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The lottery of genetics

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It's Saturday morning, which means pancakes. After a long drive out to the quiet suburbs of regional Victoria, I arrive too late for the pancakes — but I am where I need to be. Down a wide street, past an oval with cricketers, is the home of Sandra and her family. Underneath a precious family portrait, one of Sandra's 'short kids' smiles to welcome me. I'm taking Sandra out to lunch to discuss how she and her family became known to medical specialists the world over, and how her remarkable story has made it into this book.

Sandra grew up knowing there was a genetic condition in her family — haemophilia. Her father had always been a bleeder. She had seen him bruised from simple play with her and her siblings. He stayed weeks in hospital after relatively simple operations. From a young age, she'd known that half her sons would be bleeders too.

Despite this, Sandra had always wanted a big family. Smiling down from that portrait I saw the seven beaming faces of Sandra's kids. Three of those smiles live on only in memories and photographs. Two others are in the room with me, but I know their life expectancy is, at best, one third of their mother's and mine.

In the luck of the genetic draw, Sandra's family have pulled a very short straw.

Sandra carries the gene responsible for haemophilia A . One of her X chromosomes contains a mutation in the blood clotting factor VIII gene, while her other X chromosome is clear. This means that Sandra is a carrier and can be unaffected or mildly affected, but the risk is to her sons. Each son has a 50% chance of inheriting haemophilia via her affected factor VIII gene. But this is not a story about haemophilia. It is the story of how, over 35 years, Sandra came to find out that haemophilia A wasn't the most insidious disease hiding out in the combined genetics of her and her husband.

Sandra also has a fault in one of her two *BRCA2* genes, most known for its association with breast and ovarian cancer. This has meant regular screening for breast cancer and surgery to reduce her risk of ovarian cancer. She is a carrier of haemachromotosis too, a genetic disease of iron overload in the body. Most significantly for this story, both she and her husband Chris carry a copy of a faulty gene for mucolipidosis — an extremely rare and slowly progressive multisystem spectrum of diseases that affects all aspects of a child's development and significantly shortens their life expectancy. It is difficult to know the exact prevalence, but somewhere between 1 in 100,000 and 1 in 400,000 people have mucolipidosis.

Sandra and Chris don't have the disease, as they only have one copy of the mutated mucolipidosis-causing gene *GNPTAB*. They also have an intact, 'healthy' copy on each of their paired chromosome. Yet for each child they have, there is a 25% chance they will get the *GNPTAB* gene fault from both parents. Without a functional version of this gene the body isn't able to carry out normal metabolic functions. The disease is progressively debilitating, disfiguring and ultimately fatal.

Each child they conceived had a 1 chance in 4 of the disease. They fared much worse than the odds. Of Sandra and Chris's

seven children, five have been affected by mucolipidosis. Three have already died.

Sandra spoke with me about her life, her family and how her genes have changed what she expected of her life. She has faced an unavoidable conflict between her desire for a large family and the genes she can't change.

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Even though Sandra's father had what many would consider a debilitating condition, he would not let it stop him. If he wanted to do something, he'd do it and then deal with consequences. He never wore gloves at his job in a brickworks. Sandra's mother was very concerned by his rough-house games with the kids, but Sandra recognised that he just wanted to be normal. She's tried to do the same thing.

Her father was open and honest about what his doctors had told him about haemophilia. He was the first in the family with it, presumably a spontaneous mutation in the egg from which he arose. She thus learned that she carries a copy of the gene, and that half her sons would likely be bleeders.

The second eldest of seven children in a European immigrant family, Sandra expected that her role in life was to be a wife and mother to many children. She drew plans for a big hacienda-style house with 14 bedrooms, the rooms of which she hoped to fill with her own children — and perhaps some foster children and orphans. Aware of her haemophilia gene fault, she never wanted to have boys. Sandra simply desired what everybody else wanted — normal healthy children.

