**Title**

Integrated genomic characterization of endometrial carcinoma

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# Integrated Genomic Characterization of Endometrial Carcinoma

## The Cancer Genome Atlas Research Network

## Summary

We performed an integrated genomic, transcriptomic, and proteomic characterization of 373 endometrial carcinomas using array- and sequencing-based technologies. Uterine serous tumors and ~25% of high-grade endometrioid tumors have extensive copy number alterations, few DNA methylation changes, low ER/PR levels, and frequent *TP53* mutations. Most endometrioid tumors have few copy number alterations or *TP53* mutations but frequent mutations in *PTEN*, *CTNNB1*, *PIK3CA, ARID1A, KRAS* and novel mutations in the SWI/SNF gene *ARID5B*. A subset of endometrioid tumors we identified had a dramatically increased transversion mutation frequency, and newly identified hotspot mutations in *POLE*. Our results classified endometrial cancers into four categories: *POLE* ultramutated, microsatellite instability hypermutated, copy number low, and copy number high. Uterine serous carcinomas share genomic features with ovarian serous and basal-like breast carcinomas. We demonstrated that the genomic features of endometrial carcinomas permit a reclassification that may impact post-surgical adjuvant treatment for women with aggressive tumors.

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Endometrial cancer arises from the lining of the uterus. It is the fourth most common malignancy among women in the United States, with an estimated 47,000 new cases and

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8,000 deaths in 2012.[1] Most patients present with low-grade, early-stage disease. The majority of patients with more aggressive, high-grade tumors who have disease spread beyond the uterus will progress within 1 year.[2,3] Endometrial cancers have been broadly classified into two groups.[4] Type I endometrioid tumors are linked to estrogen excess, obesity, hormone-receptor positivity, and favorable prognosis compared with type II, primarily serous, tumors that are more common in older, non-obese women and have worse outcome. Early-stage endometrioid cancers are often treated with adjuvant radiotherapy, whereas serous tumors are treated with chemotherapy, similar to advanced-stage cancers of either histologic subtype. Therefore, proper subtype classification is critical for selecting appropriate adjuvant therapy.

Several prior reports suggest that *PTEN* mutations occur early in the neoplastic process of Type I tumors and co-exist frequently with other mutations in the PI3K/AKT pathway.[5,6] Other commonly mutated genes in Type I tumors include *FGFR2, ARID1A, CTNNB1, PIK3CA, PIK3R1,* and *KRAS*.[7–9] Microsatellite instability (MSI) is found in approximately one-third of Type I tumors but is infrequent in Type II tumors.[10] *TP53, PIK3CA,* and *PPP2R1A* mutations are frequent in Type II tumors.[11,12] Most of these studies have been limited to DNA sequencing only with samples of heterogeneous histologic subtypes and tumor grades. We present a comprehensive, multiplatform analysis of 373 endometrial carcinomas including low-grade endometrioid, high-grade endometrioid, and serous carcinomas. This integrated analysis provides key molecular insights into tumor classification, which may have direct impact on treatment recommendations for patients, and provides opportunities for genome-guided clinical trials and drug development.

## Results

Tumor samples and corresponding germline DNA were collected from 373 patients, including 307 endometrioid and 66 serous (53) or mixed histology (13) cases. Local institutional review boards approved all tissue acquisition. The clinical and pathologic characteristics of the samples generally reflect a cross-section of individuals with recurrent endometrial cancer (Supplementary Table 1.1).[2,3] The median follow-up of the cohort was 32 months (range, 1–195 months); 21% of the patients have recurred, and 11% have died. Comprehensive molecular analyses were performed at independent centers using six genomic or proteomic platforms (Supplementary Table 1.2). MSI testing performed on all samples using seven repeat loci (Supplementary Table 1.3) found MSI in 40% of endometrioid tumors and 2% of serous tumors.

