Copy number signatures for early diagnosis of high-grade serous ovarian carcinoma

Martin de la Fuente, Laura; Li, Minerva; Måsbäck, Anna; Malander, Susanne; Kannisto, Päivi; Hedenfalk, Ingrid

2022

Copy number signatures for early diagnosis of high-grade serous ovarian carcinoma

BY LAURA MARTIN DE LA FUENTE[1], MINERVA X. LI[1], ANNA MÅSBÄCK[2], SUSANNE MALANDER[1], PÄIVI KANNISTO[3], SRINIVAS VEERLA[1] AND INGRID HEDENFALK[1]

[1]DEPARTMENT OF CLINICAL SCIENCES LUND, DIVISION OF ONCOLOGY, LUND UNIVERSITY AND SKÅNE UNIVERSITY HOSPITAL, LUND, SWEDEN.
[2]DEPARTMENT OF SURGICAL PATHOLOGY, DIVISION OF LABORATORY MEDICINE, SKÅNE UNIVERSITY HOSPITAL, LUND, SWEDEN.
[3]DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY LUND, SKÅNE UNIVERSITY HOSPITAL, LUND UNIVERSITY, LUND, SWEDEN.

Background

The detection of ovarian carcinoma-derived somatic mutations in cervical samples and uterine lavages in several studies since 2013, has brought hope for the development of new biomarkers for early detection. High-grade serous ovarian carcinoma (HGSC) is strongly dominated by copy number alterations (CNAs). These CNAs are the consequence of underlying mutational processes in HGSC. We interrogated CNAs from low coverage whole-genome sequencing (WGS) data in HGSC tumors, plasma, endometrial biopsies, and cervical samples to explore if copy number signatures can be used as a biomarker for early detection of HGSC.

Methods

A total of 204 samples were included from 18 patients with HGSC, four *BRCA* mutation carriers and seven benign controls. Estimations of ploidy and cellularity, and thus calculation of absolute copy number, were optimized through a combination of the **ACE**, **Rascal**, and **ichorCNA** bioinformatic tools. **Mixture modelling** was used to subgroup the six fundamental copy number features and **non-negative matrix factorization** was used to generate the signatures and cluster the samples.

Table 1. Patient and sample inclusion.

	Cohort 1 2015-16			Cohort 2 2018-20
	HGSC	*BRCA* mut	Benign	HGSC
FF tissue	x	x	x	x
Blood	x	x	x	x
Endometrial biopsy	x	x	x	x
Plasma	x	x	x	x
Liquid-based DNAgard®	x	x	x	
ThinPrep® slide	x	x	x	
Liquid-based ThinPrep®				x

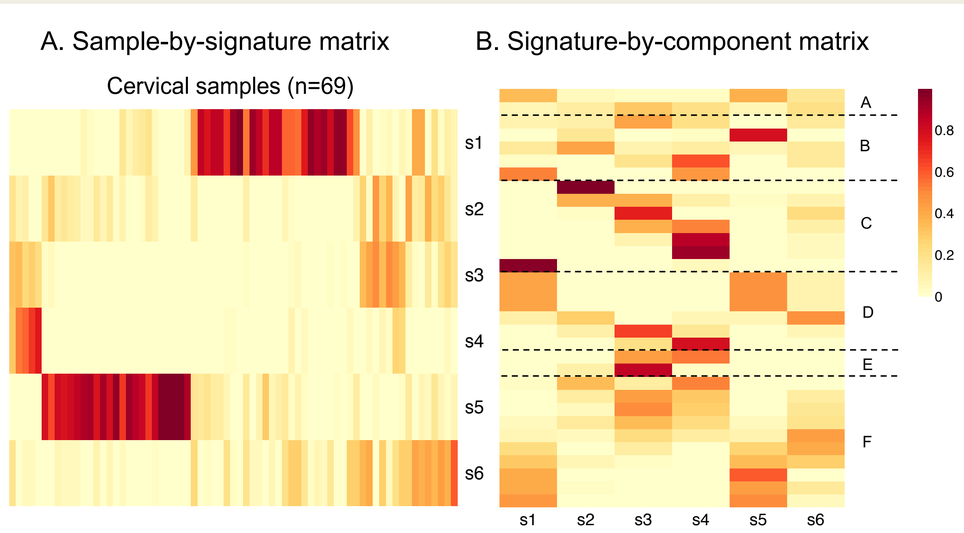

Figure 3. Construction of copy number signatures with cervical samples from HGSC patients (CerCNsig). A. Sample-by-signature matrix. **B.** Signature-by-component matrix.

