GERMLINE DRIVERS OF GYNECOLOGIC CARCINOSARCOMA

Tiffany Y. Sia*[a], Sushmita B. Gordhandas*[a], Ozge Birsoy[b], Yelena Kemel[c], Anna Maio[c], Erin Salo-Mullen[c], Margaret Sheehan[c], Martee L. Hensley[d], Maria Rubinstein[d], Vicky Makker[d], Rachel Grisham[d], Roisin E. O'Cearbhaill[d], Kara Long Roche[a], Jennifer J. Mueller[a], Yukio Sonoda[a], Dennis S. Chi[a], Nadeem Abu-Rustum[a], Mike F. Berger[b], Lora H. Ellenson[b], Alicia Latham[c], Zsofia Stadler[c], Kenneth Offit[c], Carol Aghajanian[d], Britta Weigelt[b], Diana Mandelker[b], Ying L. Liu[c,d]

*equal authorship

[a] Gynecology Service, Department of Surgery; [b] Department of Pathology and Laboratory Medicine; [c] Clinical Genetics Service; [d] Gynecologic Medical Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

OBJECTIVE

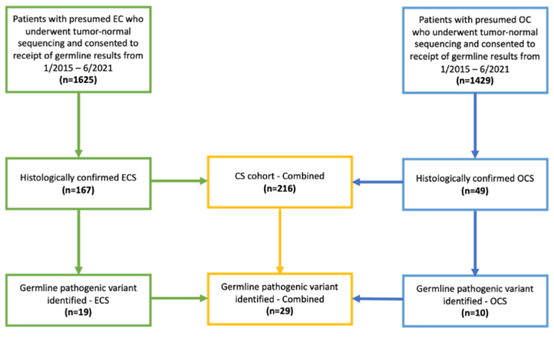
- Define the prevalence of germline pathogenic variants (gPVs) in a large cohort of unselected patients with endometrial or ovarian carcinosarcoma (CS)
- Determine if gPVs are drivers of endometrial or ovarian CS through assessment of biallelic inactivation in tumors

METHODS

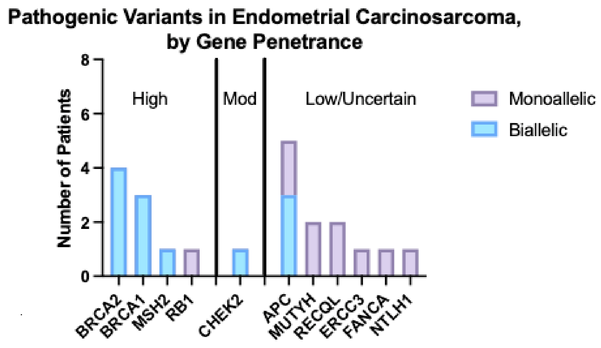
- All patients with pathology-confirmed endometrial or ovarian CS who presented to our institution and underwent clinical tumor-normal sequencing (1) from 1/2015-6/2021 were included
- gPVs were independently assessed, manually curated, and classified as high penetrance (RR>4), moderate penetrance (RR=2-4), or low/uncertain/recessive penetrance (RR<2)
- Variants of uncertain significance were excluded
- Loss of heterozygosity (LOH) in the tumor at the locus of the gPV was assessed using the previously described FACETS algorithm (2)
- Biallelic inactivation was determined by either LOH status or by presence of a second somatic pathogenic alteration in the tumor
- Additional molecular data (microsatellite instability [MSI], tumor mutational burden, tumor purity, variant allele frequency) were extracted from the chart
- Clinical characteristics were extracted from the electronic medical record

