# Respiratory genetics: joined-up thinking

March 20 2012

Model of mouse lungs. Credit: Ian Smyth, Monash University, Wellcome Images

In late 2011, Professors William Cookson and Miriam Moffatt became the Wellcome Trust's first Joint Senior Investigators. Anjana Ahuja went to meet them at the National Heart and Lung Institute in west London to talk asthma, genetics and the secrets of a successful working relationship.

William Cookson smiles ruefully as he recalls the beginning of his research career, as a young doctor in Oxford in the early 1980s. "I met Julian Hopkin (the recently retired Rector of Medicine at Swansea University), who said 'Bill, why don't we look at the genetics of asthma?' At that time people were working on single-gene disorders like cystic fibrosis - and, very naively, we thought it would be easy."

Nearly three decades later, asthma is only just beginning to yield its genetic secrets, thanks in part to painstaking studies coordinated by Bill, now Professor of Genomic Medicine at Imperial College London, and his research partner Miriam Moffatt, Professor of Human Genetics at

Imperial. They met while working for Hopkin. "Bill used to drive around the Oxfordshire countryside in his 2CV, collecting DNA samples from families," Miriam laughs.

The pair, who have worked together for 22 years, share an office at Imperial's National Heart and Lung Institute (NHLI), where they head the molecular genetics research group. In 2011 they won a £3.26 million Wellcome Trust Joint Senior Investigator Award to continue their mission of unravelling the complex causes of this common respiratory disease. The money will allow them, over the next seven years, to build on their existing world-renowned findings, which include the first gene variant to be associated specifically with severe childhood asthma, and additionally to explore the highly original idea that bacteria in the lining of the lung might play a pivotal part in development of the disease.

Such work, says Miriam, would be nigh-on impossible to fund in the private sector: "People often ask why we haven't gone to pharmaceutical companies for pots of money but you can't be as novel and innovative. We want to do the science that we think is important, and the Wellcome Trust has been fantastic at helping us do that. It's just great that we can continue." Their vision, much of which has been Trust-funded, has helped the NHLI to land a place in the top three institutions worldwide for respiratory research.

## Widespread problem

According to the charity Asthma UK, 5.4m people in the UK have asthma, about a fifth of them children. While many are able to manage their asthma with, for example, steroids, the disease still kills three people a day in the UK and there is no cure. Asthmatics are also vulnerable to other respiratory diseases, such as influenza. "There's a perception that if a child has an inhaler they're okay," Miriam says. And lower-income countries are seeing a dramatic rise in asthma incidence

too.

The fact that asthma - in which the lining of the airways becomes inflamed, leading to breathlessness and wheezing - runs in families has always suggested a genetic component. But the genetic picture is muddied - sometimes literally so - by environmental factors. Infants born into farming households or into homes with pets have a much lower risk of developing it; so do children with older siblings. Urbanisation tends to raise the risk. This led to the 'hygiene hypothesis', which posits that sterile environments hinder immune development. Add allergies into the mix - the vast majority of children who show up at clinics suffering severe asthma also have eczema or other allergies - and the attempt to understand asthma begins to look like a scientific quest without end.

Then along came the genetics revolution, which finally allowed scientists to start picking their way though the gene-environment puzzle. Genome-wide association studies, which compare the genomes of individuals who have the disease to the genomes of matched, healthy controls, can provide a route map, though. Gather enough genomes and statistical associations begin to reveal themselves. For Miriam and Bill, and a host of coauthors in Germany and Austria, a study of thousands of samples from asthmatics and non-asthmatics resulted in a landmark 2007 'Nature' paper pinpointing a gene variant called ORMDL3, on chromosome 17, as a marker of susceptibility to childhood asthma [1].

## Scaling up

The pair went on to coordinate an even bigger collaborative effort called the Gabriel Consortium. The EU- and Wellcome Trust-funded study, using samples from more than 26 000 European participants and published in 2010 [2], furnished a treasure trove of scientific information. Miriam proudly describes it as a tour de force. Bill explains: "The ORMDL3 locus on chromosome 17 shows the most

striking effect on asthma, and is associated with severe disease and with onset in childhood but not with allergies. We found another five highly significant loci, some of which were hinted at before but are now reasonably definitive."

Miriam will use some of the new grant money to investigate what these variants actually do in the body. So far, it seems that turning off the ORMDL3 gene appears to reduce airway inflammation, probably by calming down a class of immune signalling molecules known as sphingolipids. These molecules may well be a future target for asthma drugs.

One of Gabriel's big revelations was that the genetics did not support a link between asthma and allergy. Instead, a different set of gene variants was associated with high IgE levels (used as a marker for allergy). That, says Bill, might be why 20 years of looking at possible allergic mechanisms for asthma have not proved fruitful: "If you look at an asthma clinic, perhaps 80 to 90 per cent of children will test positive for allergies but outside clinics there are more asthmatics who don't have allergies and lots of people with allergy who don't have asthma. In the developing world, the association between asthma and allergy is just not there. It could be that something about severe asthma seems to predispose to allergy, so it's the asthma driving the allergy rather than the other way around."