Results

We extracted **six fundamental copy number features** from 69 diagnostic and pre-diagnostic cervical samples from patients diagnosed with HGSC and generated **six CN signatures**. We found different distributions of features in benign samples compared to tumors and cervical samples from HGSC patients. We also observed different exposures to the six signatures in different patient groups.

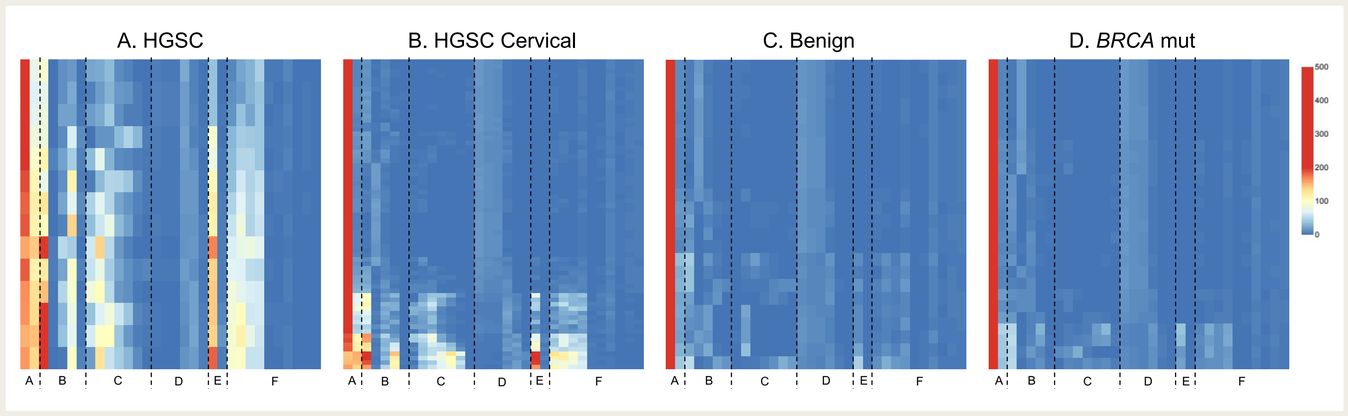

Figure 1. Sample-by-component matrix in different sample sets. X axis: 32 components grouped by the six fundamental features (A-F). A= breakpoints per 10Mb, B= copy number, C= CN change point, D= breakpoints per chromosome arm, E= length of segments with oscillating copy number and F= segment size.

