Inquiry into the convictions of Kathleen Megan Folbigg

PART 2

CHAPTER 4: GENETICS

1. Significant advances have been made in the field of genetics since Ms Folbigg's trial. Those advances permit a much broader scope of investigation than was possible in 2003.[1]

2. Genomic sequencing technologies emerged in 2009. Since 2013, two major genomics sequencing technologies have become mainstream.[2]

3. Whole Exome Sequencing sequences the exome, which is that small part of the genome (approximately 1-2% of the whole) that is involved in coding for proteins. Proteins are the key components of cells and damage to them can cause serious, if not catastrophic, problems. This part of the genome is the location of the majority of the variants that cause developmental or cognitive disabilities and disorders.[3]

4. Whole Genome Sequencing sequences all of the genome that is accessible. In addition to the exome, this comprises non-coding elements in the genome and mitochondrial DNA.[4]

5. This technology enables hypothesis-free study of DNA where a known or presumed diagnosis as a starting point is not needed. Rather, DNA sequences are studied and variants are interrogated against the known healthy human genome and the phenotype or clinical features of a person.[5]

[1] Exhibit AA, Report of Dr Alison Colley (26 November 2018) p 2; Exhibit AB, Report of Dr Michael Buckley (25 February 2019) p 2.
[2] Exhibit AA, Report of Dr Alison Colley (26 November 2018) p 2; Exhibit AB, Report of Dr Michael Buckley (25 February 2019) p 1.
[3] Exhibit AA, Report of Dr Alison Colley (26 November 2018) p 2; Exhibit AB, Report of Dr Michael Buckley (25 February 2019) p 1.
[4] Exhibit AA, Report of Dr Alison Colley (26 November 2018) p 2; Exhibit AB, Report of Dr Michael Buckley (25 February 2019) p 1.
[5] Exhibit AA, Report of Dr Alison Colley (26 November 2018) p 2; Exhibit AB, Report of Dr Michael Buckley (25 February 2019)

6. In 2015, the American College of Medical Genetics and Genomics published Standards and Guidelines ("the ACMG Standards") for the interpretation of sequence variants, including assessing the pathogenicity of variants.[6]

7. The ACMG Standards refer to variants being "pathogenic", that is, causative of disease, "likely pathogenic", "of uncertain significance", "likely benign" and "benign".[7] This terminology was employed in the reports prepared for the Inquiry.

Available samples

8. Material produced to the Inquiry by the NSW Ministry of Health in compliance with summonses included samples containing DNA from each of the four children.

9. Blood spots taken from each of the children at the time of their birth as part of the Newborn Screening Program and held at the Children's Hospital Westmead were available.[8]

10. In respect of each of Patrick, Sarah and Laura, tissue samples taken at the time of their autopsies in 1991, 1993 and 1999 respectively and fixed in glass and wax block slides held at the Coroner's Court were also available.[9]

11. In respect of Patrick, additionally available were kidney, liver, skin, skeletal muscle and heart tissue samples taken at the time of his autopsy in 1991 and frozen at minus 80 degrees Celsius.[10]

12. In respect of Sarah, additionally available was one tube of extracted genomic DNA from fibroblasts, and two ampules of archived fibroblast cells stored in liquid nitrogen, held at the Children's Hospital Westmead.[11]

13. In respect of Laura, additionally held at the Children's Hospital Westmead was formalin-immersed brain tissue taken at the time of her autopsy in 1999.[12]

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p 2.
[6] Exhibit AC, Genetics tender bundle, p 170.
[7] Exhibit AC, Genetics tender bundle, p 170.
[8] Exhibit AC, Genetics tender bundle, p 190.
[9] Exhibit AC, Genetics tender bundle, pp 191-5.
[10] Exhibit AC, Genetics tender bundle, p 238.
[11] Exhibit AC, Genetics tender bundle, p 190.
[12] Exhibit AC, Genetics tender bundle, p 190.