### Somatic copy number alterations

Somatic copy number alterations (SCNAs) were assessed in 363 endometrial carcinomas. Unsupervised hierarchical clustering grouped the tumors into four clusters (Fig. 1a). The first three copy number clusters were composed almost exclusively (97%) of endometrioid tumors without significant differences in tumor grades. Cluster 1 tumors were nearly devoid of broad SCNAs, averaging less than 0.5% genome alteration, with no significant recurrent events. Cluster 1 tumors also had significantly elevated non-synonymous mutation rates compared to all others (median $7.2 \times 10^{-6}$ vs. $1.7 \times 10^{-6}$ mutations per megabase (Mb),

$P<0.001$). Copy number clusters 2 and 3 consisted mainly of endometrioid tumors, distinguished by more frequent 1q amplification in cluster 3 than cluster 2 (100% of cluster 3 tumors vs. 33% of cluster 2 tumors) and worse progression-free survival (PFS, $P=0.003$, log-rank vs. clusters 1 and 2; Fig. 1b).

Most of the serous (50 of 53 [94%]) and mixed histology tumors (8 of 13 [62%]) clustered with 36 (12%) of the 289 endometrioid tumors, including 24% of grade 3 and 5% of grade 1 or 2, into copy number cluster 4; a single group characterized by a very high degree of copy-number alterations (Supplementary Fig. 2.1; focal SCNAs with FDR < 0.15, and Supplementary Data File 2.1). Cluster 4 tumors were characterized by significantly recurrent previously reported focal amplifications of the oncogenes *MYC* (8q24.12), *ERBB2* (17q12), and *CCNE1* (19q12),[13] and by SCNAs previously unreported in endometrial cancers including those containing *FGFR3* (4p16.3) and *SOX17* (8q11.23). Cluster 4 tumors also had frequent *TP53* mutations (90%), little MSI (6%), and fewer *PTEN* mutations (11%) than other endometrioid tumors (84%). Overall, these findings suggest that a subset of endometrial tumors contain distinct patterns of SCNAs and mutations that do not correlate with traditional tumor histology or grade.

As expected, tumors in the 'serous-like' cluster (cluster 4) had significantly worse PFS than tumors in the endometrioid cluster groups ($P=0.003$, log-rank, Fig. 1b). Potential therapeutically relevant SCNAs included the cluster 2 15q26.2 focal amplification, which contained *IGF1R;* and cluster 4 amplifications of *ERBB2, FGFR1, FGFR3,* and *LRP1B* deletion, which was recently associated with resistance to liposomal doxorubicin in serous ovarian cancer.[14]

### Exome sequence analysis

We sequenced the exomes of 248 tumor/normal pairs. Based on a combination of somatic nucleotide substitutions, MSI, and SCNA, the endometrial tumors were classified into four groups (Fig. 2a and b): 1) an ultra-mutated group with unusually high mutation rates ($232\times10^{-6}$ mutations/Mb) and a unique nucleotide change spectrum; 2) a hypermutated group ($18\times10^{-6}$ mutations/Mb) of MSI tumors, most with *MLH1* promoter methylation; 3) a group with lower mutation frequency ($2.9\times10^{-6}$ mutations/Mb) and most of the microsatellite stable (MSS) endometrioid cancers; and 4) a group that consists primarily of serous-like cancers with extensive SCNA (copy-number cluster 4) and a low mutation rate ($2.3\times10^{-6}$ mutations/Mb). The ultra-mutated group consisted of 17 (7%) tumors exemplified by an increased C→A transversion frequency, all with mutations in the exonuclease domain of *POLE,* and an improved progression-free survival (Fig. 2a and 2c). *POLE* is a catalytic subunit of DNA polymerase epsilon involved in nuclear DNA replication and repair. We identified hotspot mutations in *POLE* at P286R and V411L present in 13 (76%) of the 17 ultramutated samples. Significantly mutated genes (SMGs) identified at low False Discovery Rates ($Q$) in this subset included *PTEN* (at 94% with $Q=0$), *PIK3R1* (65%, $Q=8.3\times10^{-7}$), *PIK3CA* (71%, $Q=9.1\times10^{-5}$), *FBXW7* (82%, $Q=1.4\times10^{-4}$), *KRAS* (53%, $Q=9.2\times10^{-4}$), and *POLE* (100%, $Q=4.2\times10^{-3}$). Mutation rates in *POLE* mutant endometrial and previously reported ultramutated colorectal tumors exceed that found in any other lineage including lung cancer and melanoma.[15–17] Germline susceptibility variants have been reported in

