

Patient-partnered Research Enables Germline Characterization of **Angiosarcoma Predisposition Genes**

¹Medical Oncology, Dana-Farber Cancer Institute, Boston, MA,²Harvard Medical School, Boston, MA,⁴Cancer 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

Hoyin Chu¹, Marissa Hollyer¹, Seunghun Han², Sabrina Y. Camp¹, Riaz Gillani³, Eliezer Van Allen¹, Nikhil Wagle¹, Corrie A. Painter⁴, Saud H. AlDubayan¹

Results:



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



and THOC6 are also nominally significantly associated with Sarcoma/fibrosarcoma in **UKBioBank PheWAS**

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UK Biobank Assessment



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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)

Patient ID	Location	REF	ALT	HG
ASCProject_0166	7:124469309	СТ	С	p.A532H
ASCProject_0013	7:124482952	G	GA	p.Q358
ASCProject_0221	7:124482952	G	GA	p.Q358
ASCProject_0005	7:124482958	GC	G	p.A356I
ASCProject_0343	7:124532435	С	т	

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





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

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