14. In December 2018 the Inquiry was informed that Ms Folbigg had provided to her legal representatives a sample for the purpose of genetic testing.[13] Ms Folbigg consented to the sample being made available to the Inquiry for further genetic testing.[14]

Engagement of multi-disciplinary panel of experts

15. The interpretation of genetic data involves consideration of both the genetic pathology and the clinical presentation of a person. It is a single, but multi-faceted, interpretation process.[15]

16. Accordingly, the Inquiry gathered together a multi-disciplinary panel of experts to interpret and provide opinions about the data produced by the genetic testing undertaken for the Inquiry, and the available clinical information in respect of each of the children and Ms Folbigg.

17. These experts were associated with two separate laboratories with genetic sequencing interpretation capabilities: in Sydney and in Canberra.

18. Dr Michael Buckley is a genetic pathologist and clinical director of the NSW Health South Eastern Area Laboratory Services at the Prince of Wales Hospital in Sydney. He holds a PhD in the field of molecular genetics, obtained in 1991.[16]

19. Professor Edwin Kirk is a genetic pathologist and clinical geneticist at the NSW Health South Eastern Area Laboratory Services as well as co-head of the Centre for Clinical Genetics at the Sydney Children's Hospital. He has additionally trained in paediatrics and provides a cardiac genetics clinical service which focuses on adults and children with cardiomyopathies and disorders of cardiac rhythm.[17]

20. Dr Alison Colley is a clinical geneticist and the Director of Clinical Genetics Services for various local health districts in NSW. She has trained in paediatrics as well as clinical genetics. She is a conjoint Senior Lecturer at the University of New South Wales. Dr Colley is a renowned dysmorphologist.[18]

[13] Exhibit AG, Report of Professor Carola Vinuesa (2 December 2018).
[14] Transcript of the Inquiry, 15 April 2019 T404.3-11.
[15] Transcript of the Inquiry, 15 April 2019 T400.40-46, T410.28-411.8.
[16] Exhibit Z, CV of Dr Michael Buckley; Transcript of the Inquiry, 15 April 2019 T372.33-38.
[17] Exhibit Z, CV of Professor Edwin Kirk; Transcript of the Inquiry, 15 April 2019 T370.25-28, T370.35-47.
[18] Exhibit Z, CV of Dr Alison Colley; Transcript of the Inquiry, 15 April 2019 T373.39-50.

21. Professor Jonathan Skinner is a paediatric cardiologist and cardiac electrophysiologist working as a consultant at Starship Children's Hospital in Auckland, New Zealand. He is an Honorary Professor in Paediatrics, Child and Youth Health at the University of Auckland.[19]

22. Professor Matthew Cook is a professor of medicine at the Australian National University, and a practising clinical immunologist at Canberra Hospital. He is also co-director of the Centre for Personalised Immunology at the Australian National University, and medical director of the Canberra Clinical Genomics laboratory.[20] That laboratory is accredited to conduct bioinformatics analysis of DNA and RNA sequences, such as those produced by Whole Exome Sequencing or Whole Genome Sequencing.[21]

23. Professor Carola Vinuesa is an Australian National Health and Medical Research Council Principal Research Fellow, and Professor of Immunology at the Australian National University. She is also the chief scientist at the Canberra Clinical Genomics laboratory of which Professor Cook is the medical director. Together with Professor Cook, she is also the co-director of the Centre for Personalised Immunology.[22]

24. Professors Cook and Vinuesa were assisted by Dr Todor Arsov, a visiting fellow at the Centre for Personalised Immunology. He holds a PhD in biomedical sciences and a Masters of Genetic Counselling.[23]

Testing process

25. The Inquiry held three consultation meetings at which the interpretation panel experts discussed the options for genetic testing on the produced samples.

