Patient-partnered Research Enables Germline Characterization of Angiosarcoma Predisposition Genes

Hoyin Chu[1], Marissa Hollyer[1], Seunghun Han[2], Sabrina Y. Camp[1], Riaz Gillani[3], Eliezer Van Allen[1], Nikhil Wagle[1], Corrie A. Painter[4], Saud H. AlDubayan[1]

[1]Medical Oncology, Dana-Farber Cancer Institute, Boston, MA,[2]Harvard Medical School, Boston, MA,[3]Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA,[4]Cancer Program, Broad Institute, Cambridge, MA

Email: hoyin_chu@dfci.harvard.edu Url: hoyinchu.github.io/posters/ Twitter: @hoyin_chu

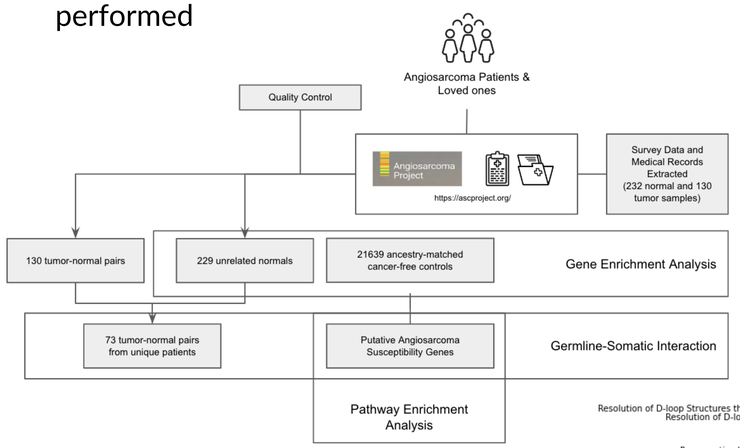
Abstract Number: 6064

Intro:

- Angiosarcoma is a rare cancer (accounts for 1-2% of all soft tissue sarcomas) that develops in the inner lining of blood vessels and lymph vessels.
- Due to its rarity, the inherited risk factors of angiosarcoma remain poorly understood

Methods:

- Angiosarcoma patients and their loved ones remotely shared their clinical information and biospecimen for research through the Angiosarcoma Project initiative (https://ascproject.org/)
- Whole-exome sequencing (WES) of normal samples and tumor samples if available
- Germline rare pathogenic variants were identified from normal samples and gene burden analysis was performed



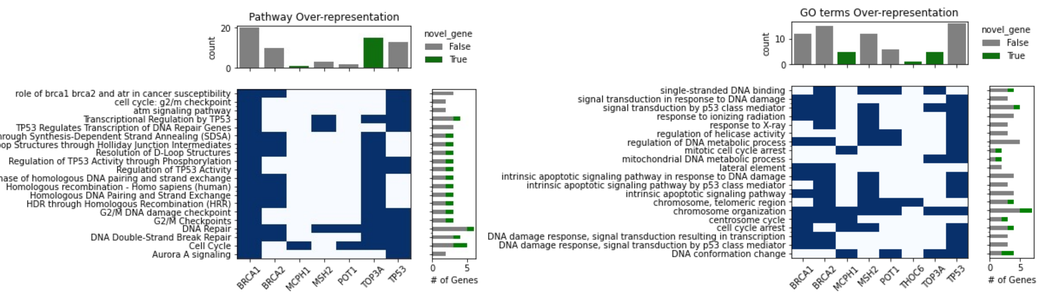
Discussions:

- Patients-partnered research is a powerful way to increase sample size for rare cancers and reveal additional candidate sarcoma-predisposition genes
- Germline *POT1* pathogenic variants predisposes to angiosarcoma across multiple disease sites
- Somatic *POT1* alterations are more frequently seen in UV-associated angiosarcoma while somatic missense in *KDR* (encodes VEGF2R) and *PLCG1* are more commonly seen in non-radiation associated angiosarcoma

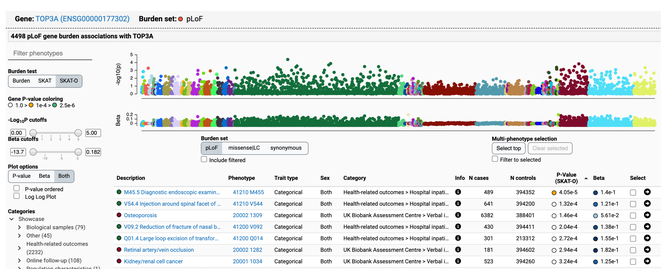
Results:

17.0% (n=39/229) of patients carried at least 1 pathogenic variant in a sarcoma-related cancer predisposition gene

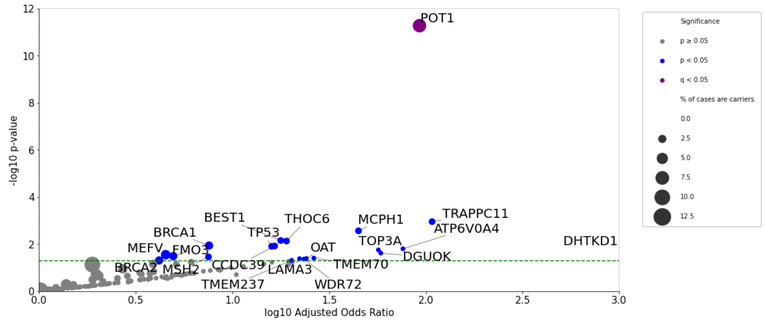
Nominally significant hits contain novel cancer-predisposition genes and are overrepresented in telomere/chromosomal regulation and DNA-damage response related pathways and functions



Nominally significant genes such as LAMA3, *TOP3A*, and *THOC6* are also nominally significantly associated with Sarcoma/fibrosarcoma in UKBioBank PheWAS



POT1 was the most significantly enriched gene with an adjusted odds ratio of 92.7 (3.5% in 229 cases vs. 0.04% in 21639 controls)



POT1 germline pathogenic variant carriers with subsequent somatic biallelic inactivation in *POT1* present 20 years earlier than other patients (Age mean: 35 vs. 54)

All germline-somatic POT1 bialleic inactivations detected in the cohort (n=5)

Patient ID	Location	REF	ALT	HGVSp	Consequence	Protein_Change (Somatic)	PRIMARY SITE	Age at Onset
ASCProject_0166	7:124469309	CT	C	p.A532HfsTer13	frameshift_variant	p.G76E	FACE	58.5
ASCProject_0013	7:124482952	G	GA	p.Q358SfsTer13	frameshift_variant	p.S523L	BREAST (PARENCHYMAL)	26.2
ASCProject_0221	7:124482952	G	GA	p.Q358SfsTer13	frameshift_variant	p.K74I	BREAST (PARENCHYMAL)	27.1
ASCProject_0005	7:124482958	GC	G	p.A356LfsTer11	frameshift_variant	p.R117C	BREAST (PARENCHYMAL)	31.1
ASCProject_0343	7:124532435	C	T	-	splice_acceptor_variant	p.R117H	CARDIAC	34.9

POT1 germline carriers have multiple sites of disease, while somatic POT1 PV carriers are more commonly found in Head and Neck cancers