

Navigating VUS Land

Dr Jodie Ingles is a cardiac genetic counsellor, navigating the winding pathways of the genetics of sudden cardiac death, and delivering help to affected families ...

DR Jodie Ingles is busy – “I don’t even have time to write a to-do list,” she tells the *MJA*.

To quote her official biography, Dr Ingles is “an early career researcher focused on understanding the most effective ways to manage families with genetic heart diseases, stemming from her 15 years’ experience as a cardiac genetic counsellor”.

“Dr Ingles and Professor Chris Semsarian established the Genetic Heart Disease Clinic, Royal Prince Alfred Hospital in 2004 ... In 2008 they established the Australian Genetic Heart Disease Registry ... Dr Ingles currently leads the Clinical Cardiac Genetics Group within the Molecular Cardiology Program at the Centenary Institute, with projects focused on clinical genetics, genetic counselling, family management and psychosocial functioning.”

It’s an impressive list but it manages to miss the point – Jodie Ingles practically invented a career when she turned her hand to cardiac genetic counselling in 2003.

“I was doing biomedical science at the University of Newcastle, and I wasn’t in love with basic medical research,” she says.

“They had a genetic counsellor come talk to us about the career and I felt like ‘wow, that’s awesome’. You get to be a scientist, and talk to patients, explaining genetic testing.”

That talk led to Dr Ingles completing a graduate diploma in genetic testing before being let loose on a job market that wasn’t offering a lot.

“There was this young cardiologist who was looking for someone to coordinate his clinic for young patients with inherited heart diseases,” she says.

“I rang him and asked if he was looking for a genetic counsellor,

and he didn’t really know what that was, so I explained, and he said, ‘yes I guess I would be’. It worked out perfectly – I was the clinic coordinator, genetic counsellor, and research assistant. The role was awesome.

“At the time I was probably the first genetic counsellor working in cardiac in Australia and I think there wouldn’t have been many in the world at that point in time, to be honest.

“It ended up being this unique period of time where we could write reviews about how we thought cardiac genetic counselling as a field should look. And those are the papers now that get cited a lot because of the timing of it. It’s exciting to think that you had that kind of impact.”

Little did the young Dr Ingles know back then just how the field of genetic research would explode in the following decade, however.

“Fifteen years ago we’d see a family and genetic testing wasn’t really an option. We could send a sample off for a research study and it might take about 2 years and maybe would look at about five genes,” she says.

“Being able to communicate complicated information that even we struggle to understand to families ... [who] ... need to make important medical decisions based on that information – it’s a unique skill”

“Now we’re doing exome sequencing on every patient and I’m drowning in exome data.

“We find genetic results that actually change the diagnosis and the management in a lot of our patients. We find compelling variants in genes that we’ve never seen before.

“It becomes a research study and what we learn directly informs

how we look after these people in the clinic.”

The most exciting thing, she says, is being able to provide crucial medical information and support to families who previously did not know why their young relative had died suddenly.

Two years ago, Dr Ingles and her colleagues were published in the *New England Journal of Medicine* with a study that examined Sudden Cardiac Death (SCD) among children and young adults (<https://www.nejm.org/doi/full/10.1056/NEJMoa1510687>).

“We found that in 40% of cases of SCD in patients under the age of 35 no cause of death was found at postmortem,” she says. “In our clinics we see a lot of families of young people who have died suddenly with no pre-existing diagnosis.

“We can take DNA post-mortem, do exome sequencing on that and

find a cause of death. That can have powerful implications.”

There is a flipside, of course, and that leads Dr Ingles into what she calls “VUS Land”.

“A variant of uncertain significance (VUS) is one where there’s not enough evidence to say, yes it’s causative or no, it’s not causative,” she says. “The gene ends up in limbo land and in



Dr Jodie Ingles

many cases, those probably aren't likely to be resolved. Many of them likely don't have any real impact.

"They're almost a consequence of looking at too many genes.

"We now have people trying to grade VUSs. You can have suspicious VUSs – rare changes in genes that you know are very important – and they are the ones that you're trying to work on. You're reaching out to anyone else in the world who might have seen that particular variant.

"You have to build a case to say if the variant is causative or not, piecing together all these bits of evidence to see if the variant is pathogenic or benign. And then you can move it out of VUS Land."

The danger for patients lies in the possibility of misinterpreting that gene variant's significance, says Dr Ingles.

"In a regular genetic test for hypertrophic cardiomyopathy, for example, you might

look at 100-200 genes. Only 10-15 of those genes have decent evidence [for their causative effect]. It just takes one person to misunderstand and act on information on one of those variants in a gene with no association ... it's a double-edged sword.

"You have to be careful about what you feed back [to the patient's family]."

Dr Ingles believes she's found her perfect job and can't see herself moving away from her current roles.

"I've found the perfect mix of clinical work and working with the families. You come across research questions that give you the chance to address unmet needs.

"The clinical work helps keep you sharp and working on the most important things. Being the one both doing the research and having the conversation with the families ... it changes the way you're able to talk with them.

"Being able to communicate that complicated information, that even we

struggle to understand, to families who don't have a degree like we do but need to make important medical decisions based on that information ... it's a unique skill and there's not many professions who do it well, but it's the focus of our training.

"This is it for me."

Cate Swannell

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Podcast with Jodie Ingles available at <https://www.mja.com.au/podcasts>

Correction

In our 2 July issue we inadvertently omitted Dr Alastair Robert Jackson from the list of Queen's Birthday honorees. Dr Jackson was awarded an AM (Member in the General Division) for "service to the performing arts, particularly to opera, through a range of governance roles, and as a patron and benefactor". The *MJA* apologises for the oversight.