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Sandra looked after her younger siblings from an early age. In Grade 7, while her mother was in hospital having her sixth

child, her father gave Sandra the ongoing task of cooking dinner for the family. She did so every night until she left home several years later. Sandra finished school after Grade 10, unable to return after a long bout of glandular fever. After a year working as a live-in nanny for a family in Melbourne, she returned home and began studies to work as a nurse in her local regional hospital.

At age eighteen, while a nursing student, her father took her and several relatives to Melbourne for genetic testing. Not only did she carry the gene, but her factor VIII clotting levels were low — making her a symptomatic carrier. As a nursing student she had access to medical literature and began educating herself about haemophilia.

Still she dreamed of having a large family.

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Sandra met Chris, a young man working for her uncle, when he was 'conned' into being her escort for a night out. Fiercely independent, she didn't feel she needed a chaperone, but once they met it was clear they got along. They did even better than get along — soon enough they were married.

They started their family knowing the risk of haemophilia, but were not expecting their first born, a girl named Judith, to be anything but healthy.

Judith didn't develop like other babies. By six months of age her development was delayed, and by nine months she began treatment for dislocated hips. At 15 months her orthopaedic specialist suspected other possibilities and referrals began. A neurologist believed it wasn't a purely neurological problem, yet an MRI showed her brain was degenerating and already shrunken. Unusual pigmentation around her eyes had Judith and her five-week-old sister Tara sent to a head and neck

specialist, who quickly booked both girls into hospital for rounds and rounds of testing.

They say a mother's instinct is never wrong and Sandra believes she knew that whatever Judith had, Tara also had.

Months later, Chris and Sandra were confronted with the diagnosis. Their daughters had a genetic disease called mucolipidosis type II (also known as Leroy's I Cell Disease) and wouldn't walk, talk or be toilet trained. They would be extremely lucky to live to their teens.

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'This has never been in our family before' was the first thing Sandra's mother-in law said when they heard about the diagnosis — implying that Sandra must be responsible. Sandra explained the recessive nature of the rare disease and that it hadn't been in her family either. It didn't help. An inherited genetic condition can do that. Blame is passed and felt deeply within families. Sandra had dreaded passing on haemophilia but wasn't prepared for this.

Denial and avoidance plagued Chris in the early months. He was adamant nothing was wrong with his girls. He told Sandra he didn't want any more children and didn't want to return to the doctor who gave them the diagnosis.

After their next children were born, twins Carol and Louis, Sandra and Chris would have to wait months for genetic testing to come back. Chris wanted a vasectomy. Sandra wasn't ready to complete her family. She couldn't sign the papers to consent for the vasectomy. In those days, the hospital wouldn't do it without her permission.

It was a difficult time for them. Chris went to his family and Sandra felt proverbial daggers when she came to bring him home. A sister-in-law voiced her outrage that Sandra would

consider having more disabled children. That wasn't her intention, Sandra explained. All she wanted was what everybody else had, a garden-variety baby. She wanted her dream family.

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The family was living in regional central NSW and were doing their best to get the right care for their children. Early intervention programs weren't offered in their town, and so Sandra travelled with another mother with a disabled child to a larger town multiple days per week. Once the twins arrived Sandra knew she couldn't keep doing that.

Fortunately she met the right person at the right time and successfully sought and gained funding for a local early intervention program.

She'd been told early intervention would be a waste of time for her girls. Yet her experience demonstrated otherwise. The kids were developing better than predictions for their grim trajectory. For instance, they could walk, and were toilet trained.

The paediatrician who shunned the idea of early intervention now told Sandra she'd taught him that it works. Doctors hadn't been so responsive in that manner before and Sandra now recognised some welcome humility in the profession. She appreciated the acceptance of not having all the answers and was not threatened by that.

What else would help her children? She and Chris had many questions but as the condition was so rare, it was hard to find answers.

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The girls were first diagnosed in 1984, and at that time information wasn't a quick Google search away.

