

Precision medicine in radiotherapy; discover a potential biomarker for treatment resistance

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Introduction

Radiotherapy is an important modality of therapy in cancer treatment. Despite of advances in technology and cancer genomics, treatment of cancer is still a big challenge, and the mutation signatures of radioresistant tumors have not yet been fully elucidated. Radiation therapy technique is evolving over time, as increasing of radiation conformity will increase therapeutic ratio, as well as the development of particle and heavy-ion therapy which provide hopes.

Precision cancer medicine is a treatment for cancer which uses the genetic information of individual tumors to guide the treatment, has become widespread in cancer treatment, especially in the field of clinical oncology. Advances in next-generation sequencing technologies provide the identification of genetic alterations that make tumor cells responsive to molecularly targeted drugs. This also showed the probability such genetic alterations may contribute to cancer cell radiosensitivity. However, genetic alterations profile in cancers associated with resistant to radiotherapy have not been fully elucidated.

Methods

We analyzed a unique set of clinical specimens from a uterine cervical cancer that repeatedly locally recurred after multiple rounds of radiotherapy. We performed next-generation sequencing with an Ion AmpliSeq Comprehensive Cancer Panel that covers 95.4% of the exons of the 409 cancer-related genes.

Results

Exon sequencing of 409 cancer-related genes in the treatment-naïve tumor and the tumors that recurred after initial and secondary radiotherapy identified (i) activating mutations in *PIK3CA* and *KRAS*, and putative inactivating mutations in *SMAD4*, as trunk mutation signatures that persisted over the clinical course; and (ii) mutations in *KMT2A* and *TET1* as acquired mutation signatures observed only in recurrent tumors after radiotherapy. Comprehensive mining of published *in vitro* genomics data pertaining to radiosensitivity revealed that simultaneous mutations in *KRAS* and *SMAD4*, which have not been described previously in uterine cervical cancer, are associated with cancer cell radioresistance.

