The lethal gene (The Sydney Morning Herald)
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Genetic testing for the disease that killed their father took three sisters to hell and back. Their reactions, writes Jennifer Cooke, surprised even themselves.

IT WAS obvious the news was grim from the faces of the genetic counselling specialists. None of the usual cheery hellos greeted the three women as they were ushered into separate rooms at the Prince of Wales Hospital at Randwick two months ago.

As they held their husbands' hands the results of the predictive testing to confirm whether they had a potentially lethal genetic inheritance from their late father, Graham Brown, was delivered in unprecedented fashion - simultaneously to all three.

They wanted it that way. They couldn't bear telling each other their results and were torn between allegiances to each other and their spouses.

When it came, the news was worse than anyone expected. DNA analysis on the blood of two of them, Mandy Newton and Lisa Bayliss, was positive for the mutation that had killed their father. It was a virtual death sentence. Susan Sampson, the eldest, felt so guilty at her reprieve - a negative result - she felt worse than during the anxious eight-week wait leading up to this day, August 2.

When the news had sunk in, all involved emerged into a larger room where, as Lisa recalls, she was numb and "everyone else was crying".

Racked with survivor guilt already, Susan provided the only light relief.

"I even said that maybe Dad wasn't my father - I was thinking of Tony Abbott," she recalled last week. "And, of course, everyone laughed."

Back at Susan's house, Lisa told their mother, Ruth Brown, who had been waiting, alone, for the news.

"I thought there might be one of you," Ruth cried, "but I didn't expect two out of three. Oh dear!"

Graham Brown's hip replacement surgery at Toronto Private Hospital in May last year marked his family's descent into a world of fear and anxiety. After the operation they noticed the initial symptoms - his shocking pallor, confusion, memory loss, gradual loss of interest in previously pleasurable activities and an inability to perform daily tasks like choosing clothes or getting out of a car. A retired pharmacist and "the rock of the family", he died after a rapid deterioration into dementia and death in just three months from an extremely rare inheritable strain of the already rare Creutzfeldt-Jakob disease (CJD). CJD belongs to a group of diseases that are - uniquely - both infectious and inheritable, and known as transmissible spongiform encephalopathies (TSEs).

When the tentative diagnosis was made just weeks before Graham's death on August 23 last year from familial CJD (fCJD), other family members confirmed that one of his uncles had died from a TSE in 1965. Graham's policeman grandfather was only 47 when he died in 1931. Sketchy details were outlined in an obituary in a Central Coast newspaper, which seemed to indicate similar symptoms to Graham, his cousin and uncle. A further impact on Susan, Lisa and Mandy's decision to be tested was the death from fCJD of a first cousin of Graham's, aged 62, in January this year.

The German neuropsychiatrist Alfons Jakob published the first report of familial CJD in the Backer family of Germany in 1923. Since then more than 100 families have been identified in the United States, Slovakia, Hungary, Chile, Poland, Japan, Britain and in Libyan-born migrants to Israel. For about a decade genetic testing has enabled scientists to definitively distinguish between different TSE strains - there are three familial variants. Before that it was thought the lightly cooked sheep's eyeballs and brain favoured by separate clusters of sufferers in the former Czechoslovakia might have transmitted the ovine version of CJD (scrapie) orally, much like bovine spongiform encephalopathy (BSE) has been from British beef products.