26. On the basis of these discussions, Whole Genome Sequencing was conducted on:

    a. DNA extracted from a frozen liver tissue sample from Patrick;

    b. DNA extracted from fibroblasts from Sarah;

[19] Exhibit Y, CV of Professor Jonathan Skinner; Transcript of the Inquiry, 15 April 2019 T369.8-9, T369.13-21.
[20] Exhibit AF, CV of Professor Matthew Cook; Transcript of the Inquiry, 15 April 2019, T366.19-25.
[21] Exhibit AF, Joint report of Canberra genetics team (29 March 2019) p 4.
[22] Exhibit AF, CV of Professor Carola Vinuesa; Transcript of the Inquiry, 16 April 2019 T460.15-18.
[23] Exhibit AF, Joint report of Canberra genetics team (29 March 2019) p 6; Transcript of the Inquiry, 16 April 2019 T462.19-21, T462.25-26.

c. DNA extracted from a blood spot sample from Caleb; and

d. DNA extracted from the sample from Ms Folbigg.[24]

27. Whole Exome Sequencing was conducted on DNA extracted from a blood spot sample from Laura, which was unsuitable for Whole Genome Sequencing because of microbial contamination of the sample.[25]

28. The Australian Genome Research Facility conducted the sequencing on the samples of Sarah, Patrick and Ms Folbigg. The Victorian Clinical Genetics Service conducted the sequencing on the samples of Caleb and Laura.

29. Professor Kirk gave evidence that:

> *I think it's remarkable that it was possible to perform testing of this type on these samples, and the resulting data quality was good... I don't know that something like this has been attempted before, at least not in this kind of context, and the outcome was that we got very high quality data that was able to be interpreted.*[26]

Analysis and reports

30. At the NSW Health Pathology Genetics Laboratory at the Prince of Wales Hospital in Sydney, variant analysis of the sequencing data was conducted through a genomic analysis bioinformatics pipeline called the Genomic Annotation and Interpretation Application.[27]

31. At the Canberra Clinical Genomics laboratory, variant analysis of the sequencing data was conducted through a separate bioinformatics pipeline.[28]

32. Ultimately, each laboratory analysed the same data and the same genes. Almost 1,400 unique candidate genes were identified for analysis.[29]

33. In addition, the data was re-analysed considering:

[24] Transcript of the Inquiry, 15 April 2019 T403.24-T404.1; Exhibit Z, Joint report of Sydney genetics team (29 March 2019) p 4.
[25] Transcript of the Inquiry, 15 April 2019 T407.3-20; Exhibit Z, Joint report of Sydney genetics team (29 March 2019) p 4.
[26] Transcript of the Inquiry, 15 April 2019 T407.36-44.
[27] Exhibit Z, Joint report of Sydney genetics team (29 March 2019) p 6.
[28] Exhibit AF, Joint report of Canberra genetics team (29 March 2019) p 3.
[29] Exhibit AW, Genes lists.

a. cardiac/non-cardiac genes which had been published in relation to sudden death in infancy/childhood;

b. genes associated with childhood neurological disorders;

c. genes associated with immunology;

d. genes associated with metabolics; and

e. likely pathogenicity in any phenotype not restricted to sudden death in infancy/childhood.[30]

34. It was agreed by the expert panel that the ACMG Standards would be used for assessing the pathogenicity of variants.[31]

35. All experts involved in the interpretation of the sequencing data were provided with documents relevant to the phenotype or clinical presentation of the children and Ms Folbigg.[32] The phenotype or observable clinical features of the children is of healthy, well grown, normally developing children who are normal in appearance, each of whom suffer a catastrophic event leading to death in three of them, and severe neurological sequelae in the fourth child which precedes his later death.[33]

36. The relevant medical history and results of historical and other recent cardiac-related investigations on Ms Folbigg have been considered by the experts in the interpretation process.

37. Dr Buckley, Dr Colley and Professor Kirk ("the Sydney team") prepared a joint report interpreting the significance of genetic variants, identified through the Sydney pipeline, present in the children and in Ms Folbigg and potentially relevant to the children's causes of death ("the Sydney report").[34]

38. Professor Cook and Professor Vinuesa, with the assistance of Dr Arsov, ("the Canberra team") prepared a joint report and a supplementary report interpreting

[30] Exhibit Z, Joint report of Sydney genetics team (29 March 2019).
[31] Transcript of the Inquiry, 15 April 2019 T402.25-31.
[32] See generally Exhibit AC, Genetics tender bundle.
[33] Exhibit Z, Joint report of Sydney genetics team (29 March 2019) p 5; Transcript of the Inquiry, 15 April 2019 T367.26-30, T381.9-382.21.
[34] Exhibit Z, Joint report of Sydney genetics team (29 March 2019) p 6.

