Evolution of marine contagious cancers in cockles characterized by genomic instability.

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Transmissible cancers are malignant cell clones that spread among individuals through transfer of living cancer cells. Several such cancers, collectively known as bivalve transmissible neoplasia (BTN), are known to cause leukaemia-like disease in marine molluscs such as the common cockle which inhabits the Atlantic coasts of Europe and Africa. To investigate the origin and evolution of contagious cancers in common cockles, we collected 6,854 specimens and diagnosed 390 cases of BTN. We then generated a reference genome and assessed genomic variation in the genomes of 61 BTN tumours. Tumour-specific variants confirmed the existence of 2 cockle BTN lineages with independent clonal origins, and gene expression patterns supported their status as haemocyte-derived blood cancers. Mitogenomes revealed several mitochondrial capture events in BTN, as well as co-infection of cockles by different tumour lineages. Cytogenetic and copy number analyses uncovered genomes marked by pervasive instability and karyotypic plasticity. Whole-genome duplication, amplification of oncogenes *CCND3, MDM2* and *MYC*, and deletion gene *MGMT*, are likely drivers of BTN evolution. Characterization of satellite DNA identified elements that are absent from tumours despite vast expansions in the cockle germ line, suggesting ancient BTN clonal origins. Our study illuminates the evolution of transmissible cancers under the sea and reveals indefinite tolerance of extreme instability in neoplastic genomes.