Assessment of activating estrogen receptor 1 (*ESR1*) mutations in gynecologic malignancies

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Background

- Endocrine therapy is frequently considered to treat hormone-responsive gynecologic malignancies, such as low-grade endometrial cancer, low-grade serous ovarian cancer, and endometrial stromal sarcoma.
- Mutations in *ESR1* leading to constitutive transcriptional activity have been reported in estrogen receptor positive (ER+) breast cancers[1] and may contribute to acquired resistance to endocrine therapy.
- Using comprehensive genomic profiling (CGP) we assessed the frequency of *ESR1* activating genomic alterations in gyn malignancies.

Methods

- DNA from FFPE tumor tissue obtained during routine clinical care for 9645 gyn malignancies (ovary, fallopian tube, uterus, cervix, vagina, vulvar, and placenta) was analyzed for all classes of GA [base substitutions (muts), indels, rearrangements, and amplifications] in *ESR1* by hybrid capture, next generation sequencing.
- Public databases of gyn malignancies were queried for *ESR1* activating mutations (*mutESR1)* using cBioportal[2,3] and COSMIC[4].
- Clinical data from eight cases was reviewed with approval of the respective Institutional Review Boards.

Conclusions

- *mutESR1* are uncommon in gyn malignancies, but are enriched in hormone-responsive histologic subtypes.
- Activating mutations occurred within and outside of the known ESR1 hotspot region (codons 536-538).
- *mutESR1* have important treatment implications. They are likely to be resistant to aromatase inhibitors, but may continue to be responsive to anti-estrogen receptor directed therapy (SERMs/SERDs).

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References

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Results

- Among 9645 gyn malignancies, amplifications and substitution variants were the most common genomic alterations (Table 1). Activating *ESR1* mutations (*mutESR1*) were more frequent in uterine cancers (63/3101, 2%) than in other primary sites (24/6530, <1%) (p<0.0001).
- A total of 38 *mutESR1* were identified in 37 gyn malignancy cases reported in public database: LGSOC[5]: 1/26 (3.8%); AACR GENIE[6]: 1/271 (0.4%) Cervix, 2/1473 (0.1%) Ovary, 26/1076 (2.4%) Endometrial, 2/199 (1.0%) Uterine Sarcoma; TCGA[7-9]: 5/248 (2.0%) Uterine Corpus, 0 Ovary, 0 Cervix; Uterine Carcinosarcoma[10]: 1/22 (4.5%).
- Y537S and D538G were the most common individual mutations identified, but other sites were also identified (Figure 1).
- *mutESR1* are enriched in endometrioid histology and possibly ESS (Table 2).
- Clinical data were available for 8 patients (Figure 2). Paired CGP analyses showed enrichment/development of *mutESR1* after aromatase inhibitor exposure occurred in 3 cases (A, D, G) and in the absence of prior endocrine therapy in 3 cases (B, C, F). Some tumors harboring *mutESR1* responded to anti-estrogen receptor directed therapy (i.e. tamoxifen or fulvestrant) for extended duration.

Table 1 Types and frequency of ESR1 alterations identified in gyn malignancies

Type of alteration	Frequency N=9645	Ovary/FT N=5594	Uterus N=3101	Cervix N=720	Vulva/Vagina N=216
Total, N (%)	295 (3.1)*	120 (2.1)	160 (5.2)	9 (1.2)	6 (2.8)
Amplification	80 (0.8)	45 (0.8)	34 (1.1)	1 (0.1)	-
Deletion	1 (<0.1)	-	1 (<0.1)	-	-
Fusion	2 (<0.1)	1 (<0.1)	-	-	1 (0.5)
Rearrangements	18 (0.2)	9 (0.2)	9 (0.3)	-	-
Substitution Variants	194 (2.0)	65 (1.2)	116 (3.7)	8 (1.1)	5 (2.3)
Codon 536-538	75 (0.8)	18∞ (0.3)	56∞ (1.8)	1 (0.1)	-
Other Activating Mut	12 (0.1)	3 (<0.1)	7 (0.2)	-	2 (0.9)

"-": none present, FT: fallopian tube, Mut: mutation *Includes 10 cases with 2 alterations each, ∞1 ovarian case & 2 uterine cases w/ 2 codon 536-538 mutations each