the significance of genetic variants identified through the Canberra pipeline ("the Canberra report").[35]

39. Professor Skinner prepared a report specifically addressing cardiac-related variants in the children's and Ms Folbigg's genes as reported by the Sydney and Canberra pipelines, and the cardiac-related clinical presentation of each of them.[36] Upon receipt of additional cardiac testing information in relation to Ms Folbigg, he prepared a supplementary report and provided a further advice addressing the results of the additional testing and Ms Folbigg's clinical presentation.[37]

The phenotype

40. It became clear during Professor Vinuesa's evidence that she was not satisfied that there was sufficient clinical information about the children and Ms Folbigg and that this accounted for the Canberra team assigning different scores using the ACMG Guidelines.[38] Professor Vinuesa also gave evidence that she did not consider using the ACMG criteria was appropriate.[39] By contrast, the Sydney team comprising three clinical geneticists and/or pathologists (including one with specific cardiac and metabolic experience), and one paediatric cardiologist, were confident of the phenotype[40] and in applying the ACMG Guidelines.[41]

41. It was suggested to Dr Colley that:

> *MORRIS SC: …In relation to the phenotypes, we talked about phenotypes yesterday, and to that extent is it a fair comment - I know that the postulated phenotype has been sudden infant death, unexplained infant death, for the purpose of everybody's analysis. And is it fair to say that because of the breadth of the phenotype it's a little difficult from a genetic point of view to target genetic investigation or not really?*
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> *WITNESS COLLEY: … The phenotype is not only both sudden unexpected early death, but also normalcy. The children were well grown, appeared normal, did not have any dysmorphic features, did not have any birth defects or malformations, were meeting their milestones, and then had a*

[35] Exhibit AF, Joint report of Canberra genetics team (29 March 2019) p 3.
[36] Exhibit Y, Report of Professor Jonathan Skinner (31 March 2019).
[37] Exhibit BJ, Further report of Professor Jonathan Skinner (24 April 2019); Exhibit BK, Letter from Professor Jonathan Skinner to the Inquiry (30 April 2019).
[38] Transcript of the Inquiry, 16 April 2019 T475.8-12.
[39] Transcript of the Inquiry, 16 April 2019 T504.31-33.
[40] Transcript of the Inquiry, 16 April 2019 T480.9-19, T520.5-14, T520.30-33.
[41] Transcript of the Inquiry, 17 April 2019 T579.1-18.

catastrophic acute onset life threatening event. Now, because of that we don't have a particular disease phenotype that we were targeting, so that's why we used Whole Genome Sequencing and when we couldn't, Whole Exome Sequencing, to look with as much breadth as possible at all possible genetic causes of being entirely normal and then having a catastrophic event.

So no, I think that phenotype was quite clear because it was so consistent between the four children, including Patrick up to four and a half months…[42]

We haven't found something in a phenotype which is not in the genotype or vice versa, and that would have worried us if we'd had inconsistency. We would definitely have gone back and done further testing, or worried about what that might have been, but we didn't find any inconsistency.[43]

42. There was also a question whether the unavailability of Craig Folbigg's DNA rendered the results of the genetic testing less reliable. The following evidence was given:

WITNESS BUCKLEY: Rather surprisingly it didn't have much effect. We did not identify any variant in the children that we were concerned about that appeared to have been inherited from Craig, and the interpretation did not hinge on his clinical state.

WITNESS KIRK: Yeah, I'd agree with that. If, if upfront we had had the option, we would certainly have preferred to do that because there is a possibility of a mechanism for which interpretation would require both parents. But in the end it didn't make any difference.

