



DISCOVER

ENGAGE

IMPACT



AIMING TO END ENDO

UQ researchers are working hard to help our daughters in the battle against endometriosis, a crippling disease that affects 10 per cent of women of child-bearing age.

A silent disease is invading reproductive and surrounding organs inside one in every 10 women.

With this disease, tissue similar to the normal uterine lining grows and invades areas around the pelvis.

It can create rigid scar tissue that impedes the function of organs by reducing their mobility.

It causes serious pain.

And, in some cases, it causes infertility.

If you know 10 women, there's a good chance that one of them is suffering from this insidious disease and they may not even know it.

The disease is called endometriosis, and we know very little about it.

But that's about to change.

Professor Grant Montgomery and his team at UQ's Institute for Molecular Bioscience are currently working on solutions to this disease, which affects women in their most productive years (between puberty and menopause) and which is estimated to cost the Australian economy around \$6 billion a year.

What do we know about 'endo'?

According to current research:

- Endometriosis is strongly influenced by genetic factors, so women with a family history are more likely to develop it.
- 50 per cent of the risk factors are genetic.
- 50 per cent of the risk factors are environmental.

- The average delay in diagnosis is around eight years from when symptoms start.
- To effectively diagnose the disease, women need to go through an invasive surgical procedure where tissue is extracted to be examined under a microscope.
- Current treatment is only effective for some.
- The disease presents differently in different people.

A complex disease

Like many complex diseases, the contributing environmental and genetic risk factors are like a giant jigsaw puzzle and, 25 years ago, a project commenced to try and understand what the genetic component of that jigsaw puzzle might be.

With a background in reproductive biology and gene mapping, Professor Montgomery joined the project, which he now leads.

"The genetic contribution to complex diseases is made up of lots of genes of small effect. It is not one gene mutation that causes the disease, but multiple genetic variants that contribute to incrementally increasing risk," he says.

"Somewhere along the continuum of genetic and environmental risk factors, you cross a threshold where the disease develops. Also, some women have very mild disease, while others have quite severe disease, and treatment is effective for some but not others.

"So, we want to understand: across the spectrum of the disease, is it a continuum with the same risk factors or are there different types of disease?"

Uncovering how each of those factors contribute to disease will open the door to more effective prevention, diagnosis and targeted treatment, but it is a slow process.

Uncovering the genetic risk factors: the long game

Professor Montgomery's research team measures genetic markers from across the genome to determine the genetic regions associated with risk.

"Uncovering these regions is the first step in a process. Genetic markers tell us which genomic regions we need to look at, but in each of those regions a number of genes could be the culprits (or targets).

"So, the important next step is to go through the genomic regions to uncover which genes in each area are influencing risk and how."

A recent international study – the largest ever completed with 200,000 participants worldwide – led by Professor Montgomery's research team, confirmed nine previous results and uncovered five new regions. This study follows similar smaller studies of European and Japanese women.

Professor Montgomery's research team has also recently published an example of taking one of those regions and uncovering what the likely targets are.

"It's at an exciting stage. We have a number of regions to work on and we know how to go about identifying gene targets. Hopefully it will also redirect the research being done in other labs in this area."

Understanding the other 50 per cent: environmental factors

How do you identify the environmental factors influencing a woman's risk of disease?

It's a vital piece of the puzzle because, while you can't change genetic factors, it may be possible to influence environmental factors. Researchers need to find better methods to shine a light on the offending environmental effects.

"The environmental factors are really hard to study because we don't know what they are or when the environmental triggers occurred. We may have to track women from conception to understand any input that might be a factor," Professor Montgomery says.

But Professor Montgomery may have a solution. "I believe there is potential to use genomics to identify the environmental factors."

Our interaction with environmental factors can leave information in our DNA.

"Some environmental factors will leave signatures (epigenetic signals) on the DNA. So, the information may be there. If it is, we can work backwards – finding the signatures and then designing experiments to determine what caused them.