*POLE* (L424V) and *POLD1* (S478N), but were not found in our endometrial normal exome-seq reads.[18]

The MSI endometrioid tumors had a mutation frequency approximately 10-fold greater than MSS endometrioid tumors, few SCNAs, frame-shift deletions in *RPL22*, frequent non-synonymous *KRAS* mutations, and few mutations in *FBXW7, CTNNB1, PPP2R1A,* and *TP53*. The MSS, copy number low, endometrioid tumors had an unusually high frequency of *CTNNB1* mutations (52%); the only gene with a higher mutation frequency than the MSI samples. The copy number high group contained all of the remaining serous cases and one-quarter of the grade 3 endometrioid cases. Most of these tumors had *TP53* mutations and a high frequency of *FBXW7* (22%, $Q$=0) and *PPP2R1A* (22%, $Q$=1.7×10$^{-16}$) mutations, previously reported as common in uterine serous but not endometrioid carcinomas. Thus, a subset of high-grade endometrioid tumors had similar SCNAs and mutation spectra as uterine serous carcinomas, suggesting these patients might benefit from treatment approaches that parallel those for serous tumors.

There were 48 genes with differential mutation frequencies across the four groups (Fig. 2d, Supplementary Data File S3.1). *ARID5B*, a member of the same AT-rich interaction domain (ARID) family as *ARID1A*, was more frequently mutated in MSI (23.1%), than in either MSS endometrioid (5.6%) or high SCNA serous tumors (0%), a novel finding for endometrial cancer. Frame-shifting *RPL22* indels near a homopolymer at Lys15 were almost exclusively found in the MSI group (36.9%). The *TP53* mutation frequency (>90%) in serous tumors differentiates them from the endometrioid subtypes (11.4%). However, many (10 of 20; 50%) endometrioid tumors with a non-silent *TP53* mutation also had non-silent mutations in *PTEN,* compared to only 1 of 39 (2.6%) serous tumors with *TP53* non-silent mutations. Though *TP53* mutations are not restricted to serous tumors, the co-existing *PTEN* mutations in the endometrioid cases suggest a distinct tumorigenic mechanism.

Comparisons of 66 SMGs between traditional histologic subtypes are provided (Supplementary Methods S3) and SMGs across other subcohorts can be found in Supplementary Data File S3.2. The spectrum of *PIK3CA* and *PTEN* mutations in endometrial cancer also differs from other solid tumors (Supplementary Methods S3). Integrated analysis may be useful for identifying histologically misclassified cases. For example, a single serous case was identified without a *TP53* mutation or extensive SCNA and with a *KRAS* mutation and high mutation rate. Upon re-review of the histologic section, the case was deemed consistent with a grade 3 endometrioid tumor demonstrating how molecular analysis could reclassify tumor histology and potentially impact treatment decisions.

## Multiplatform subtype classifications

All of the endometrial tumors were examined for mRNA expression (n=333), protein expression (n=293), miRNA expression (n=367), and DNA methylation (n=373) (Supplementary Methods S4–S7). Unsupervised k-means clustering of mRNA expression from RNA sequencing identified three robust clusters termed 'mitotic', 'hormonal', and 'immunoreactive' (Supplementary Fig. 4.1) that were significantly correlated with the four integrated clusters; *POLE*, MSI, CN low and CN high (*P*<0.0001). Supervised analysis