WITNESS COLLEY: Yes, I'd agree with what's being said, and I was pleased that I had had an opportunity to meet him in person, so I did know that he was of normal statute, normal intelligence and normal appearance.[44]

43. Dr Colley was also asked whether the absence of other members of the Folbigg family gave rise to uncertainty as to the phenotypes so as to render the results less reliable:

WITNESS COLLEY: No, I don't think so. I think if we had found a possibly pathogenic or likely pathogenic variant, that we wanted to trace or we

[42] Transcript of the Inquiry, 17 April 2019 T553.19-38
[43] Transcript of the Inquiry, 17 April 2019 T554.23-26.
[44] Transcript of the Inquiry, 15 April 2019 T404.28-44.

say segregate through the family, then it would have been a disadvantage not to have DNA from other family members. But as such, as you've heard we didn't actually identify such a variant, so therefore we didn't need the DNA from the other family members.[45]

Findings

44. The findings of each of the teams were almost identical. Neither found variants in genes which were assessed as pathogenic or likely pathogenic in all four children so as to cause their sudden death.[46]

45. The Sydney report identified nine variants worthy of close examination. After analysis, five were deemed variants of uncertain significance (including CALM2), two were considered benign and one was classified as likely benign. The final gene they determined had no definite association with a disease (MYH6). They concluded none of the variants identified were deemed causal for the phenotype in the children.[47]

46. The Canberra report identified two variants as being likely pathogenic (IDS [found in Patrick] and CALM2 [found in all but Patrick and Caleb]), and one borderline variant of uncertain significance or likely pathogenic (MYH6 [found in all but Sarah]), which were missense novel or ultrarare variants that could contribute to the observed phenotypes found in the children.[48]

47. Professor Kirk gave the following reason for these three variants being interpreted slightly differently by the Sydney and Canberra teams:

I think this highlights the difference of approach. Professor Vinuesa is a very experienced and eminent researcher and is, I guess, approaching this in the way that you might approach a research project, thinking about possibilities, expanding the different, the different areas of knowledge that we currently have. Whereas our approach is more focused on known disease associations.[49]

[45] Transcript of the Inquiry, 15 April 2019 T404.50-405.5.
[46] Exhibit Z, Joint report of Sydney genetics team (29 March 2019) p 8; Exhibit AF, Joint report of Canberra genetics team (29 March 2019) p 13.
[47] Exhibit Z, Joint report of Sydney genetics team (29 March 2019) pp 8-9.
[48] Exhibit AF, Joint report of Canberra genetics team (29 March 2019) p 13.
[49] Transcript of the Inquiry, 16 April 2019 T514.38-43.

CALM2

48. CALM2 was present in Sarah, Laura and Kathleen and not present in Caleb and Patrick. The clinical presentation associated with the gene is a severe form of Long QT syndrome.[50] Professor Kirk gave the following evidence:

> *WITNESS KIRK: Kathleen Folbigg does not have clinical features that would be consistent with any of the known manifestations of the condition. It is true that we could not exclude the possibility of [CPVT] in her without additional testing, but then that would not be consistent with infant deaths in the family because it's a less severe form of the condition, and also, as I say, associated with death while awake, usually during exercise…*
>
> *And yes, it is conceivable that there could be something that is completely outside the experience we've had so far, but I think we're addressing current knowledge and within current knowledge I think I feel quite strongly that we can apply BS2, which makes this a variant of uncertain significance, because we've got conflicting evidence, and one where the weight of evidence is against it being pathogenic, but I accept that there are limitations to our knowledge and it's not inconceivable that this could prove to be relevant to the death of two of the children. I think very unlikely but not inconceivable.*[51]

49. On the basis of the results of exercise testing conducted on Ms Folbigg and received after the oral evidence, Professor Skinner concluded he was confident Ms Folbigg does not have CPVT and found no evidence of Long QT syndrome or significant ventricular arrhythmia.[52]

50. Professor Skinner gave a further reason for not assigning this variant as being likely pathogenic: that it has not appeared in any study of SIDS victims.[53]

51. Professor Vinuesa's evidence at its highest is that she "would not feel comfortable with excluding its potential for pathogenicity" on the basis that it is "conceivable" that the mutation in Ms Folbigg was non-penetrant, that is, not yet manifested.[54]

[50] Exhibit Z, Joint report of Sydney genetics team (29 March 2019) p 12.
[51] Transcript of the Inquiry, 16 April 2019 T471.8-13, T482.16-23.
[52] Exhibit BK, Letter from Professor Jonathan Skinner to the Inquiry (30 April 2019) p 1; Exhibit BJ, Report of Professor Jonathan Skinner (24 April 2019) pp 3-4.
[53] Transcript of the Inquiry, 16 April 2019 T474.29-41.
[54] Transcript of the Inquiry, 16 April 2019 T476.10-16; T479.9-10.

