

Contagious cancers in cockles sequenced, showing unexpected instability

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Transmissible cancers in cockles—marine cancers that can spread through the water—have been sequenced for the first time, unearthing new insight into how these cancers have spread across animal

populations for hundreds, possibly thousands, of years.

The study, from researchers at the Wellcome Sanger Institute, the CiMUS research center at the Universidade de Santiago de Compostela in Spain, and collaborators across multiple countries, found that these cockle tumors are highly genetically unstable. The [cancer cells](#) within a single tumor contained vastly different numbers of chromosomes, something not seen in other cancers.

Published in *Nature Cancer*, the team also created the first high-quality reference genome of the common cockle, a species which belongs to one of the oldest groups of animals on Earth, unraveling its genome and evolution for the first time.

The researchers hope that studying how cockle cancer cells overcome the effects of genomic instability will have implications for understanding this in all forms of cancer, including in humans. Additionally, gaining more knowledge about this cancer and its impact can help protect cockle populations in the future.

Cockles are a type of small shellfish and there are more than 205 species of cockle worldwide. Cockles belong to one of the oldest groups of animals on Earth, bivalve mollusks, which have inhabited the Earth for over 500 million years, first appearing about 300 million years before the dinosaurs.

These animals can catch transmissible cancers that are spread by living cancer cells, passing from one cockle to the next through seawater. The cancers cannot be passed to humans, spreading only between susceptible cockles.

The contagious cancers that infect cockles are termed bivalve transmissible neoplasia (BTN). These are cancers of the cockle's

[immune cells](#), causing a disease similar to leukemia. BTN spreads throughout the body and is usually lethal to the infected animal. Eight independent types of BTN have been identified so far in clams, cockles and mussels across the world.

This study focused on the common cockle (*Cerastoderma edule*) which inhabits the coasts of Europe and north-west Africa and is often harvested for food. The team, from the Wellcome Sanger Institute, the CiMUS-Universidade de Santiago de Compostela and collaborators, produced the first high-quality reference genome of this animal, an essential step in investigating its cancers evolution.

Dr. Zemin Ning, an author from the Wellcome Sanger Institute, said, "Marine transmissible cancers are less well-understood than contagious cancers in species like dogs and Tasmanian devils, due to the lack of robust reference genomes of the animals they impact."

"Our study provides the first quality reference genome of the common cockle, which is vital if we are to uncover and understand the genetic changes seen in cockle cancers. To keep learning about transmissible cancers, it is important to continue to provide quality genetic data on the affected species."

The authors then collected around 7,000 cockles at 36 locations from 11 countries including Spain, Portugal, the UK, Ireland, and Morocco. From this, they genetically sequenced 61 cockle tumors and were able to show the existence of two different types of BTN, with both [cell types](#) looking visually different under the microscope.

The researchers also identified a number cockles that had unexpectedly been co-infected by cells from both types of cancers at the same time.

Through genetically tracking the evolution of the tumors, they found

multiple types of [genetic changes](#), including evidence that the cancer cells have captured mitochondria—the small organelles that generate the cell's energy—from their host cockles at least seven times in the past.

While it is difficult to precisely estimate the age of cockle cancers, the findings from this study suggest that these cancers probably emerged centuries or even millennia ago. It is thought that these cancers have spread slowly through European cockle populations, occasionally capturing mitochondria from host cells as replacements for their own when they become damaged.

Dr. Alicia Bruzos, co-first author and previously at CiMUS -Universidade de Santiago de Compostela during the research, said, "Tumors were first found in cockles around 40 years ago, but our study is one of the first to sequence and analyze the whole genomes of these animals. We clarified the existence of two independent transmissible cancers, and we suspect that there are many more different types out there. Having a wider view of the different types of transmissible cancers can give us more insight into the conditions necessary for tumors to evolve and survive long-term."

Notably, the team discovered that BTN tumor genomes are highly unstable. The number and size of chromosomes varied remarkably between different tumors, and between cells from the same tumor. Some cells contained as few as 11 chromosomes and others as many as 354. The number of chromosomes in a normal cockle cells is 38.

This degree of "chromosomal instability" is far greater than anything previously observed in human tumors and suggests that a stable genome is not needed for the long-term survival of these transmissible cancers. This is surprising, as human cancer cells cannot survive high levels of chromosomal instability—although moderate levels often make tumors more likely to spread to other organs and become resistant to treatment.

Understanding more about how BTN cells tolerate this instability could help inform new approaches to target human cancer cells in the future.

Dr. Daniel Garcia-Souto, co-first author previously at the Wellcome Sanger Institute and currently at CiMUS-Universidade de Santiago de Compostela, said, "Our study showed that the cells in these cockle tumors contain highly variable amounts of genetic material, which is very unusual compared to other types of [cancer](#). These cancers have been undergoing extreme chromosomal changes and continuous genetic reorganization, probably for hundreds or thousands of years, which challenges the theory that cancers require stable genomes to survive long-term."

In addition to this, understanding BTN and its impact is vital to protecting cockle populations against threats in the future. Sometimes transmissible cancers can combine with multiple other factors including pollution, rising sea temperatures, and viral outbreaks, to trigger episodes of mass mortality, killing more than 90% of cockles in a given area.

The loss of cockle populations threatens food security and jobs in the fishing industry, along with wider impacts on the ecosystem. Future research into contagious cancers in cockles and [other bivalves](#) will allow us to understand better how to prevent these catastrophic episodes, which appear to have become more common in recent years.

Dr. Adrian Baez-Ortega, joint senior author from the Wellcome Sanger Institute, said, "Cockles are an important part of life for many people in Europe, and are a crucial part of coastal ecosystems. They have been around for many millions of years, but now they face a variety of threats of which transmissible cancers are only one example."

"Understanding more about the origins and evolution of cockle transmissible cancers, and how their cells interact with cockle cells and

the marine environment, could help protect [animal populations](#) in the future, while providing insight into how cancers can survive for thousands of years as marine parasites."

More information: Adrian Baez-Ortega, Somatic evolution of marine transmissible leukemias in the common cockle, *Cerastoderma edule*, *Nature Cancer* (2023). [DOI: 10.1038/s43018-023-00641-9](https://doi.org/10.1038/s43018-023-00641-9).
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