identified signature genes of the *POLE* cluster (n = 17) mostly involved in cellular metabolism (Fig. 3a). Among the few signature genes in the MSI cluster was decreased *MLH1* mRNA expression likely due to its promoter methylation. Elevated progesterone receptor (*PGR*) expression was noted in the CN low cluster, suggesting responsiveness to hormonal therapy. The CN high cluster, which included most serous and serous-like endometrioid tumors, exhibited the greatest transcriptional activity exemplified by increased cell cycle deregulation (e.g. *CCNE1, PIK3CA, MYC*, and *CDKN2A*) and *TP53* mutation (Supplementary Figs. 4.2 and 4.3). This is consistent with reports that elevated CDKN2A can distinguish serous from endometrioid carcinomas.[19] Approximately 85% of cases in the CN high cluster shared membership with the 'mitotic' mRNA subtype.

Supervised clustering of the RPPA expression data was consistent with loss of function for many of the mutated genes (Fig. 3b). *TP53* was frequently mutated in the CN high group ($P=2.5\times10^{-27}$) and its protein expression was also elevated, suggesting these mutations are associated with increased expression. By contrast, *PTEN* ($P=2.8\times10^{-19}$) and *ARID1A* ($P=1.2\times10^{-6}$) had high mutation rates in the remaining groups, but their expression was decreased, suggesting inactivating mutations in both genes. The CN high group also had decreased levels of phospho-AKT, consistent with down regulation of the AKT pathway. The CN low group had elevated RAD50 expression, which is associated with DNA repair, explaining some of the differences between the CN high and CN low groups. The *POLE* group had high expression of ASNS and CCNB1, whereas the MSI tumors had both high phospho-AKT and low PTEN expression.

Unsupervised clustering of DNA methylation data generated from Illumina Infinium DNA methylation arrays revealed four unique subtypes (MC1-4) that support the four integrative clusters. A heavily methylated subtype (MC1) reminiscent of the CpG island methylator phenotype (CIMP) phenotype described in colon cancers and glioblastomas,[20–22] was associated with the MSI subtype and attributable to promoter hypermethylation of *MLH1*. A serous-like cluster (MC3) with minimal DNA methylation changes was composed primarily of serous tumors and some endometrioid tumors (Supplementary Fig. 7.1) and contained most of the CN high tumors.

Integrative clustering using the iCluster framework returned two major clusters split primarily on serous and endometrioid histology highlighting *TP53* mutations, lack of *PTEN* mutation and encompassing almost exclusively CN high tumors (Supplementary Fig. 8.1).[23] We developed a new clustering algorithm, called SuperCluster, to derive overall subtypes based on sample cluster memberships across all data types (Supplementary Fig. 9.1). SuperCluster identified 4 clusters that generally confirmed the contributions of individual platforms to the overall integrated clusters. No major batch effects were identified for any platform (Supplementary Methods S10).

## Structural Aberrations

To identify somatic chromosomal aberrations, we performed low-pass, paired-end, whole-genome sequencing on 106 tumors with matched normals. We found recurrent translocations involving genes in several pathways including WNT, EGFR-RAS-MAPK, PI3K, Protein Kinase A, RB and apoptosis. The most frequent translocations (5/106)

involved a member of the BCL family (*BCL2, BCL7, BCL9* and *BCL2L11*). Four of these were confirmed by identification of the translocation junction point and two were also confirmed by RNA-Seq. In all cases the translocations result in in-frame fusions and predicted to result in activation or increased expression of the BCL family members (Supplementary Fig. 3.2). Translocations involving members of the BCL family leading to reduced apoptosis have been described in other tumor types[24] and our results suggest that similar mechanisms may be operative here.