MHY6

52. The MYH6 variant was present in Kathleen, Caleb, Patrick and Laura Folbigg. The MYH6 variant was not present in Sarah Folbigg.

53. Professor Kirk gave evidence, with which Professor Skinner agreed:[55]

> *So, interpretation of this variant, the starting point has to be understanding the relationship between the gene and a relevant condition... Now, there is a great deal of evidence linking changes in this gene to congenital heart disease and also to cardiomyopathy. But we know that the children do not have congenital heart disease and nor does Kathleen and there is no evidence of cardiomyopathy on any of the post-mortems. In any case, it would not present at this very early age, and there's no evidence on echocardiogram in Kathleen Folbigg of a cardiomyopathy. So, those phenotypes are not really relevant.*[56]

54. Professor Vinuesa was asked whether she would defer to Professor Kirk's opinion, given their respective areas of expertise:

> *WITNESS VINUESA: Yes, with one comment. That, again, many of these cardiac problems manifest for the first time with sudden unexpected death and may be autopsy negative. So, with that, I still think we have to take into consideration variable expressivity and the potential for alternative pathogenic mechanisms.*[57]

Cardiac variants generally

55. Professor Skinner also gave evidence about the "top" gene variants which were *not* identified as present in any of the children and which have been associated with sudden infant death:

> *Genes that have been associated with sudden infant death. For example, SCN5A, sodium channel disease, this is not found here. Triadin, autosomal recessive, this causes severe disease, could potentially cause cardiac death in infancy. CACNA1C, that's not here and caveolin is another one. So the four top genes that I came into, in terms of causing infant - sudden infant cardiac death and no, no significant variants, no variants have been*

[55] Transcript of the Inquiry, 16 April 2019 T487.1-23; Exhibit Y, Report of Professor Jonathan Skinner (31 March 2019) p 9.
[56] Transcript of the Inquiry, 16 April 2016 T483.3-12.
[57] Transcript of the Inquiry, 16 April 2019 T487.28-32.

produced in this list and I find that an important thing to document at this stage.[58]

56. Professor Skinner concluded that the available clinical phenotype data and genetic analyses in respect of the children and Ms Folbigg provide no convincing evidence for the presence of any known form of cardiac inherited disease as a potential cause for the sudden death of the four children.[59]

IDS

57. The Sydney team excluded IDS from consideration primarily on the basis that there was strong evidence that Patrick, the only person with the variant, did not have the condition to which it relates, namely Hunter syndrome. In its supplementary report, the Canberra team stated that "we would defer to a metabolic disease specialist on this matter".[60] Professor Vinuesa was asked about the statement and gave evidence, "I think it would be good to consult with a metabolic expert for sure."[61]

58. Professor Kirk, a metabolic disease specialist, provided this explanation of the variant:

> *This relates to a condition called Hunter syndrome, which is a condition in which there is abnormal storage of material in a component of the cell called the lysosome and it's one of a group of, of lysosomal storage disorders. And the effect of this progressive accumulation of material is both enlargement of the tissues that are involved, but also damage to the function of some of the organs, particularly the brain.*
>
> *This is a condition which is not always clinically obvious in the first year of life, although there may be features present as early as birth, but they are generally not the most distinctive features of the condition.*
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> *The reason that we felt confident in excluding this from consideration is that a very - two very sensitive biochemical tests had been done which were not consistent with the diagnosis and we were aware of that information. So, we, we, deemed that it did not need further evaluation…*

[58] Transcript of the Inquiry, 15 April 2019 T450.5-12.
[59] Exhibit Y, Report of Professor Jonathan Skinner (31 March 2019) p 10.
[60] Exhibit AY, Written response from Professor Carola Vinuesa and Professor Matthew Cook to written response of Sydney genetics team (12 April 2019) p 5.
[61] Transcript of the Inquiry, 16 April 2016 T489.29-30.