But there are limits to this approach: genome-wide association studies only pick up variants that affect at least 5 per cent of the population. In addition, the top three variants already uncovered affect roughly a third of total asthma cases. That leaves the genetics involved in two-thirds of asthma patients unexplained. So, are there rarer genetic mutations that explain the familial clustering of severe asthma? The grant will help to answer this, by funding the sequencing of the whole genomes of people in families afflicted by severe childhood-onset asthma. They also plan to

investigate the role of epigenetics - whether the environment in which one generation is raised alters the genetic picture in subsequent generations.

Perhaps most excitingly, the Gabriel study led scientists to a critical hub of asthma-related activity: many of the implicated genes exert influence in the lining of the airways. "The contribution of genes and environment to the causes of asthma is about 50:50, but all the genetic and epidemiological findings [3] were directing us to the same place: the lining of the lungs," says Bill.

"So we decided to look at the airway microbiome [the bacteria that live there], and we found quite striking differences between the airways of healthy people and the airways of children and adults with asthma. The airways of those with asthma contained known respiratory pathogens. But we also found higher levels of healthy bacteria in controls. When the paper [4] came out, people wondered if it was true, because medical textbooks say the lungs are sterile."

Separate studies have shown that mice raised in sterile environments develop inflamed airways - which can be soothed by administering 'good' bacteria. But that doesn't mean that therapies are around the corner: while faecal transplants of beneficial microbes have been shown to help with inflammatory bowel disease (IBD), tinkering with the airways is more likely to be perceived as a risky thing to do. Bill, who trained in medicine in Australia, believes it won't be long before someone tries to stick 'good' bacteria down asthmatic lungs.

Miriam, whose first degree fortuitously happens to be in microbiology, seems quietly horrified at the prospect: "With faecal transplants of bacteria in IBD, things are constantly being excreted, so you can alter the regime if it's not right. But it's different going into the lungs - you can't wipe out bacteria and stick microbes down there. We'd need to find out

how the body will respond."

## Complementary pair

Most of the interview runs along these lines: Bill, the more loquacious of the two, giving me the broad-brush picture, and Miriam chipping in to sharpen up the details. You can see how they work so well together. Even their personas balance: Bill, with a salt-and-pepper beard, has a somewhat chaotic air about him, becoming slightly flustered when I accept his offer of a hot drink (he is flummoxed by the disappearance of the instant coffee). Tea-drinker Miriam cuts a quieter, more composed figure, elegantly dressed and accessorised.

"For quite a while, people presumed I was Bill's secretary," sighs Miriam, who spent a year after graduating as an administrator in the Society for General Microbiology, before realising she really wanted to be back at the lab bench. "Someone else thought I was one of his daughters! But we're on the same wavelength. We've been through a lot together over the years because being a scientist is tough. It's not easy having your papers rejected. But we work really well together: Bill is big picture and I'm very fine detail. Bill's a clinician who understands disease in depth and knows about statistics, and I'm a classical scientist who thinks about how to achieve our research goals."

Miriam is also alive to unfounded suspicions that she's the junior partner: "When I went up for my chair [she was made professor in 2008], a senior referee commented that it should not be assumed that all our research is driven by Bill. We bounce ideas off each other all the time; it's a true partnership. We sometimes disagree but we don't hold grudges." If the NHLI were to offer them separate offices, they'd turn it down, says Bill. "We might have gone for it a few years ago but not now."

Miriam recalls walking to the Tube after the Wellcome Trust grant interview: "I turned to Bill and said, 'What do we do if we don't get it?' I've been in this field for 22 years and I don't want to do anything else. It sounds a cliché to say it's what you live for - but everyone wants to do something that's fulfilling, that makes a difference. We might not see a cure for asthma in our lifetime but I like to think we've helped to progress the field in the last 20 years. And I think a lot's going to change in the next 20 too."

**More information:** References

1. Moffatt MF et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. Nature 2007;448(7152):470-3.
2. Moffatt MF et al. A large-scale, consortium-based genomewide association study of asthma. N Engl J Med 2010;363(13):1211-21.
3. Ege MJ et al. Exposure to environmental microorganisms and childhood asthma. N Engl J Med 2011;364(8):701-9.
4. Hilty M et al. Disordered microbial communities in asthmatic airways. PLoS ONE 2010;5(1):e8578.

Further reading

Dixon AL et al. A genome-wide association study of global gene expression. Nat Genet 2007;39(10):1202-7.
Cookson WO, Moffatt MF. Genetics of complex airway disease. Proc Am Thorac Soc 2011;8(2):149-53.

Provided by Wellcome Trust