### Pathway alterations

Multiple platform data were integrated to identify recurrently altered pathways in the four endometrial cancer integrated subgroups. Because of the high background mutation rate and small sample size, we excluded the *POLE* subgroup from this analysis. Considering all recurrently mutated, homozygously deleted, and amplified genes, we used MEMo[25] to identify gene networks with mutually exclusive alteration patterns in each subgroup. The most significant module was found in the CN low group and contained *CTNNB1, KRAS,* and *SOX17* (Fig. 4a). The very strong mutual exclusivity between mutations in these three genes suggests that alternative mechanisms activate WNT signaling in endometrioid endometrial cancer. Activating *KRAS* mutations have been shown to increase the stability of beta-catenin via GSK3beta leading to an alternative mechanism of beta-catenin activation to APC degradation.[26] *SOX17*, which mediates proteasomal degradation of beta-catenin,[27,28] is mutated exclusively in the CN low group (8%) at recurrent positions (A96G and S403I) not previously described. Other genes with mutually exclusive alteration patterns in this module were *FBXW7, FGFR2, and ERBB2*.[29] *ERBB2* was focally amplified with protein overexpression in 25% of the serous or serous-like tumors, suggesting a potential role for HER2 targeted inhibitors. A small clinical trial of trastuzumab found no activity in endometrial carcinoma, but accrued few HER2 FISH-amplified serous carcinomas.[30]

*PIK3CA* and *PIK3R1* mutations were frequent and showed a strong tendency for mutual exclusivity in all subgroups, but unlike other tumor types, they co-occurred with *PTEN* mutations in the MSI and CN low subgroups as previously reported (Fig. 4b).[5,9] The CN high subgroup showed mutual exclusivity between alterations of all three genes. Overall, 93% of endometrioid tumors had mutations that suggested potential for targeted therapy with PI3K/AKT pathway inhibitors.

Consensus clustering of copy number, mRNA expression, and pathway interaction data for 324 samples yielded 5 PARADIGM clusters with distinct pathway activation patterns (Fig. 4c, Supplementary Methods, S11).[31] Paradigm cluster 1 had the lowest level of MYC pathway activation and highest level of WNT pathway activation, consistent with its composition of CN low cases having frequent *CTNNB1* mutations. PARADIGM cluster 3 was composed predominantly of the CN high cases with relatively high MYC/Max but low ER/FOXA1 signaling and p53 activity. Only *TP53* truncation and not missense mutations were implicated as loss-of-function mutations, suggesting different classes of p53 mutations may have distinct signaling consequences. Paradigm cluster 5 was enriched for hormone receptor expression.

### Comparison to ovarian and breast cancers

The clinical and pathologic features of uterine serous carcinoma and high-grade serous ovarian carcinoma (HGSOC) are quite similar. HGSOC shares many similar molecular features with basal-like breast carcinoma.[32] Focal SCNA patterns were similar between these three tumor subtypes and unsupervised clustering identified relatedness (Fig. 5a, Supplementary Fig. 12.1). Supervised analysis of transcriptome datasets showed high correlation between tumor subtypes (Supplementary Fig. 12.2). The MC3 DNA methylation subtype with minimal DNA methylation changes also was similar to basal-like breast and HGSOCs (Supplementary Fig. 12.3). High frequency of *TP53* mutations is shared across these tumor subtypes (uterine serous, 91%; ovarian serous, 96%; basal-like breast, 84%),[33,34] as is the very low frequency of *PTEN* mutations (uterine serous carcinoma, 2%; HGSOC, 1%; basal-like breast carcinoma, 1%). Differences include a higher frequency of *FBXW7, PPP2R1A,* and *PIK3CA* mutations in uterine serous compared to basal-like breast and HGSOCs (Fig. 5b). We show that uterine serous carcinomas share many molecular features with both HGSOC and basal-like breast carcinomas, despite more frequent mutations, suggesting new opportunities for overlapping treatment paradigms.

## Discussion

This integrated genomic and proteomic analysis of 373 endometrial cancers provides insights into disease biology and diagnostic classification that could have immediate therapeutic application. Our analysis identified four novel groups of tumors based on integrated genomic data, including a novel *POLE* subtype in ~10% of endometrioid tumors. Ultra-high somatic mutation frequency, MSS, and common, newly identified hotspot mutations in the exonuclease domain of *POLE* characterize this subtype. SCNAs add a layer of resolution, revealing that most endometrioid tumors have few SCNAs, most serous and serous-like tumors exhibit extensive SCNAs, and the extent of SCNA roughly correlates with PFS.