in addition, we had post mortem evidence that it was not consistent with the diagnosis…

And then, lastly, I would say that, as far as I can tell, none of the information I received about Patrick in any way connects this condition to the events of his life and death…

Look I think, possibly, your Honour, I should walk back slightly on what I said. I think there is a very remote possibility that this child had Hunter Syndrome. My confidence is more about whether this was the cause of his death. I'm extremely confident that this was not the cause of his death. So, I think it's very unlikely he had the condition and if he did, then it would not have been the cause of his death.[62]

Other variants

59. Professor Vinuesa gave evidence that there were three other variants in relation to which there was a "theoretical possibility" of causing the phenotype seen in the children: DMPK, ADAMT56 and SCLC12A9.[63]

60. The Sydney team did not consider any of the variants causative of the phenotype, largely because there was no evidence linking the genes to human disease.[64]

Limitations

61. The expert panel was asked about the limitations of the work they undertook given the rapidly progressing nature of the science.

WITNESS COLLEY: I think the likelihood, even in a decade's time that we would find something startlingly different is low, because of the Whole Genome Sequencing techniques that have been used and the quality of the data that we have been told about. Now in saying that, there is clearly going to be new technology and new interpretation, but at this stage, looking to the future as much as we can, I am not envisaging that we're going to have to redo all this in a different way…

Now our genomes aren't going to change that much, I don't think. I mean, there is natural selection, but I don't think we're going to see a change in

[62] Transcript of the Inquiry, 15 April 2019 T424.41-425.11, T427.28-30; 17 April 2019 T562.41-46.
[63] Transcript of the Inquiry, 16 April 2019 T499.48-500.14.
[64] Transcript of the Inquiry, 16 April 2019 T499; Exhibit AX, Written response from Professor Edwin Kirk and Dr Michael Buckley to joint report of Canberra genetics team (9 April 2019).

the genome and we've done the test hypothesis-free to interrogate the genome as much as we can.[65]

WITNESS BUCKLEY: … this is a multifaceted test with clinical components and laboratory components and interpretive components. The clinical component is going to be the same in another five years. The features of these – of this family is of well grown, developmentally normal children who have a sudden and catastrophic event, but without many features of a genetic disorder of early childhood onset. That clinical setting, together with the power of the Whole Genome Sequencing result in combination, I think means it is very unlikely that despite the advances and we will expect that there will be new diseases, but I think that the new diseases that are discovered are not going to be relevant to this clinical situation. So I - anything is possible but in my professional opinion I think that the likelihood in this particular situation is quite low…[66]

WITNESS KIRK: Yeah, I'd concur with my colleagues…

From what I've seen during my career, I think I agree, that it's, it's very unlikely that we're going to identify something in the future that will, that will explain this…[67]

WITNESS SKINNER: Yes. The principles aren't really going to change, I don't think. If you have four very young children who have a catastrophic event, then the parent, if they carry the same genetic marker, would not be expected to be alive…

we could come back here in ten years and have this same conversation. I think - this is really up for the Court to decide but we can speculate forever about what might be and what might happened and what experiments in mice might mean for the human being. Right now all we can look at what we know now or what we have reasonable confidence in knowing now and I, I think we're going to end up in, in a circular conversation unless we agree what the endpoint is here. I, I think the ideas that are put forward by Professor Vinuesa's team are great. It's, it's, it's a good thing to think laterally and to think wisely, multigene inheritance and so on, but at this stage we just don't have enough information about that to make meaningful judgments in, with the current knowledge of phenotype genotype data…[68]

[65] Transcript of the Inquiry, 15 April 2019 T432.46-50, T433.1-2, T433.13-16.
[66] Transcript of the Inquiry, 15 April 2019 T433.20-31.
[67] Transcript of the Inquiry, 15 April 2019 T433.35, T433.41-43.
[68] Transcript of the Inquiry, 15 April 2019 T433.48-50, T434.1; 16 April 2019 T524.9-20.