Identical mutations on the prion protein gene now prove they all inherited the same disease. Familial CJD has very similar symptoms to sporadic CJD (see box), which kills about one person per million each year around the world. Of about 20 cases of

CJD referred to the Australian CJD Case Registry in Melbourne each year, two or three are likely to be familial.
As well there are at least 20 families in Australia affected by fCJD mutations. Marie Tehan, the former Victorian health minister, died last year of CJD, 20 years after her sister.
Familial CJD is among a group of rare adult-onset neurological conditions that can be fatal and for which predictive testing is available - but only to those people with a strong family history (parent or close blood relative) of the disease. The most well-known of these conditions is the degenerative illness Huntington's disease. Others are early-onset Alzheimer's disease and spinocerebellar ataxia.
According to the director of the Centre for Genetics Education, Dr Kristine Barlow-Stewart, these diseases follow an autosomal dominant pattern of inheritance.
"This means it can be inherited by either males or females, and if a parent has it there is a one-in-two chance that the child will inherit the faulty gene."
Barlow-Stewart said that for other more common conditions like familial cancers, some forms of breast and ovarian cancers, some forms of bowel cancer and melanoma, inheriting a faulty gene means only an increased risk of developing the disease. It does not mean a definite progression to the disease - mostly because cancer does not merely result from a single mutant gene but is affected by ageing and/or the environment.
Since learning their test results, life has changed irrevocably for Graham Brown's daughters. There were many steps involved, starting with Lisa's initial call to Royal North Shore Hospital's genetic counselling service early this year, referral from their GPs, visiting their father's neurologist in Newcastle, and meeting as a group several times with counsellors and geneticists. They were made to think hard about a decision that may bring mixed results, strong emotions and guilt.
While Susan and Mandy oscillated almost daily between having and not having the test, from the time of their joint decision to go ahead while visiting their father's grave just before Christmas last year, Lisa, 38, has never regretted her decision. She was "relieved" in a way that her gut feeling was proved right but at the same time pleased to have had the opportunity to find out if she was negative.
"So be it," she says philosophically. "I feel it was the responsible thing to do for our family and also for research into CJD."
Susan, 44, "most definitely" regrets being tested. "I feel like, even though we are still a family and we love one another and we still have bonds in other ways, I'm not part of this team," she says.
"Now that I'm negative people say to me: 'Well, what are you worried about?' They can't understand that I've got to worry about my sisters and my nephews and I still am - all the nightmares and everything - just about the whole thing . It's so new and fresh, and it's just like I can almost relive every moment from last August when Dad died. It's all such a part of me and I feel guilty that I've escaped it. I want to be part of it."
Mandy, 36, the driving force on a new familial section of the national CJD Support Group Network, also regrets wanting to know whether she is a walking time bomb, not knowing when the symptoms that follow the decades-long and variable incubation period may start. The mother of two little boys, she admits she is obsessed with dying of fCJD.
"And to watch someone [her father] suffer like that, someone that you love so much, is just really, really hard," she explained last week in an effort to reach other affected families that may need to talk. "Then the double whammy is thinking: 'I'm going to be there one day'."
Much of Mandy's non-parenting free time is now taken up with tasks associated with her recent appointment as the fCJD representative on the support group managing committee. The network is a Federal Government-funded group set up more than a decade ago in response to the deaths of Australians who received government-sponsored, CJD-contaminated pituitary-derived drugs to treat short stature and infertility. It has evolved into a group providing information to families on all types of CJD.

Mandy Newton, her sisters and her mother all want Graham Brown's legacy to be one of helping others in a similar situation. Although it is sometimes harrowing helping other grief-stricken family members come to terms with the disease's relentless progression to inevitable death, they feel it will be ultimately rewarding. They want to inform sufferers, affected family members and health-care workers about fCJD, which many doctors would never encounter in their entire careers.

While appreciative of the care and attention they received during their genetic counselling, it was obvious that fCJD was so rare that the experts had had to undertake intensive research themselves. Explaining to others why they wanted to know whether they had inherited the gene that had killed other family members was delicate. It was also time-consuming and sometimes complicated by understandable ignorance, including comparisons with the newest variant of the disease (variant CJD) stemming from mad cows in Britain, and other diseases that started with the letter "C".

Friends and family members worried about how to best support them. "And," says Mandy, "there is some sort of stigma attached to going mad. I think that's got a lot to do with it."