Endometrial cancer has more frequent mutations in the PI3K/AKT pathway than any other tumor type studied by TCGA to-date. Endometrioid endometrial carcinomas share many characteristics with colorectal carcinoma including a high frequency of MSI (40% and 11%, respectively), POLE mutations (7% and 3%, respectively) leading to ultrahigh mutation rates, and frequent activation of WNT/CTNNB1 signaling; yet endometrial carcinomas have novel exclusivity of *KRAS* and *CTNNB1* mutation and a distinct mechanism of pathway activation. Uterine serous carcinomas share many similar characteristics with basal-like breast and HGSOCs; three tumor types with a high frequency non-silent *TP53* mutations and extensive SCNA. However, the high frequency of *PIK3CA, FBXW7, PPP2R1A*, and *ARID1A* mutations in uterine serous carcinoma are not found in basal-like breast and HGSOCs. The frequency of mutations in *PIK3CA, FBXW7,* and *PPP2R1A* was ~30% higher than in a recently reported study of 76 uterine serous carcinomas,[11] but similar to another study.[12] Uterine serous carcinomas have *ERBB2* amplification in 27% of tumors and *PIK3CA* mutations in 42%, which provide translational opportunities for targeted therapeutics.

Early stage Type I endometrioid tumors are often treated with adjuvant radiotherapy, while similarly staged Type II serous tumors are treated with chemotherapy. High-grade serous and endometrioid endometrial carcinomas are difficult to correctly subtype, and intra-observer concordance among specialty pathologists is low.[7,34–36] Our molecular characterization data demonstrate that ~25% of tumors classified as high-grade endometrioid by pathologists have a molecular phenotype similar to uterine serous carcinoma, including frequent *TP53* mutations and extensive SCNA. The compelling similarities between this subset of endometrioid tumors and uterine serous carcinomas suggest that genomic-based classification may lead to improved management of these patients. Clinicians should carefully consider treating copy number altered endometrioid patients with chemotherapy rather than adjuvant radiotherapy and formally test such hypotheses in prospective clinical trials. Further, the marked molecular differences between endometrioid and serous-like tumors suggest that these tumors warrant separate clinical trials to develop the independent treatment paradigms that have improved outcomes in other tumor types, such as breast cancer.

## Methods Summary

Biospecimens were obtained from 373 patients after institutional review board-approved consents. DNA and RNA were co-isolated using a modified AllPrep kit (Qiagen). We used Affymetrix SNP 6.0 microarrays to detect SCNA in 363 samples and GISTIC analysis to identify recurrent events.[37] The exomes of 248 tumors were sequenced to a read-depth of at least 20×. We performed low-pass whole-genome sequencing on 107 tumors to a mean depth of 6×. Consensus clustering was used to analyze mRNA, miRNA, RPPA, and methylation data with methods previously described.[38–40] Integrated cross-platform analyses were performed using MEMo, iCluster, and PARADIGM. [25,31]