WITNESS BUCKLEY: … It's very unlikely that we're going to be able to retest all of these samples using a putative technology that comes along in another five years. I think the data we have are reliable. I think the very fact that our Canberra colleagues and ourselves analysed these data, using different approaches, similar, using different models, but very largely we came up with a very similar set of variants that we thought were plausible, that we were confident in, that we thought should be considered as part of this matter. I, I don't see that, that we're going to come up with a very substantially different view into the future unless there is some radical change in sequencing technologies in the next few years. We have what we have. These are the data that we are best able to explain.

They seem to be consistent between two groups by and large and where we depart is where - it's the different weighting and interpretation that we put on those, and I think to a degree some of the analysis reflects, says more about ourselves perhaps than about the data, that it reflects our different views. I think together the data presented by Professor Vinuesa, the data presented by us, are a remarkable snapshot of the genetics of this family at this time which we are trying to understand in the light of current knowledge.[69]

WITNESS VINUESA: I agree that in terms of technology, we will probably not come up with a substantial number of different variants, but we are only analysing 1% of the genome, we have not even considered 99% of the non-coding mutations. We know that - we have agreed that 50% of genetic conditions cannot be diagnosed today - of monogenic genetic conditions, and the expectation is that as soon as we have better tools to explore the significance of structural variants, other missense mutations in enhancers or cryptic supplies in sites throughout the genome might give us a, a whole new list of variants to look at.

Also, we are limited by current knowledge of genes and their function. We still don't understand how at least one third of the genes in the genome work or what their function is, so I expect that over the next few years there will be more genes that will have been implicated in cardiac disease, there will be more variants. So, I think the interpretation can significantly change in a few years, not the raw data. I agree with you, the technology will not change, the raw data will not change, but we will make better sense of it in a few years.[70]

[69] Transcript of the Inquiry, 16 April 2019 T529.7-25.
[70] Transcript of the Inquiry, 16 April 2019 T529.30-46.

Conclusion

62. We submit that the Judicial Officer can be satisfied that the samples obtained, the methodology used and the processes followed resulted in good quality data.

63. The Judicial Officer can be further satisfied that the process of filtering and prioritising the variants using:

    a. hypothesis free analyses;

    b. literature and database searches for sudden unexplained death in infancy, cardiac conditions and epilepsy;

    c. gene panel analyses on genes associated with:

        i. sudden death in infancy/childhood;

        ii. childhood neurological disorders;

        iii. immunology; and

        iv. metabolics;

    d. any variant annotated as pathogenic or likely pathogenic related to any phenotype; and

    e. chromosomal microarray analysis,

    has resulted in there being no reasonable possibility that the children had a known pathogenic or likely pathogenic variant which caused their death which was not identified by this exercise.

64. In our submission, the Judicial Officer can be satisfied that the absence of a sample from Craig Folbigg and limited information available about other members of the Folbigg family did not lead to uncertainty in the phenotype or about a particular variant and therefore detrimentally affect the reliability of the results.

65. There were three variants about which the teams differed in their interpretation. Each concerned matters within the expertise of clinical geneticists and cardiologists. Professor Vinuesa properly conceded Professor Skinner's expertise in relation to MHY6 and Professor Kirk's knowledge and training in IDS and did defer to them in respect of those variants. We submit that that expertise of

Professor Kirk and Professor Skinner should also be accepted and preferred in the interpretation of CALM2.

66. Those variants about which Professor Vinuesa considered a "theoretical possibility" existed of being pathogenic cannot by definition be considered to represent a reasonable possibility of causing the death of any of the children.

67. Accordingly, in our submission, the Judicial Officer should be satisfied that no variant was identified as being pathogenic or likely pathogenic in relation to the Folbigg children. It follows that there is no reasonable possibility that the death of any of the Folbigg children was caused by a recognised genetic variant.

68. The testing that was carried out is necessarily defined by the data identified and the processes and knowledge currently available. Any proposition that tomorrow more may be known and therefore there is a reasonable possibility that the children died from an as yet unrecognised genetic cause must be rejected. The phenotype will not change and the genome will remain unaltered. It is our submission that the Judicial Officer should accept the results obtained by this Inquiry and not adjourn for five years because of possible scientific advances which may or may not alter the findings made in 2019.