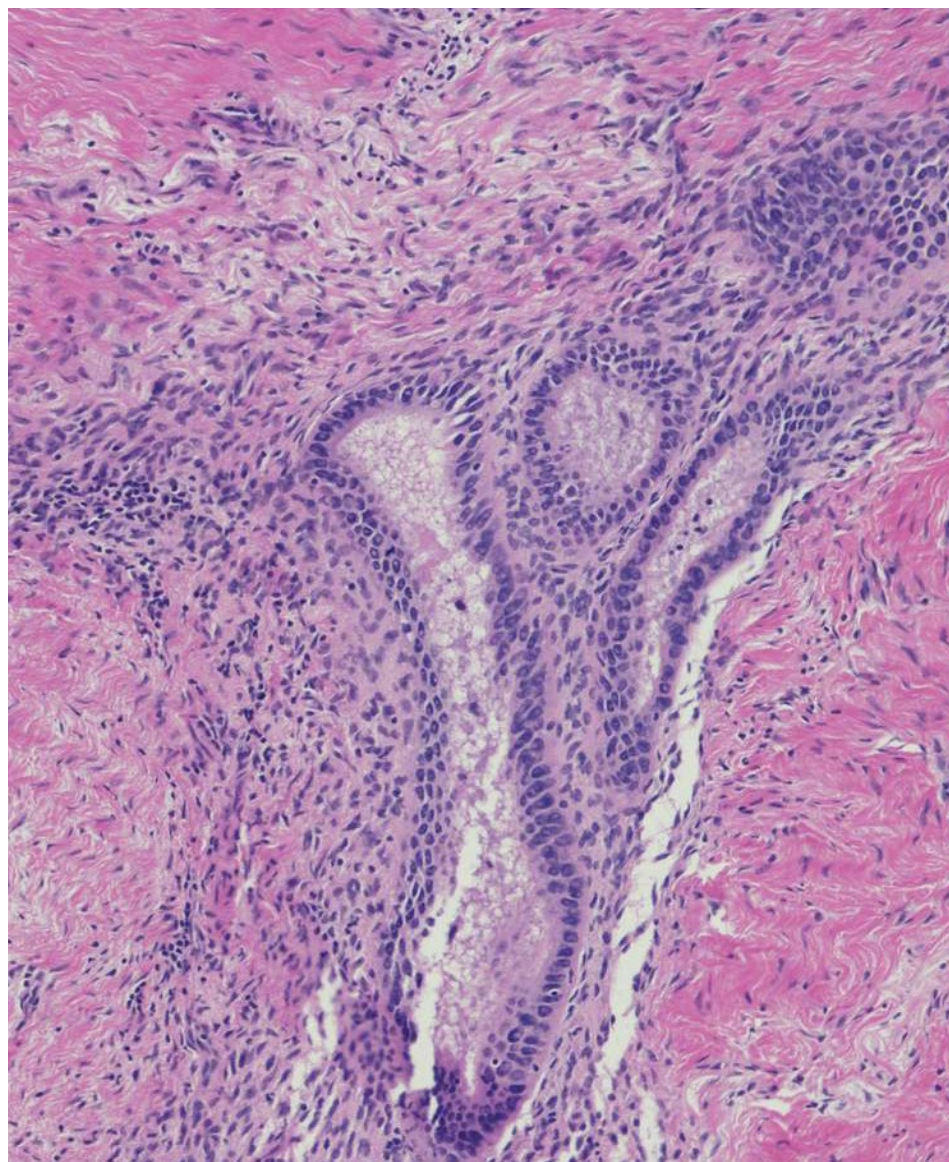
"It's not going to be easy and, like genetic approaches, there are no shortcuts.

"We are working with several international groups to analyse epigenetic signals in women with endometriosis to look for signatures of the environmental factors contributing to the disease."

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The journey so far:

1989: Professor Montgomery co-founds the New Zealand Sheep Genomics Program at the University of Otago to work on genome mapping methods for farm animals

1999: He joins the Queensland Institute of Medical Research in a genome mapping program for human complex disease

2002: He publishes a joint article in *Fertility and Sterility*, 'The international endogene study: a collection of families for genetic research in endometriosis'

2008: He presents paper at the 10th World Congress on Endometriosis on genetic variation and endometriosis risk, and publishes a joint paper in *Human Reproduction Update*, 'The search for genes contributing to endometriosis risk'

2012: Professor Montgomery receives an NHMRC grant for defining mechanisms for novel risk loci in endometriosis and is elected Fellow of the Society for Reproductive Biology; he publishes a joint paper in *Nature Genetics*, 'Genome-wide association meta-analysis identifies new endometriosis risk loci'

2015: He is elected Fellow of the Australian Academy of Health and Medical Sciences

2016: He is awarded Honorary Fellowship of the Royal Society of New Zealand; receives an NHMRC Fellowship, and moves to a joint position at The University of Queensland (IMB and QBI) to focus his research on the discovery of critical genes and pathways increasing risk for common diseases, especially endometriosis

2017: Professor Montgomery's article identifying five new gene regions linked to the disease (that he and eight international colleagues discovered) is published in *Nature Communications*; the Australian Government announces a National Action Plan for Endometriosis

2018: He receives an NHMRC Project Grant for Differential regulation of endometrial gene expression in endometriosis and disease subtypes

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