (PSS) and 14 prostatic stromal tumor of uncertain malignant potential (STUMP) using targeted DNA and RNA next generation sequencing. They found that 19/22 (86%) successfully sequenced cases harbored pathogenic somatic variants, largely nonrecurrent. They detected eight gene rearrangements and four of them were characteristic of other specific sarcoma subtypes. They suggest that tumors of purported specialized prostatic stromal origin are molecularly heterogeneous and may not represent a single diagnostic entity.

Their findings are partly discrepant with those of our previous studies using array comparative genomic hybridization, whole exome sequencing, and fluorescence in situ hybridization [2, 3]. While we detected chromosomal 13 and/or 14 losses in a total of 14 out of 15 cases of STUMP and 2 out of 3 cases of PSS by using at least one of the aforementioned methods, Acosta et al. detected such findings in only 1 STUMP (case 17) and 4 PSS (cases 5, 6, 8, 11) [1]. They attribute the discrepancy to different next generation sequencing platforms. Although targeted panel is more sensitive to detect SNV of low fraction, comparative genomic hybridization and whole exome sequencing benefit from broad genome-wide coverage to more effectively detect somatic copy number alterations. Remarkably, cases 1–4 and 12–14 which did not have chromosome 13/14 loss in the series of Acosta et al. [1] harbored a variety of gene rearrangements and fusions, while none of the cases with chromosome 13/14 losses had gene rearrangement. It appeared that chromosomal 13/14 losses and gene rearrangement are mutually exclusive; thus raising the possibility of two disparate groups of neoplasm from a molecular perspective.

Regarding the pathogenic somatic variants, we also detected a few cancer-related mutations, such as *RB1*, *MET* and *TSC1* but they were most likely sporadic [3]. Since we employed a vigorous process to filter out spurious mutations and MutsigCV to select significant ones above background mutations, it is possible some of the mutations were removed from our analyses. We reexamined our raw output data for the 14 genes reported in the series of Acosta et al. [1]. We discovered additional somatic mutations in four STUMP and one PSS (Table 1, Fig. 1). The *CHEK2* and *ATRX* mutations had low allelic fraction (0.25 and 0.2). *CHEK2* and one *KMT2D* mutations had low impact or were predicted to be *benign*. The *TP53* mutation was found in 1 PSS, compatible with its more aggressive behavior. Interestingly, that case also harbored *RB1* mutation [3]. Given that the allelic fractions of those mutations reported by Acosta et al. are not disclosed in the article [1], it is uncertain whether they represented major oncogenic events or minor subsequent clonal evolution.

Specific mesenchymal neoplasms, such as solitary fibrous tumor, have been well-documented in the prostate [4]. It is not surprising that other rarer sarcomas, for example, endometrial stromal sarcoma, sarcomas with *NTRK1* or *BCOR* rearrangement, may also involve the prostate [1]. We entirely agree with the authors' comment that prostatic mesenchymal tumors should be classified as specific entities with available diagnostic methodologies. Nevertheless, after those entities are carefully excluded, we believe that benign and malignant neoplasms of specialized prostatic stromal origin exist.

Table 1. Additional somatic mutations in prostatic stromal tumors.

#	Diagnosis	Gene	Alteration	SIFT	Poly-phen2	Allele fraction	dbSNP	Cosmic	Clinvar
c6	STUMP	*KMT2D*	c.A821C:p.K274T	T	D	0.56	rs894562087		
		POT1	c.T155G:p.V52G	D	D	0.39	rs200464979	COSM304691	
c19	STUMP	*KMT2D*	c.C7144T:p.P2382S	D	P	0.48	rs3741626	COSM6494180	Benign
c21	STUMP	*CHEK2*	c.G1423C:p.E475Q	T	B	0.25	rs587782489		Uncertain
c22	STUMP	*ATRX*	c.G6212A:p.R2071K	T	D	0.2			
c9	PSS	*TP53*	c.C59T:p.P20L	D	D	0.56	rs587782705	COSM10790	Pathogenic

STUMP Stromal tumor of uncertain malignant potential, *PSS* prostatic stromal sarcoma, *T* tolerated, *D* damaging, *P* probably damaging, *B* benign.

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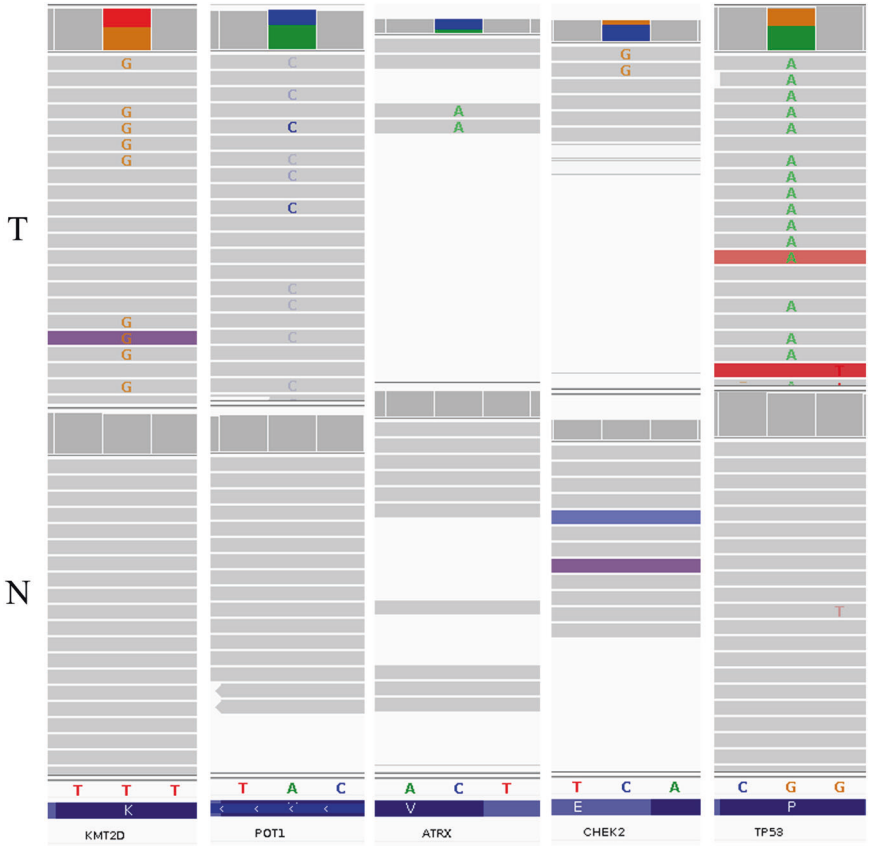

Fig. 1 The whole exome sequencing results of somatic mutations of *KMT2D*, *POT1*, *ATRX*, *CHEK2*, and *TP53* in prostatic stromal tumors. T tumor, N normal.

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CONFLICT OF INTEREST

The authors declare no competing interests.

ADDITIONAL INFORMATION

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