Research reveals Orkney cancer gene link—now testing will take place

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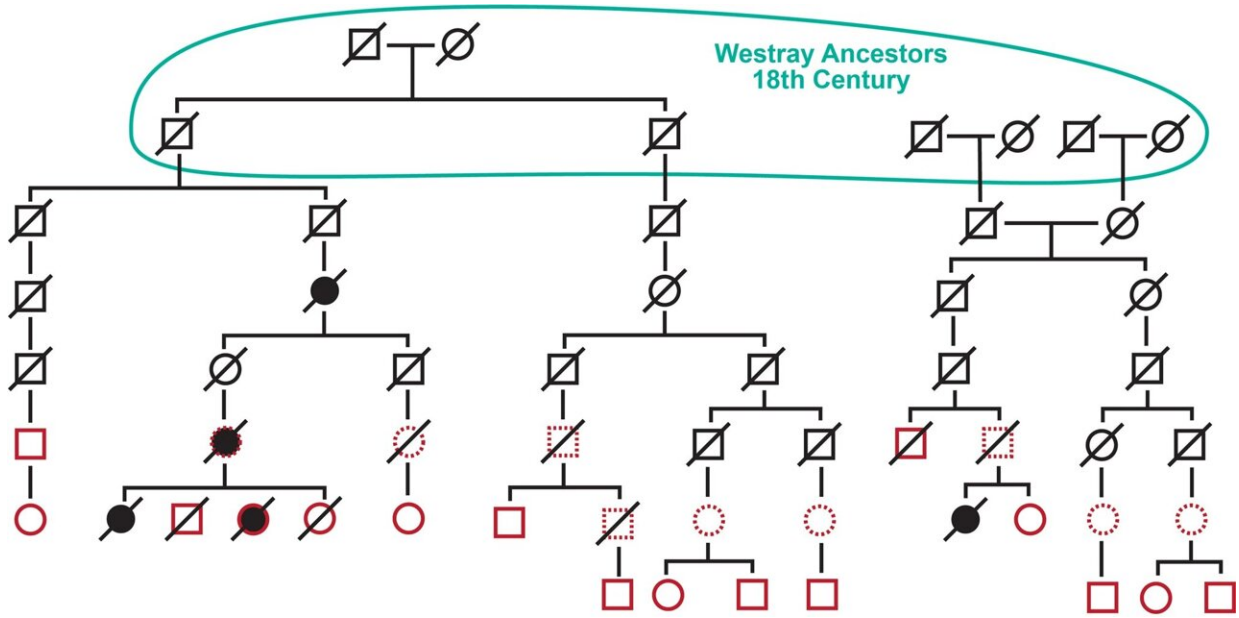

Outline pedigree of two kindreds (A and B) from the ORCADES study. Filled circles are breast or ovarian cancers, red outlines are sequenced V1736A carriers, dotted red outlines are obligate carriers. The founders of kindred A, the largest, were born in Westray in the 1760s. All four of the other kindreds also eventually lead back to Westray common ancestors, in the 19th century (but with deeper ancestry there back to the same time depth). In kindred C, mostly resident in the East Mainland of Orkney, the Westray common ancestors were born in the early 1800s. Credit: *European Journal of Human Genetics* (2023). DOI: 10.1038/s41431-023-01297-w

One in 100 people who have grandparents from Orkney have a gene variant that causes a higher risk of developing breast and ovarian cancer, a study has found.

Published in the *European Journal of Human Genetics*, leading geneticists from the Universities of Aberdeen and Edinburgh have linked a variant in the gene BRCA1 to a historic origin in Westray, Orkney.

Currently in Scotland the test is available to those who know of a direct family connection to the gene or have a history of ovarian or breast cancer in their family.

Now planning is underway for a small pilot trial organized by NHS Grampian that will offer testing for the gene variant to anyone living in Westray with a Westray-born grandparent, regardless of a family history.

If the pilot is successful, the long-term aim is to offer the test to everyone in Scotland with a Westray-born grandparent who wants it.

Most breast and ovarian cancers happen due to chance damage to genes. However, some cases are caused in part by inherited alterations which increase the chances that women will get one or both of these conditions. One of the most common of these predisposing genes is BRCA1.

Around one in 1,000 women across the UK have a BRCA1 variant giving them a high lifetime chance of developing breast cancer and ovarian cancer.

Over many years, the North of Scotland NHS genetics clinic team found the same specific single variant in the BRCA1 gene repeatedly in women from Orkney with breast and/or ovarian cancer. The genetics team used clinical genealogy to show that the patients with the variant linked into

one large family with an origin in the Orkney outer isle of Westray.

University of Edinburgh scientists examined genetic data from more than 2000 volunteers with Orkney grandparents in the Orkney Complex Disease Study (ORCADES). The study is part of Viking Genes, a project which aims to discover the genes and variants that influence the risk of disease.

They found the BRCA1 variant in 1% of men and women with Orkney grandparents. Many of the ORCADES participants with the variant are not closely related to branches of the family identified in the clinic, but all share historic Westray ancestors.

Professor Zosia Miedzybrodzka, professor of medical genetics at the University of Aberdeen, is Director of the NHS North of Scotland Genetic Service based within NHS Grampian in Aberdeen and has run the Orkney genetic clinic for over 20 years.

She said, "Developing cancer is not solely down to carrying the BRCA1 variant alone. There are many complex factors, and some people with gene alterations will not get cancer. However, we know that testing and the right follow-up can save lives."

"Many people who have the gene alteration are unaware of it. Not everyone wants to have a genetic test that looks into their future. In the long run we want to make a test available to those with Westray grandparents who want to know if they have the gene variant."

"As it is hereditary, the gene variant can affect multiple members of families. Risk-reducing surgery, breast screening with MRI from age 30 and lifestyle advice can all improve health for women with the gene. Men do not need to take any particular action for themselves, but they can pass the gene onto female descendants."

Professor Jim Wilson, professor of human genetics, University of Edinburgh added, "The fact that one in a hundred Orcadian women carry a high-risk variant for breast and ovarian cancer highlights the value of population studies such as Viking Genes, without which we would not know this. It is imperative that Scottish island populations are represented in research, to allow equitable delivery of genomic medicine across the country."

Orcadian Karen Scott was tested for this BRCA1 gene variant following her own cancer diagnosis in 2018. She also works for charity Clan Cancer Support in Kirkwall which provides emotional and practical support to people affected by a cancer diagnosis.

She said, "This important medical finding reflects Orkney's unique heritage. Having personally taken part in this test, I understand the significance of this research for my family and the Orkney community. We must act on this new knowledge to improve our children's future."

Professor Henry Watson, from Friends of ANCHOR said, "It is clear there is a strong case for offering this targeted testing. The Friends of ANCHOR committee promptly approved the application for funding so that this program can be rolled out to the Westray population as soon as possible."

"This project will give Westray residents who have a grandparent from the island, control over the decision to find out more about their heritage-related risk factors."

"On a personal note my maternal grandmother came from Westray and so the outcomes of testing may have implications for my family. This shows why the research impacts beyond Westray."

More information: Shona M. Kerr et al, Clinical case study meets

population cohort: identification of a BRCA1 pathogenic founder variant in Orcadians, *European Journal of Human Genetics* (2023). DOI: 10.1038/s41431-023-01297-w