LHP1 and EMF1, which was not the case for downregulated genes, confirming a predominantly repressive role for EBS.

The BAH–EMF1 complex may not be so plant specific after all

Taken together, plant complexes reading H3K27me3 contain two distinct classes of proteins with affinity for H3K27me3, LHP1 and EBS/SHL, as well as EMF1 and a protein related to BMI1 (Fig. 1). Although these four proteins are specific to plants, their functional domains are old friends and are also encountered in animal H3K27me3 readers such as the canonical PRC1, which contains domains present in LHP1, EMF1 and BMI1[2]. Furthermore, recent reports have shown that animal proteins with a BAH domain, such as human BAHD1, can bind to H3K27me3 and are able to promote chromatin compaction[9], indicating that BAH domains within the Polycomb pathway represent another example of convergent evolution. ❒

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Published online: 29 August 2018
https://doi.org/10.1038/s41588-018-0201-1

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Competing interests
The authors declare no competing interests.

CANCER GENOMICS

Copy number signatures in ovarian cancer

A new study uncovers novel copy number signatures in ovarian cancer genomes. This work sheds light on mutational processes driving ovarian cancer, reveals the distribution of copy number features across the patient population and identifies new genomic properties related to treatment response.

Sohrab P. Shah

Taming the complexity of ovarian cancer genomes

High-grade serous ovarian cancer (HGSOC) genomes are replete with complex somatic structural alterations[1]. The etiologic nature of these alterations is poorly understood, and their biological and clinical consequences are only minimally defined. Brenton and colleagues[2] have contributed work representing a significant step forward in inferring the mutational processes giving rise to different classes of structural alterations, leading to statistical association with mutated pathways and prognostic association with clinical outcome. Their work provides a new and different viewpoint on the landscape of mutational processes in HGSOC through the lens of copy number signatures (Fig. 1).

Structural alterations typically accrue as a result of endogenous DNA repair deficiency—a defining property of HGSOC. As such, distinct DNA repair deficiencies in ovarian cancers elicit specific patterns of somatic mutation in the corresponding genomes, giving rise to a key concept: the pattern, and not necessarily the gene content, of alteration is a critical property of interest. In ovarian cancer, the genomic consequences of DNA repair deficiency have been shown at nucleotide-level scales in the form of point mutation[3–5] and rearrangement breakpoint[5] signatures through whole-genome sequencing and computational analysis. The most well-known and well-studied example is the scenario in which *BRCA1* and/or *BRCA2* loss leads to a particular form of DNA repair defect known as homologous recombination deficiency (HRD). However, *BRCA1* and *BRCA2* loss only explain some cancers with HRD. Point mutation signatures can reflect HRD[6] more comprehensively and may represent a theoretically meaningful marker of response to new therapeutic agents called PARP inhibitors. The contribution of Brenton and colleagues[2] takes this concept further by focusing on copy number alterations. Copy number alterations represent a subset of structural variations and dominate the landscape of HGSOC genomes[1,3]. Their computational detection from genome sequencing is enabled through the compilation of read abundance over segmental regions of the genome, without a need for the nucleotide-level scales required for identification of rearrangement breakpoints or point mutations. This makes their detection feasible in low-coverage (and therefore low-cost) whole-genome sequencing data. Brenton and colleagues[2] astutely asked whether low-coverage whole-genome sequencing coupled with a new statistical method for computing copy features from these genomes could be used as a route to identifying mutational processes in HGSOC.

The authors' findings contribute both methodological and conceptual advances to the cancer genomics field by introducing copy number signatures, derived from novel 'features' of copy number alterations. Through computation of measurable copy number features informed by hallmarks of known mutational processes, the authors reduce each genome into a features vector that can be decomposed using the popular non-negative matrix factorization (NMF) approach, commonly used in point mutation signature analysis[7]. They contribute two additional novel components: application to cancer genomes from the BriTROC-1 clinical trial led by the investigators and the technique of inferring copy number features from low-pass (0.1× coverage) whole-genome sequencing data. The first point ensures high-quality, uniformly collected clinical outcomes data, while the latter point provides proof of principle that