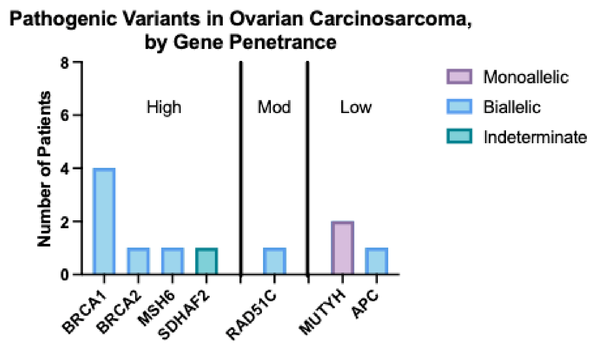
RESULTS

- In the entire cohort of 216 patients:
  - 33 gPVs were observed in 29 patients (13%)
  - Of these gPVs, 20 (61%) had biallelic loss in the CS tumor
  - The rate of high-penetrance gPVs was 7% (16 of 216)
  - The rate of biallelic loss was 88% (14 of 16)
- In the endometrial CS cohort:
  - 22 gPVs were found in 11% of patients
  - 11 gPVs (50%) had biallelic loss in the tumors
  - Among 9 patients with high-penetrance gPVs, 8 (89%) had biallelic loss in tumors and 1 (11%) had monoallelic loss
- In the ovarian CS cohort:
  - 11 gPVs were found in 20% of patients
  - 8 gPVs (73%) had biallelic loss in the tumors
  - Among 7 patients with high-penetrance gPVs, 6 (86%) had biallelic loss in tumors and 1 (14%) had indeterminate LOH
- All gPVs in homologous recombination (HR) genes (*BRCA1*, *BRCA2*, *RAD51C*) (n=13) were associated with biallelic loss
- All tumors associated with Lynch syndrome (n=2) had biallelic loss (1 endometrial CS and 1 ovarian CS) and exhibited an MSI-high phenotype



Flowchart demonstrating generation of patient cohort.
EC, endometrial cancer; ECS, endometrial carcinosarcoma; CS, carcinosarcoma; OC, ovarian cancer; OCS, ovarian carcinosarcoma





CONCLUSIONS

- 13% of patients with gynecologic CS who underwent tumor-normal sequencing harbored a gPV
- Tumors exhibited high rates of biallelic inactivation, particularly in HR and mismatch repair genes, implying germline drivers of disease development

	Overall	Endometrial CS		Ovarian CS	
		gPV	No gPV	gPV	No gPV
		No. of patients (%)			
Total	216	19 (11.4)	148 (88.6)	10 (20.4)	39 (79.6)
Age at diagnosis, years					
Median (range)	65 (32, 96)	61 (52, 81)	66 (32, 96)	64.5 (48, 82)	64.8 (47, 81)
Stage					
I	75 (34.7)	7 (36.8)	64 (43.2)	2 (20.0)	2 (5.1)
II	11 (5.1)	1 (5.3)	7 (4.7)	0 (0)	3 (7.7)
III	68 (31.5)	6 (31.6)	35 (23.6)	5 (50.0)	22 (56.4)
IV	60 (27.8)	4 (21.1)	41 (27.7)	3 (30.0)	12 (30.8)
Unknown	2 (0.9)	1 (5.3)	1 (0.7)	0 (0)	0 (0)
TCGA Subgroup					
POLE	0 (0)	0 (0)	0 (0)	NA	NA
MSI-H	14 (8.4)	2 (10.5)	12 (8.1)	NA	NA
CN-L	4 (2.4)	1 (5.3)	3 (2.0)	NA	NA
CN-H	147 (88.0)	16 (84.2)	131 (88.5)	NA	NA
Unclassifiable	2 (1.2)	0 (0)	2 (1.4)	NA	NA
Self-Reported Race					
Asian/Indian	13 (6.0)	2 (10.5)	9 (6.1)	0 (0)	2 (5.1)
Black	37 (17.1)	2 (10.5)	31 (20.9)	0 (0)	4 (10.3)
White	149 (69.0)	13 (68.4)	95 (64.2)	10 (100.0)	31 (79.5)
Other/ Unknown	17 (7.9)	2 (10.5)	13 (8.8)	0 (0)	2 (5.1)
Ethnicity					
Hispanic	15 (6.9)	1 (5.3)	10 (6.8)	1 (10.0)	3 (7.7)
Non-Hispanic	196 (90.7)	18 (94.7)	133 (89.9)	9 (90.0)	36 (92.3)
Unknown	5 (2.3)	0 (0)	5 (3.4)	0 (0)	0 (0)
AJ Ancestry					
Yes	41 (19.0)	7 (36.8)	25 (16.9)	2 (20.0)	7 (17.9)
No	166 (76.9)	12 (63.2)	117 (79.1)	7 (70.0)	30 (76.9)
Unknown	9 (4.2)	0 (0)	6 (4.1)	1 (10.0)	2 (5.1)
Body Mass Index, kg/m²					
Median (range)	28 (18.4, 59.5)	28.3 (20.4, 42.6)	28.3 (18.4, 59.5)	30 (23.1, 37.1)	24.8 (20, 43.9)
<25	66 (30.6)	7 (36.8)	36 (24.3)	2 (20.0)	21 (53.8)
≥25	150 (69.4)	12 (63.2)	112 (75.7)	8 (80.0)	18 (46.2)

TCGA, The Cancer Genome Atlas; *POLE*, polymerase epsilon; MSI-H, microsatellite instability-high; CN-L, copy number-low; CN-H, copy number-high; AJ, Ashkenazi Jewish.

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