She asked her paediatrician how to learn more about this most challenging condition. Sandra had always been an avid reader, eager to learn, and resourceful. So, proactively, she requested information sheets and even pursued academic papers, and was provided one or two each appointment. She'd already joined the Australian Society for Mucopolysaccharide and Related Diseases and found the Canadian, UK and American societies and requested their newsletters too. The United Kingdom was at the forefront of using bone marrow transplant as treatment, and the United States was always advertising trials for families to join.

The evolving understanding of mucolipidosis and related diseases meant that, at times, Sandra was even able to provide information to her doctors. She travelled to the United States to attend a conference and returned with the cassette tapes of the talks as a present to her paediatricians.

In 1985 Australia held its first conference on mucolipidosis and related conditions. There she met families with children of similar ages with similar life expectancies. It was a sobering experience though — children who had surpassed milestones would rapidly deteriorate. Was this exactly what she would face?

Sandra's kids had medical appointments for their own care but also so that they could be closely tracked and studied by their doctors. It was becoming clear that they didn't fit easily into the categories of mucolipidosis first described and more likely had an intermediate milder condition. This was confirmed 15 years later.

Getting her kids to appointments in the city was a logistical feat on the best of days, yet attending the extra appointments was crucially important to Sandra. She wanted to be part of improving the understanding of mucolipidosis so future

families could be spared some of the uncertainties she faced and had to endure.

One hundred years ago, conditions like mucolipidosis were called gargoylism. Over the years, different syndromes (clusters of symptoms) were named after the doctors who described them. Now, given the precise genetic understanding of the separate conditions, we are relieved of the use of crude terms such as gargoylism, and different symptoms and syndromes can be addressed in more measured and informative terms.

Today, Sandra doesn't go to the doctor expecting answers. From the very start there were no easy answers and many predictions were proved wrong. Her relationship with doctors isn't a 10-minute consultation, it's a rapport requiring development over months or years. Having a knowledgeable and sympathetic someone to talk to about what she is going through is of immense help to Sandra, and by extension to her family. She values an egalitarian approach where she is given access to scans and specialist's letters shared with her GP. That written information has been key. Sandra and Chris found that the emotions that came up during medical appointments meant they each remembered different, and sometimes conflicting, details.

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Sandra and Chris eventually had seven children. United as a family unit, they faced many people who simply could not relate to the complex issues facing the couple, particularly why they chose to have additional children knowing the risks involved.

Sandra explains that she expected some negative treatment from the community, but did not expect similar difficulties with their own families. Feeling deeply shunned, they decided to move their nuclear family, hoping for a more understanding social environment elsewhere.

Initially, they scoped out the services in their new town and found the allied health and support services and networks in their new home improved upon what they were used to.

Navigating the medical and social support systems, both local and in the nearby city, has been a challenge for Sandra, and she found only a few people who could help her find her way through the mazes. The family weathered changing governments and the funding of hospitals and programs that seemed to be always in motion.

Sandra's family's personal workload is enormous. During one particular month, they attended 150 medical appointments. Clearly Sandra is a force of nature, and I ask her how she copes with the many and varied challenges. She acknowledges she's a 'rescuer' and will always do the best she can to fix what needs fixing. No shrinking violet, Sandra says exactly what she is thinking, and while she says that might make her seem tactless, she feels justified in being focused on being the best advocate that she can be for her family and nothing less.

A realist, Sandra doesn't engage in self-pity. She knows she doesn't have many years with their 'short' kids and so does whatever she can to maximise each child's potential and quality of life on an unrelenting daily schedule.

The family celebrates every milestone, big or small. Humour and good cheer are important, at any cost! An 18th birthday party includes a cake in the shape of breasts with embarrassed blushing and hoots of laughter all around.

Sandra has friends who have similar life experiences. Their children may have different rare and complex diseases, but she and her friends can relate to each other's difficulties and successes, however small or fleeting. Always focused on their children, they debrief routinely about their experiences with specialists. Her new friends have helped Sandra fill in endless

Centrelink forms, and they provide the necessary sounding board for Sandra to work through new challenges.