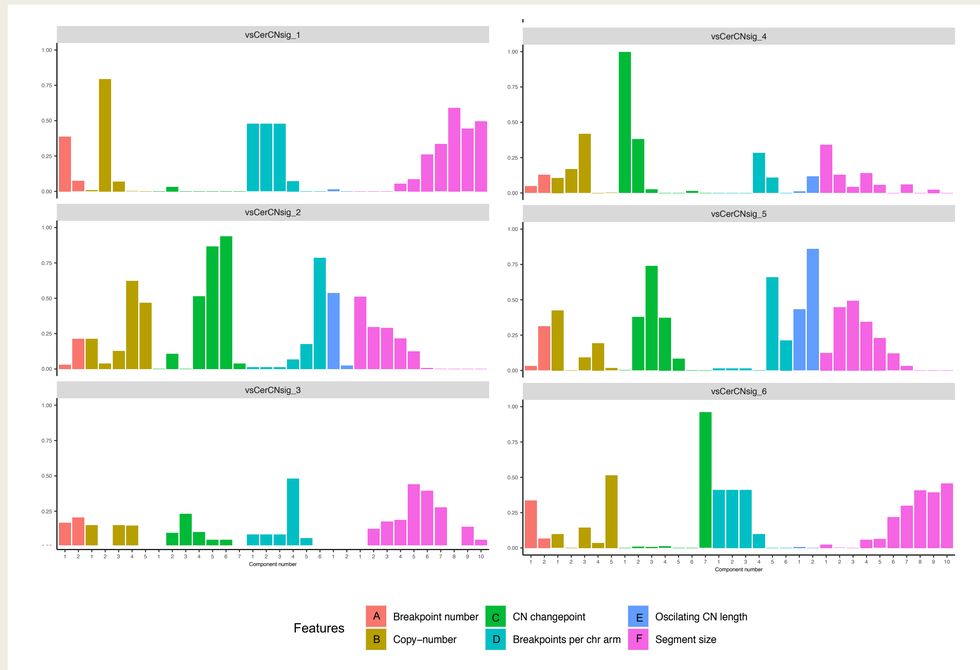

Figure 4. Distribution of features in the six copy number signatures, CerCNsig, in cervical samples from HGSC patients.

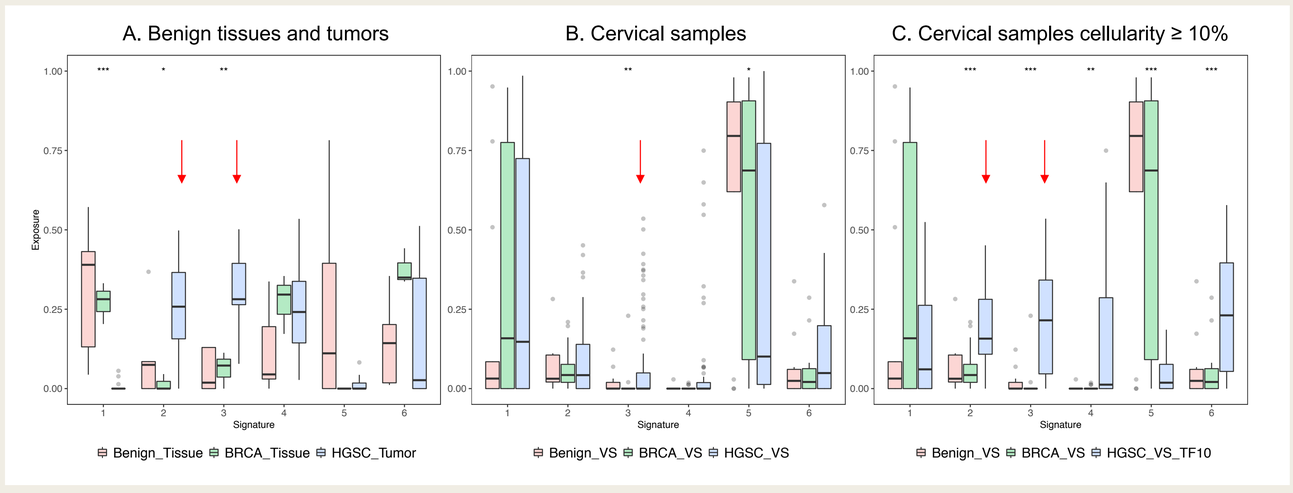

Figure 2. Signatures exposures in different sample sets. A. Tissue from controls (n=11), *BRCA* mutation carriers (n=7) and tumors (n=14). **B.** Cervical samples (CS) from controls (n=13), *BRCA* mutation carriers (n=20) and HGCS patients (n=69). **C.** CS from controls, *BRCA* mutation carriers and HGSC patients with cellularity ≥ 10% (n=17).

Red arrows point out higher exposure to Signature 2 and 3 in tumors and cervical samples from HGSC patients. Significant differences are highlighted using asterices (* P<0.05, ** P<0.01, ***P<0.001).

Conclusions

Further understanding of the components and cell types contributing to each signature, and inclusion of more cervical samples into the approach, will hopefully identify a novel tumorigenic signature for early detection of HGSC in cervical samples.

Contact

Laura Martin de la Fuente

Division of Oncology, Department of Clinical Sciences, Lund, Sweden

Lund University Cancer Center, Medicon Village 404-B3

SE-22381 Lund, Sweden

Email: laura.martin_de_la_fuente@med.lu.se