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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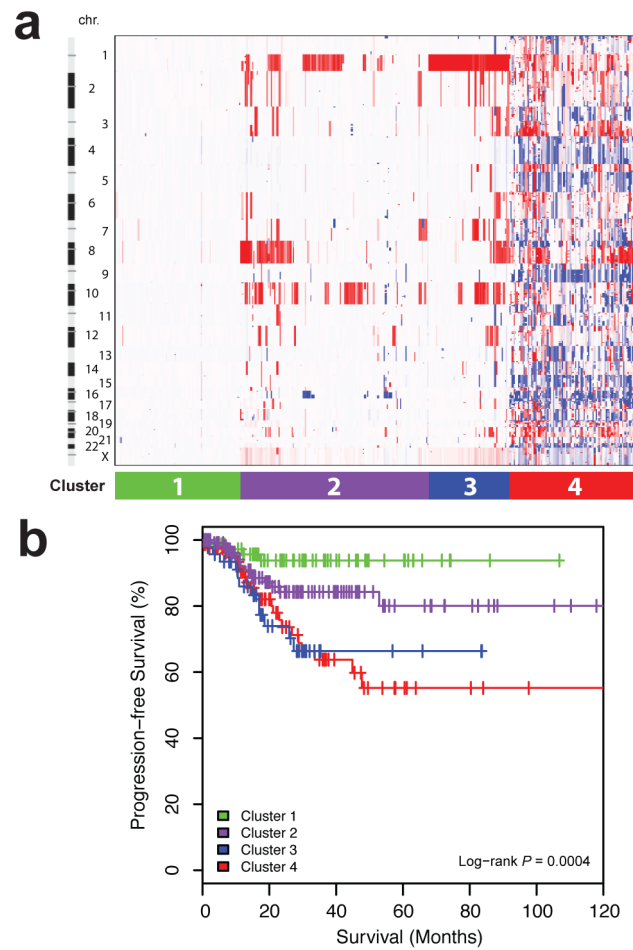
**Figure 1. Somatic copy number alterations in endometrial carcinomas**
**a**, Tumors were hierarchically clustered into four groups based on SCNAs. The heatmap shows SCNAs in each tumor (vertical axis) plotted by chromosomal location (horizontal axis). Vertical color bars to the right of the heatmap show genomic features. **b**, Kaplan-Meier curves of PFS for each copy number cluster.
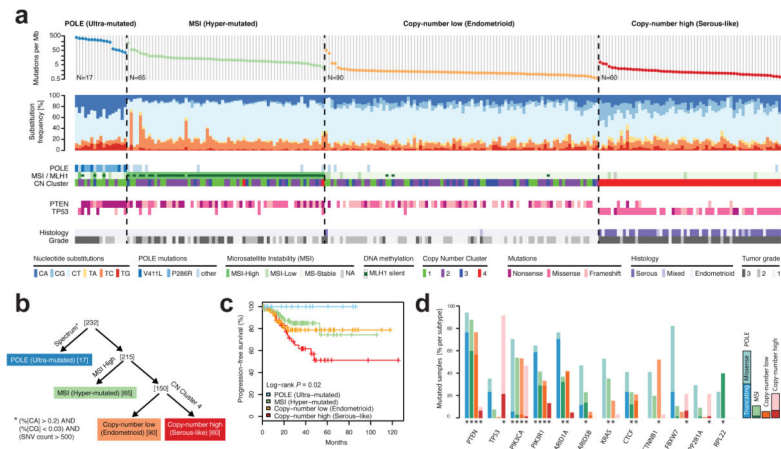
**Figure 2. Mutation spectra across endometrial carcinomas**