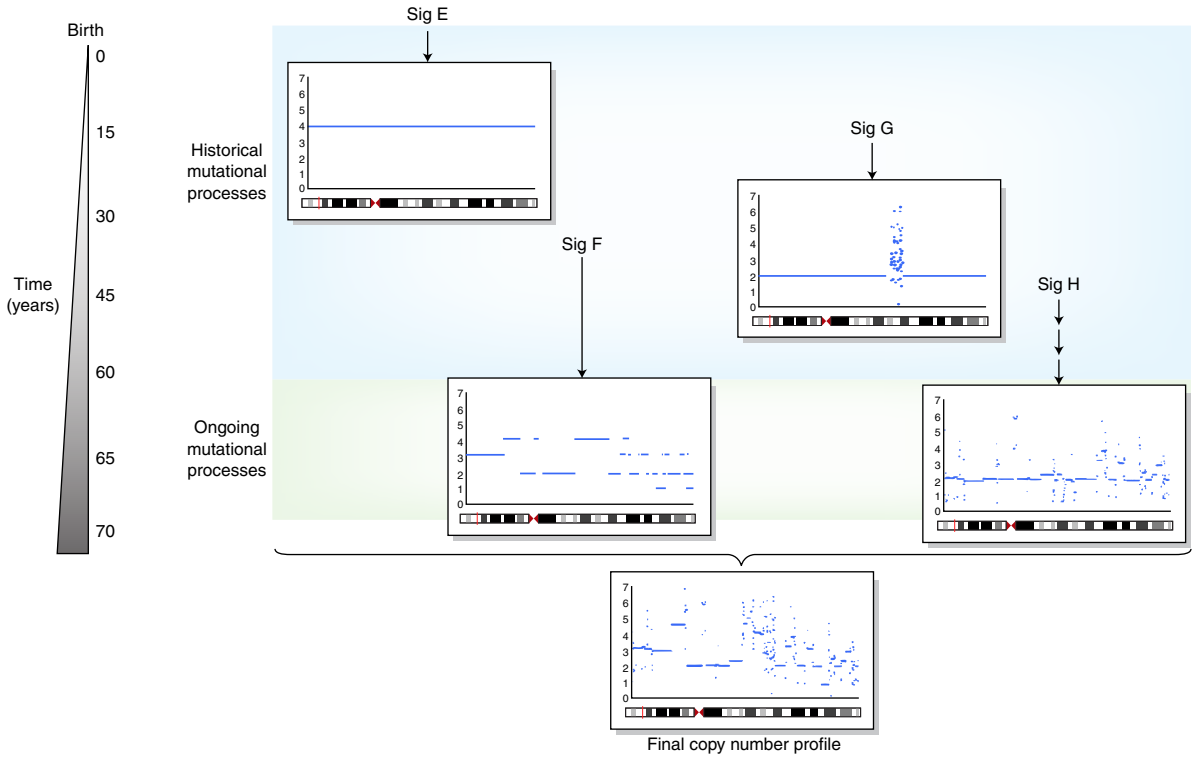

Fig. 1 | Active copy number signatures over time create a composite portrait that can be observed with genome sequencing. Brenton and colleagues[2] decompose the final copy number profile into a finite set of exposures. These exposures can then be used to infer copy number mutational processes and stratify patients with ovarian cancer.

cost-effective whole-genome sequencing assays could potentially be deployed in clinical settings for HGSOC.

The central result reveals seven copy number signatures patterning the genomes of HGSOC. Through associative statistical analysis, the authors interpret these signatures by mapping them to previously reported single-nucleotide variant (SNV) and structural variation (SV) signatures and also determine how they associate with mutations in biological pathways, putatively linking biological etiology with signature exposure. In contrast to previous reports on SNV and SV signatures, the copy number signatures suggest a continuous spectrum and a more refined stratification of patients who have HGSOC, with clinical implications.

Moving forward with copy number signatures

The work presented by Brenton and colleagues[2] should provoke further study into the generalizability of copy number signature inference in a pan-cancer setting. It is easy to envision how the study of cancers with genomic instability properties such as prostate, pancreas, triple-negative breast, lung and many other cancers might also benefit from copy number signature analysis for patient stratification. The methods introduced in this paper will be an excellent starting point for such scaled-up analysis. Furthermore, as single-cell whole-genome sequencing is poised for commercialization, assessing cell- or clone-level mutational processes from the copy number features presented will be accessible. This will have implications for understanding evolutionarily contemporaneous versus ancestral components of the dynamics of mutation accrual in a cancer's life history. Finally, the results presented by Brenton and colleagues[2] show a continuous spectrum of signature exposures across the patient cohort, leaving open the question of how copy number signatures could be practically used to engender treatment decisions. Addressing the decision points to achieve optimal patient outcomes will constitute an essential step on the path toward implementing the genome-as-a-biomarker approach to guiding therapy for patients with HGSOC. The field will watch with interest in anticipation of the utility of copy number signatures in directing women with HGSOC toward improved, patient-centered treatment options. ❐

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Published online: 29 August 2018
https://doi.org/10.1038/s41588-018-0212-y

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Competing Interests

S.P.S. is a principal shareholder of Contextual Genomics, Inc.