Their family now includes the families who take in their 'short' children for needed respite. Their Christian faith also supports them on their sometimes lonely journey. The next generation of extended family are more tolerant — they visit their cousins without hesitation or judgement.

Sandra is straightforward with everybody, including her children. She and Chris use terms their children will understand and pictures to illustrate and frame things in a story format. Each child has a basic understanding of the disease in their bodies. They have also focused on making sure the children know their disease doesn't define them entirely and that their bodies are normal for them. The children are infused with the understanding that they are loved and accepted and that their parents are proud of them. Chris and Sandra don't shy away from the tough questions —- something Sandra learned from her father. Sandra tells me she can't run away from it and she needs her children to know what is facing them.

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Sandra has buried three of her children, aged 21, 23 and 14. She shares with me the story of each of their deaths. None of them have been alone. In their own ways, the kids accepted their mortality and Sandra and Chris have too.

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Sandra is currently studying a Dual Diploma in Community Services and Counselling. She accepts that when she no longer has children at home — when her two children living with mucolipidosis die — she may choose to go back to work. Her life experience has been in caring, both as a nurse and mother.

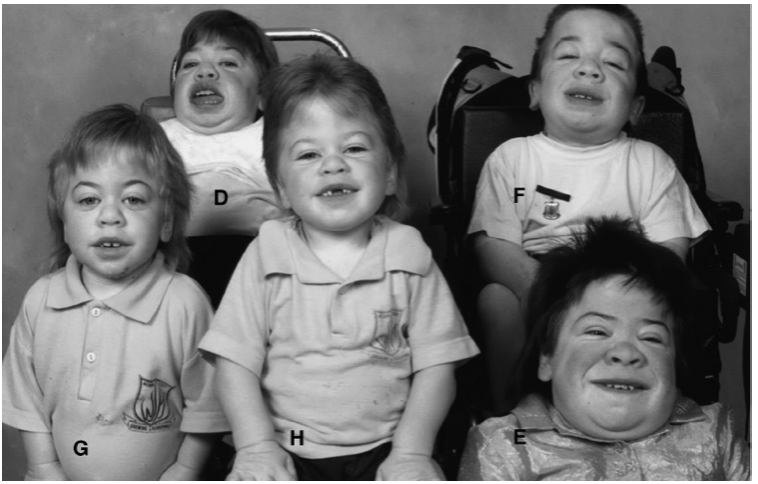
She believes this will make her a more empathetic practitioner and I couldn't agree more.

When she began nursing, Sandra remembers the focus only being on diseases you could cure. Those incurable conditions, like the one her children have, were neglected. She feels the pattern of care is now more solidly in the middle. There is more focus on supportive therapies and symptom management rather than only on curative intent. Doctors seem more comfortable letting the course of a disease happen and death to occur naturally.

Eventually, Sandra will once again be a valued member of the allied health professions supporting people who are unwell. Over the last 35 years, she's noticed a positive shift to more patient-focused care and collaborative decision making between patients, their families and their health care providers. She sees each experience and skill she has developed as an extra arrow in her quiver, an armoury she can count on when facing challenging times.

She didn't choose the genes that sent her family on such an extraordinarily difficult path. Rather, she has equipped herself with the knowledge and acceptance that supports her partner Chris and the children they love. Her family is much more than the genes they carry and that is what she celebrates every day.

So what is mucolipidosis? Mucolipidosis occurs because the person does not have sufficient quantity of a particular enzyme whose job it is to break down substances in cells. This leads to a build-up of these substances in cells and ultimately to the symptoms that occur. Affected tissues include skin, bones, joints and the heart. This slowly leads to damage to these tissues. Affected individuals are short, have characteristic facial features, joint stiffness and pain, and ultimately affected breathing and heart function that shortens life span. Intellect may or may not be affected.



Clinical features in five siblings. D: Patient 4 at 21.5 years; E: Patient 5 at 20 years; F: Patient 6 at 17.5 years; G: Patient 7 at 7.5 years; H: Patient 8 at 6 years.

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