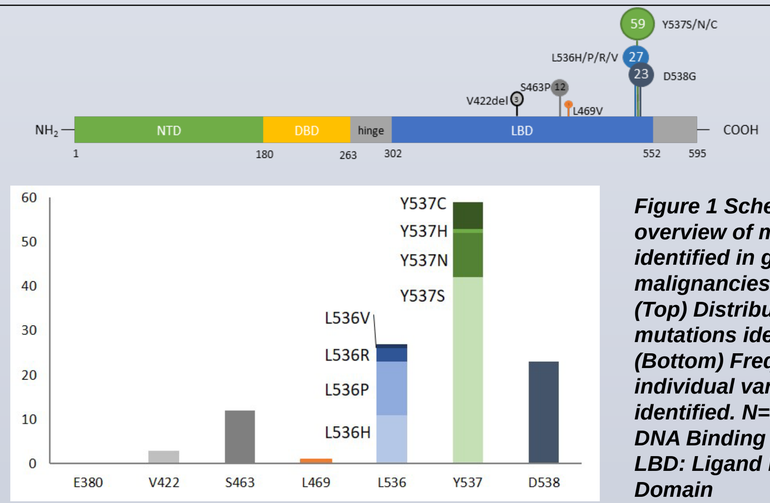

Figure 1 Schematic overview of mutESR1 identified in gynecologic malignancies (Top) Distribution of mutations identified (Bottom) Frequency of individual variants identified. N=125, DBD: DNA Binding Domain, LBD: Ligand Binding Domain

Table 2 mutESR1 enriched in endometrioid and ESS histology

Dataset	Histology	N	*mutESR1* N (%)	p
CGP analysis				
Ovary	serous	3502	12 (0.3)	0.0004
	endometrioid	144	5 (3.5)	
Uterus	serous	446	1 (0.2)	<0.0001
	endometrioid	548	24 (4.4)	
Sarcoma	LMS	421	3 (0.7)	0.09
	ESS	103	3 (3.0)	
AACR GENIE				
Ovary	high-grade serous	687	0	0.006
	endometrioid	57	2	
Uterus	serous	203	0	0.0004
	endometrioid	518	25 (4.8)	
Sarcoma	LMS	113	0	0.018
	ESS	16	2 (12.5)	

P value calculated using Fisher's exact test

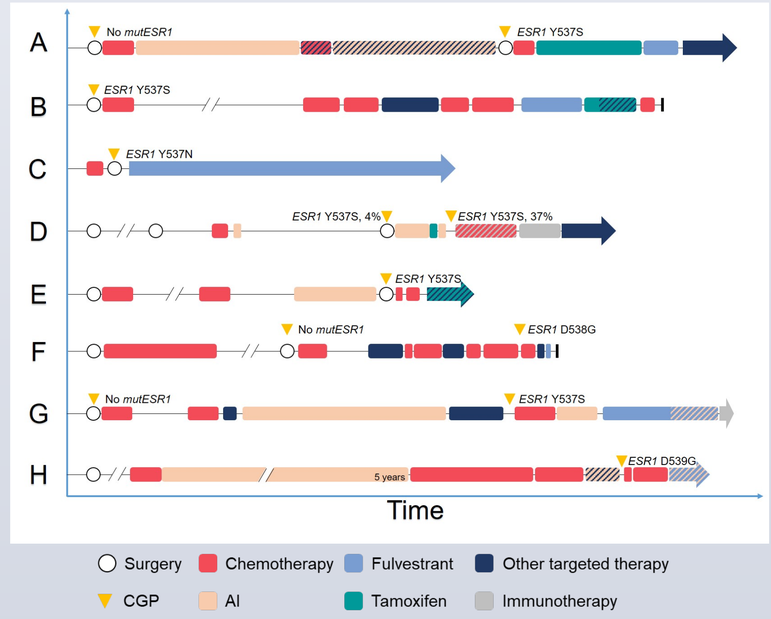

Figure 2 Clinical course of patients identified with gynecologic malignancies harboring mutESR1. Eight individual patients (A-H) with mutESR1 were identified. Each box or wide arrow delineates a treatment received colored according to the legend and the width reflects relative duration of therapy. A wide arrow represents ongoing therapy. Hashed boxes/arrows reflect combined therapy. The triangle reflects when the sample evaluated by CGP was procured. Percentages reflect allelic frequency of the mutation within the sample.

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