Mandy and Lisa will tell their boys about the mutant gene and how it may pass to them when they are older or start asking questions. Susan's children cannot inherit mutations on a gene that she does not have herself.

Reaching others who have "walked the same path" with fCJD is difficult, as the Australian CJD Case Registry cannot give out personal information.

"Privacy issues are a big stumbling block," admits Suzanne Solvyns, a national co-ordinator for the support network.

Facing a future in which discrimination will surely be an issue in relation to medical, surgical or dental needs that involve expensive instruments that may not be able to be sterilised adequately to neutralise the disease-causing prion, Lisa and Mandy may soon carry medical-in-confidence letters. These letters are carried with them to inform doctors and hospitals that they should not donate blood, tissue or organs because of their high-risk status in transmitting the disease through medical procedures.

Despite their fear for the future, there is hope Lisa and Mandy may live to see their grandchildren and beyond. Their paternal grandmother, Leila, tested positive to the same mutations as her son before she died in April this year. She was 88 and, after suffering from an unrelated dementia for some years, did not die of fCJD.

As the registry's head, Professor Colin Masters, explains, some people have "incomplete penetrance" of the gene, which means that the incubation period can be longer than that person's life span. "If you have the mutation you will almost certainly get the disease," Masters says.

"I get sad," Lisa says, "that maybe [her husband] Pete and I won't grow into old age together, but it has certainly made me look at life differently and appreciate it a whole lot more. I plan on it being quality if it may not be quantity."

Speaking for all her daughters, Ruth Brown adds: "If we can be out there to help promote this thing, public awareness, it's our role in life and Graham hasn't died in vain."

Mandy and Ruth's accounts of Graham Brown's illness can be found at http://www.cjdsupport.org.au/fcjdsupportgroup/fcjd/.

The inaugural meeting of the fCJD support group will be held in Melbourne on Saturday, November 12. For more information ring 1800 052 466.

Variations on a rare disease

CJD, first reported in the 1920s, is a Transmissible Spongiform Encephalopathy (TSE), or prion, disease.

Prion diseases are a family of human and animal diseases that include BSE in cattle, scrapie in sheep, transmissible mink encephalopathy in farmed mink, and chronic wasting disease in deer and elk.

CJD is closely related in humans to:

KURU: found in the eastern highlands of Papua New Guinea in the Fore people, who cannibalised dead relatives, in the 1950s, with spasmodic cases still occurring;
Gerstmann-Straussler-Scheinker syndrome: a familial variant of CJD first reported in 1936; and
Fatal Familial Insomnia: another familial variant of CJD with a noted sleeplessness symptom, first reported in 1986.
CJD strains or variants:
Sporadic (classic): infectious. Kills mainly elderly people at the rate of one in a million people per year. Cause unknown. First reported in 1920.
Familial: inherited. Runs in families with specific genetic variant, first reported in 1923.
Iatrogenic: infectious. First reported in 1974 (but dates back to historically verified cases in England in the 1950s). Transmitted via CJD-contaminated corneal grafts (at least three), surgical instruments (at least four), stereotactic electrodes (two), pituitary-derived human pituitary gonadotropin (four - only in Australia), pituitary-derived human growth hormone (more than 180), dura mater grafts (more than 130).
Variant: infectious. Since 1995, 180 people have died or are dying in Britain and elsewhere. Newest strain of CJD, comes from cattle rather than humans and is caused by eating infectious bovine brain-spinal cord material added for flavour and bulk to hamburgers, pies, stock cubes, consommes, sausages, pates, baby food. Incubation periods could mirror those of kuru (currently 40 years or more) or be longer than the human lifespan.
Story Picture: Portrait of sisters Mandy Newton left , Susan Sampson centre ,Lisa Bayless right .Chatswood, Sydney, NSW. Mandy and Lisa suffer with Creutzfeldt-Jakob a hereditary disease which their father died last year off.Today 21 October, 2005. NEWS.