

The Inverdale and Booroola genes are famous for increasing fertility in sheep. But what else can these "super genes" tell us? As it turns out, probably a lot.



Ewes with the Inverdale or Booroola genes are significantly more fertile than those without. AgResearch scientists are collaborating with their colleagues in New Zealand, Finland, the US and the UK to find if these genes can be exploited in other ways as well.

Fertile genes.

Any sheep farmer will tell you that one of the simplest ways to increase profitability is to increase the fertility of your flock.

In fact, a 2003 Ministry of Agriculture and Forestry paper calculated that increasing the number of lambs sold per ewe by 5% increases returns to the average farm by \$8000.

Spread over the national flock, that equates to \$100 million a year.

Many things affect fertility, including nutrition, survival rates of lambs and so on. But ovulation rate is where it all starts – if it's low, no amount of nutrition or care will result in more lambs. So researchers have long been interested in ewes that ovulate prolifically.

That led to the discovery of the now-famous Inverdale gene by scientists from AgResearch's Invermay campus – and later the Booroola gene. Now researchers are asking if insights into how genes like these function might lead to products that regulate fertility in sheep and other mammals.

Inverdale is actually a mutation of the BMP15 gene, which is common to all mammals. How it increases fertility in sheep, and what the implications might be for fertility in other mammals, is the big question.

"We already know the gene plays a role in regulating the granulosa cells, which surround and support the egg," says AgResearch reproductive physiologist Jenny Juengel. "This structure is called a follicle.

"BMP15 controls how fast the granulosa cells multiply and what products they produce. This in turn modifies communication between the ovary and the pituitary gland."

In a sheep without the mutation, usually only one or two mature follicles are needed to provide the signal to the pituitary to cause ovulation. In a sheep with the mutation, two or three follicles are needed.

So when another research group in the US "knocked out" BMP15 in mice, rendering the gene non-functional, and those mice were still fertile, that raised the question whether BMP15 is only important in sheep fertility.

Further research by a group in Italy, however, has confirmed that it also plays a role in human fertility – but it doesn't call all the shots.

"We thought the granulosa cells prepared the egg for release, with the egg being quite passive," says Jenny. "But our research has now made it clear that the egg is most likely co-ordinating the whole process."

In other words, fertility is influenced by many factors, genetic and environmental. This is not exactly news. For instance, it's well established that as more eggs are produced at ovulation, fertilisation and foetal survival rates drop. A flock of sheep ovulating two eggs each will produce an average 1.7 lambs per ewe. Three eggs at ovulation results in 2.3 lambs on average. That's a drop from 85% live births per egg to 77%.

"We are beginning work to determine why this occurs and how we can reduce the loss," says Jenny.

Also, significant numbers of lambs die at or soon after birth, with the number increasing with litter size. Reduction of these losses will also provide a significant return to farmers.

A companion programme headed by Julie Everett-Hincks of AgResearch's Animal Genomics group is investigating genetic and environmental factors contributing to lamb survival from mid-pregnancy to weaning, with a particular focus on the first few days after birth, when 75% of losses occur. "That programme and ours have a lot of natural links," says Jenny. "We expect collaboration between us to increase."

But why is it important to understand the mechanisms at work in sheep fertility? Surely by discovering these genes, all we need to do is use a marker test to crossbreed sheep that have them with sheep that don't, in order to "spread" the genes throughout the national flock. In fact, this is happening – the process is called introgression.

But what if we could also use these genes to make fertility products for sheep *without* the need for introgression. That could raise average fertility faster than crossbreeding programmes.

And what if we could also make fertility products for other species, like cattle? Or products to suppress reproductive cycles (think possum control or human contraceptives). All are potential outcomes, but not without understanding how genes like Inverdale work, and how they interact with other mechanisms that influence fertility.

That is what this programme is about. It involves experts from different disciplines, including AgResearch's Sue Galloway (gene mapping and molecular mapping), George Davis (animal breeding and genetics), Sara Edwards (cell biology), Julie Everett-Hincks (lamb survival) and Jenny, with funding from FRST, the Marsden Fund and Ovita. Collaborators include the Biotech Visions group from the University of Helsinki, as well as researchers from the University of Wyoming, University of Otago and Oxford Brookes University in the UK as well as a great number of New Zealand sheep farmers.

While any products are still many years in the future, the search for more Inverdale- and Booroola-like genes continues. Recent discoveries include the Woodlands gene (named after the Southland farm where it was found), the Wishart gene (from a sheep breeder's flock, again in Southland) and the Davis gene, found in a flock owned by breeder Stan Davis.

It came as a surprise that when a research group in the US "knocked out" the BMP15 gene in mice, those mice were still fertile.