**a,** Mutation frequencies (vertical axis, upper panel) plotted for each tumor (horizontal axis). Nucleotide substitutions are shown in the middle panel with a high frequency of C to A transversions in the samples with *POLE* exonuclease mutations. **b,** Tumors were stratified into the four groups by 1) nucleotide substitution frequencies and patterns, 2) MSI status, and 3) copy-number cluster. **c,** *POLE*-mutant tumors have significantly better PFS, while CN high tumors have the poorest outcome. **d,** Recurrently mutated genes are different between the four subgroups. Shown are the mutation frequencies of all genes that were significantly mutated in at least one of the four subgroups (MUSiC, FDR < 0.05, indicated by asterisk).
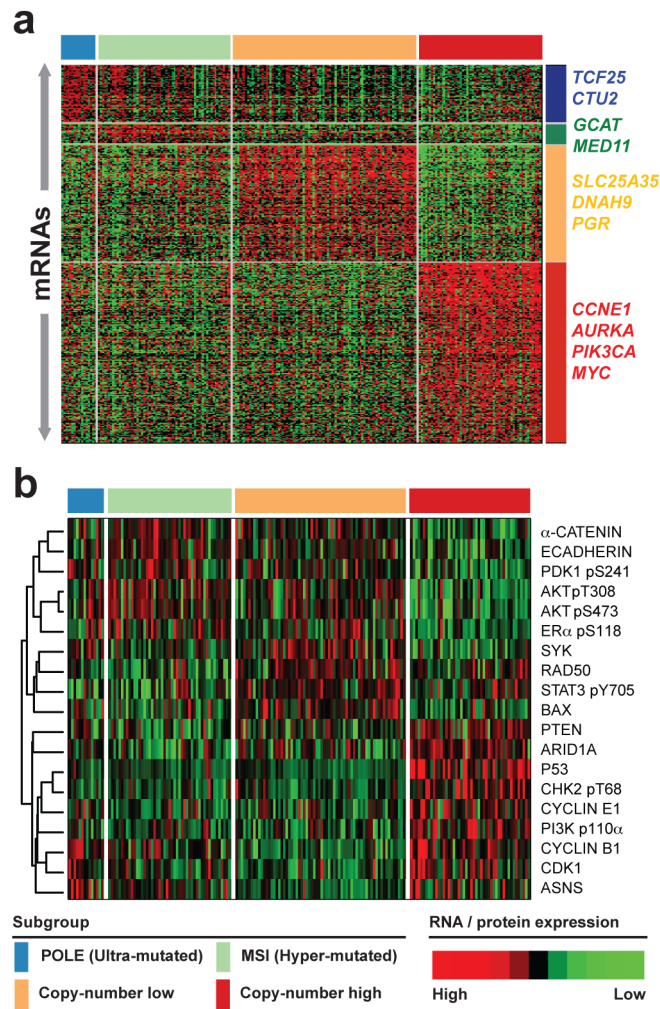
**Figure 3. Gene expression across integrated subtypes in endometrial carcinomas**
**a**, Supervised analysis of ~1500 genes significantly associated with integrated subtypes **b**, Heat map of protein expression clusters, supervised by integrated subtypes. Samples are in columns; genes or proteins are in rows.
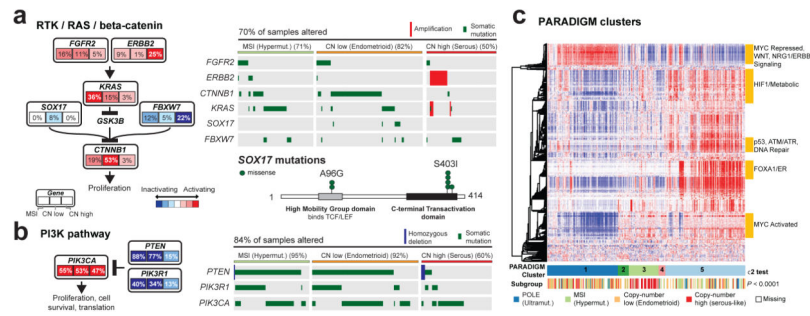
**Figure 4. Pathway alterations in endometrial carcinomas**

**a**, The RTK/RAS/beta-catenin pathway is altered through multiple mechanisms that exhibit mutually exclusive patterns. Alteration frequencies are expressed as a percentage of all cases. The right panel shows patterns of occurrence. **b**, The PI3K pathway has mutually exclusive *PIK3CA* and *PIK3R1* alterations that frequently co-occur with *PTEN* alterations in the MSI and CN low subgroups. **c**, Heatmap display of top 1000 varying pathway features within PARADIGM consensus clusters. Samples were arranged in order of their consensus cluster membership. The mutation spectrum for each sample is displayed below the consensus clusters.

**Figure 5. Genomic relationships between endometrial serous, ovarian serous, and basal-like breast carcinomas**

**a**, Somatic copy number alterations for each tumor type. **b**, Frequency of genomic alterations present in at least 10% of one tumor type.