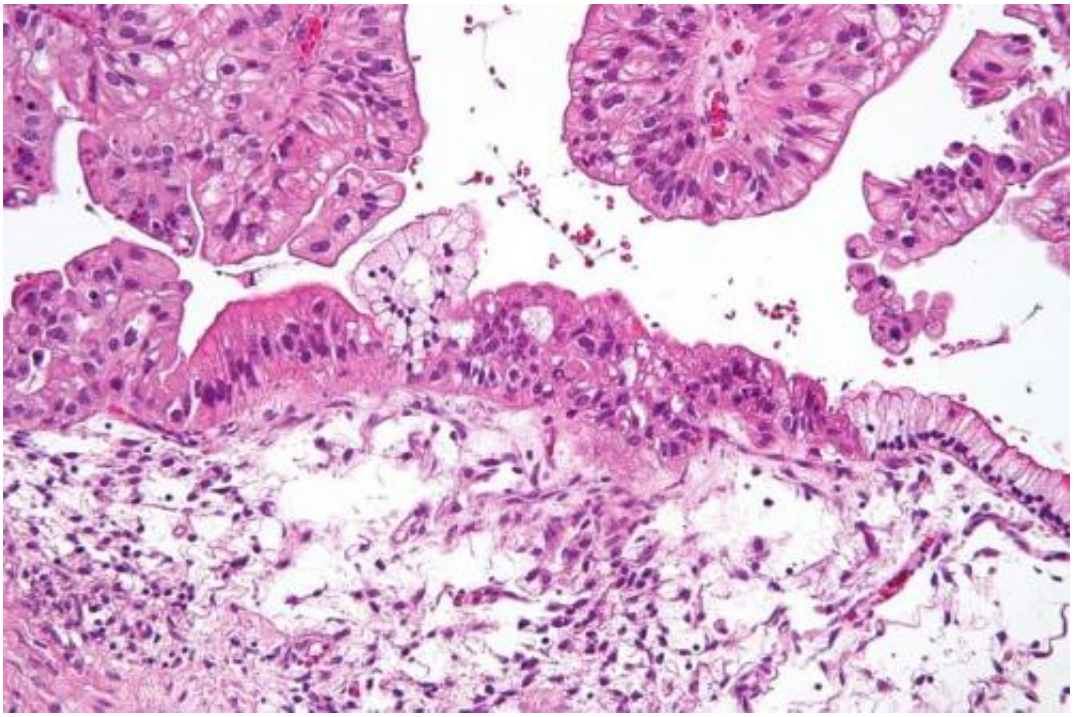
Major genetic study identifies 12 new genetic variants for ovarian cancer

March 27 2017



Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. H&E stain. The micrograph shows: Simple mucinous epithelium (right) and mucinous epithelium that pseudo-stratifies (left - diagnostic of a LMP tumour). Epithelium in a frond-like architecture is seen at the top of image. Credit: Nephron /Wikipedia. CC BY-SA 3.0

A genetic trawl through the DNA of almost 100,000 people, including 17,000 patients with the most common type of ovarian cancer, has identified 12 new genetic variants that increase risk of developing the

disease and confirmed the association of 18 of the previously published variants.

Published today in the journal *Nature Genetics*, the findings are the result of work by the OncoArray Consortium, a huge endeavour led by scientists in the UK, the USA and Australia. This particular study involved 418 researchers from almost 300 different departments worldwide.

According to Cancer Research UK, there were 7,378 new cases of ovarian cancer in the UK in 2014. Around nine out of ten of these cases was epithelial ovarian cancer. The peak rate of cases is among women aged 75-79 years old.

"We know that a woman's genetic make-up accounts for about one third of her risk of developing ovarian cancer. This is the inherited component of disease risk," explains Professor Paul Pharoah from the University of Cambridge, UK, one of the joint leads. "We're less certain of environmental factors that increase our risk, but we do know that several factors reduce the risk of ovarian cancer, including taking the oral contraceptive pill, having your tubes tied and having children."

Inherited faults in genes such as BRCA1 and BRCA2 account for about 40 per cent of the inherited component. These faults are rare in the population (carried by about one in 300 people) and are associated with high lifetime risks of ovarian cancer - about 50 per cent for BRCA1 and 16 per cent for BRCA2 on average - as well as a high risk of breast cancer. Variants that are common in the population (carried by more than one in 100 people) are believed to account for most of the rest of the inherited component of risk.

Before the OncoArray Consortium, researchers had identified 27 common variants across the genome associated with ovarian cancer risk.

However, some of these are associated only with rare subtypes of ovarian cancer. The magnitude of the associated risk however is modest: together, the variants account for only about 4 per cent of the inherited component of disease.

The OncoArray Consortium studied the genomes of over 25,000 people with epithelial ovarian cancer and compared them to almost 41,000 healthy controls. They then analysed results from a further 31,000 BRCA1 and BRCA2 mutation carriers, which included almost 4,000 epithelial ovarian cancer patients. This enabled them to identify a further 12 variants associated with risk and confirm the association of 18 of the previously published variants; some of the other variants failed to replicate.

In total, there are now known to be 30 risk variants, accounting for 6.5 per cent of the inherited component of risk.

"Ovarian cancer is clearly a very complex disease - even the 30 risk variants that we now know increase risk of developing the disease account for just a small fraction of the inherited component," says Dr Catherine Phelan from the Moffitt Cancer Center, Tampa, USA. "We believe that there will likely be many more genetic variants involved, each with extremely small effects. Most of these are likely to be common, but some will be rare."

The researchers point out that while the common view is of our genes influencing disease risk, in fact most of the variants discovered to date do not fall in our genes, but rather in 'non-coding' regions of the human genome, so named because, unlike our genes, they do not provide the code to make proteins. Instead, these regions are often involved in regulating the activity of our genes.

Because the variants are common, some women will carry multiple risk

variants. However, even in combination these variants do not have a large effect on risk, say the researchers. Women carrying the greatest number of these risk variants will still have a lifetime risk of ovarian cancer of just 2.8 per cent. To put this into context, family cancer clinics commonly offer surgery to remove the ovaries - and hence prevent the possibility of disease - to women with a lifetime risk of 10 per cent or more.

However, these variants also affect the risk of ovarian cancer in women who carry a fault in the BRCA1 or BRCA2 genes and this might be sufficient to affect the decision of a carrier about when or if to have preventive surgery.

"In some ways, the hard work starts now," says Dr Simon Gayther from Cedars-Sinai Medical Center, Los Angeles, USA. "We really have little idea of the functional effect these variants have at the molecular or cellular level and so there are few clues as to how they might affect risk. If we can understand how they work, we will be in a better position to treat - and possibly prevent - ovarian cancer."

The OncoArray Consortium used a customised Illumina genotyping array, which allowed them to analyse around 533,000 variants and has been used to genotype over 500,000 samples, including the samples in this study of ovarian cancer

More information: Catherine M Phelan et al, Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer, *Nature Genetics* (2017). DOI: 10.1038/ng.3826

Provided by University of Cambridge