Figure 2. Somatic mutations in treatment-naïve and recurrent tumors

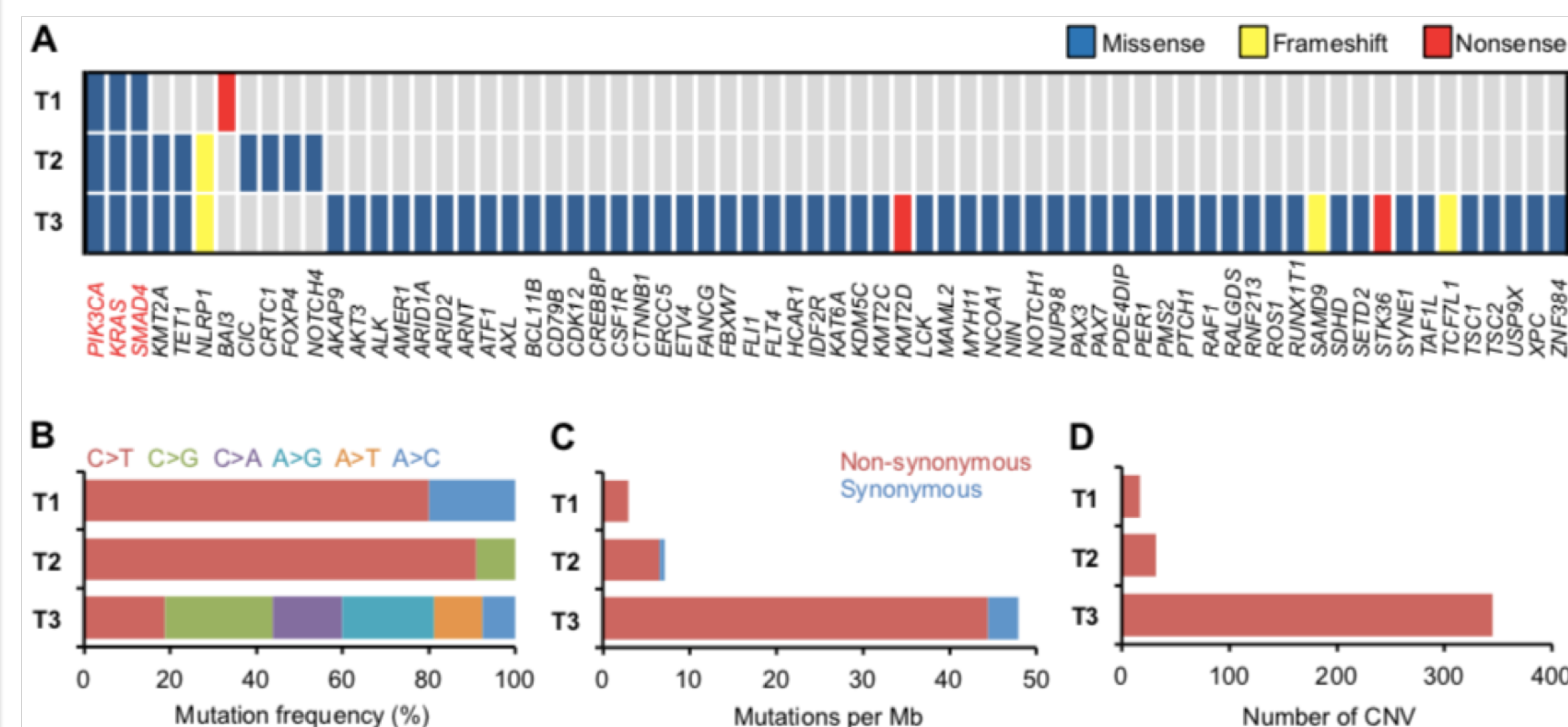
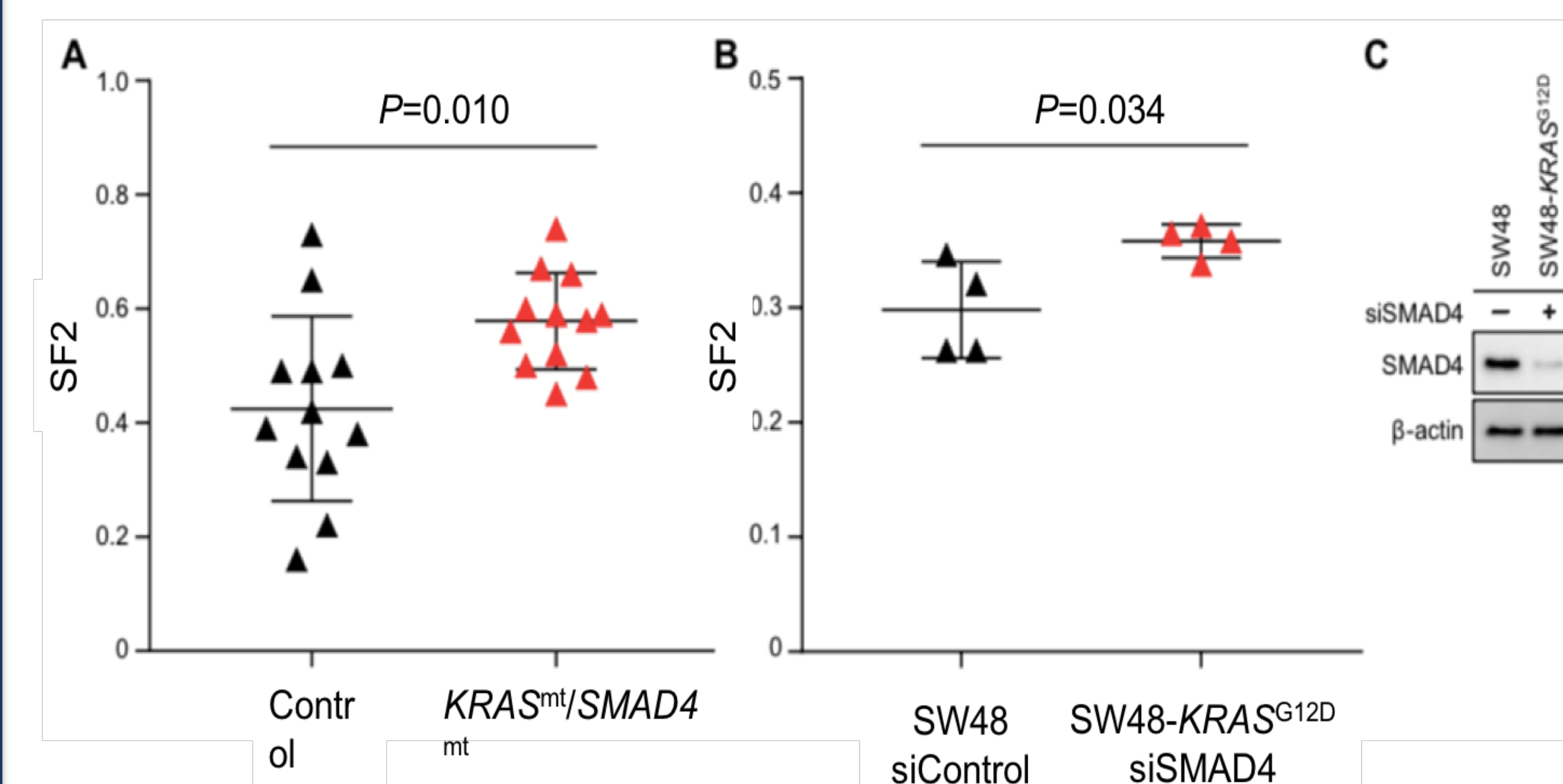


Figure 1. Clinical history of the patient

34 y.o., Adenocarcinoma of Uterine Cervical Cancer pT1b2N1Mx				
Year	Event	Sample	Treatment	Months
20xx	First diagnosed (treatment-naïve tumor)	T1		0
20xx		Normal	Surgery	1
201x			Adjuvant chemotherapy	3
20xx + 1	First recurrence at vaginal stump			11
20xx + 1			Radiotherapy (EBRT + Intracavitary brachytherapy)	13
20xx + 2	Second recurrence at vaginal stump	T2		31
20xx + 2			Interstitial brachytherapy (ISBT)	32
20xx + 3	Third recurrence at vaginal stump	T3		46
20xx + 3			Interstitial brachytherapy (ISBT)	47
20xx + 5	Patient died			71

Figure 3. Simultaneous mutations of *KRAS* and *SMAD4* associated with less radiosensitivity



Conclusion

- The results of this study indicated that next-generation sequencing analysis of clinical specimens is a promising strategy to explore the mutation signatures that contribute to tumor radioresistance, which is worth pursuing with larger cohorts in the future.
- Co-mutations of *KRAS* and *SMAD4* can be a potential predictive value for radioresistance