EXHIBIT Z

JOINT EXPERT WITNESS STATEMENT
Prepared by Dr Michael Buckley, Prof Edwin Kirk, Dr Alison Colley

- My name is Michael Francis BUCKLEY
- I have read the Expert Witness code of Conduct provided to me, and I agree to be bound by it.
- I am an employee of New South Wales Health Pathology which is the NSW State public pathology service, with my work address being NSW Health Pathology Genetics Laboratory, Level 4 of the Campus Centre Building, Prince of Wales Hospital, Barker Street, Randwick NSW 2031.

- I have the following training, qualifications, experience and continuing professional development in Medicine and in the specialist field of Genetic Pathology:
  - Qualification list BHB, MBChB, PhD, FRCPA, FHGSA, FRCPath, FFSc
  - I graduated MBChB from the University of Auckland on 3 May 1984 and am an AHPRA-registered medical practitioner
  - Between January 1986 and December 1990 I was the Anti-Cancer Council Medical Postgraduate Fellow in the Dept of Pathology and Immunology at Monash Medical School, conducting a joint training program in research molecular genetics together with the pre-Part 1 examination component of pathology training with the Royal College of Pathologists of Australasia (RCPA).
  - I graduated PhD from Monash University in the field of molecular genetics on 22 March 1991.
  - Between January 1990 and December 1991 I completed two years of advanced training for the RCPA in cancer genetics/cytogenetics at the Victorian Cancer Cytogenetics Service.
  - I was admitted to Fellowship of the RCPA on 28 September 1991.
  - I was awarded an NHMRC Australian Postdoctoral Fellowship based at the Cancer Biology Division of the Garvan Institute for Medical Research commencing in 1992
  - I was certified as an associate cytogeneticist by the Human Genetics Society of Australasia (HGSA) on 22 August 1994.
  - I was recognised by the Health Insurance Commission as a specialist pathologist on 1 January 1997.
  - I was appointed as a staff specialist and head of genetic pathology by NSW Health's South Eastern Sydney Area Health service on 9 January 1997, and was regraded to senior staff specialist on 13 October 2003.
  - I was admitted to the Fellowship in molecular genetics of the HGSA on 9 July 2002.
  - Between the 09/05/2008 – 31/12/2011 I held a Marie Curie International Fellowship in the Department of Human Genetics at Radboud University Nijmegen Medical Centre in the Netherlands, awarded by the Science Directorate of the European Union
  - I was admitted as a founding Fellow of the Faculty of Science of the RCPA in January 2011
  - I was admitted to Fellowship of the Royal College of Pathologists in the United Kingdom on 26 January 2012.
  - I have continued to be employed by NSW Health Pathology as the Clinical Director of the Genetics laboratory at Prince of Wales Hospital since my return to my substantive position from the Netherlands on 2 January 2012.
  - I am compliant with the AHPRA requirements for Continuing Professional Development.
  - I have published 60 journal articles in the field of genetics
  - I currently hold the position of President of the Human Genetics Society of Australasia.

- My name is Edwin Philip Enfield KIRK
- I have read the Expert Witness code of Conduct provided to me, and I agree to be bound by it.
- I am an employee of New South Wales Health Pathology which is the NSW State public pathology service, with my work address being NSW Health Pathology Genetics Laboratory, Level 4 of the Campus Centre Building, Prince of Wales Hospital, Barker Street, Randwick NSW 2031. I am also an employee of the Sydney Children's Hospital network, with my work address being Centre for Clinical Genetics, Level 9 Bright Alliance building, Sydney Children's Hospital, High St, Randwick NSW 2031.

- I have the following training, qualifications, experience and continuing professional development in Medicine and in the specialist fields of Clinical Genetics and Genetic Pathology:

- Qualification list MB BS PhD FRACP FRCPA
- I graduated MB BS from the University of Western Australia in May 1990. I am an AHPRA-registered medical practitioner.
- I subsequently trained in paediatrics and clinical genetics at hospitals including Princess Margaret Hospital for Children in Perth, Western Australia; St Mary's Hospital in Paddington, London, UK; the Women's and Children's Hospital, Adelaide, South Australia; the Children's Hospital at Westmead, Sydney; and Sydney Children's Hospital. This included 12 months of training in inborn errors of metabolism as an Advanced Trainee in Adelaide.
- I completed training in clinical genetics and was admitted to Fellowship of the Royal Australasian College of Physicians (RACP) in December, 1998.
- Since March, 1999, I have been employed on a part-time basis as a Clinical Geneticist at Sydney Children's Hospital. My position was as a Staff Specialist until January, 2008 when I was promoted to Senior Staff Specialist.
- From 1999 until October, 2011, I was head of the Metabolic Diseases service at Sydney Children's Hospital. I have continued clinical involvement with this area, including participation in the after hours on call roster; since January, 2018 this has been a combined roster with the Children's Hospital of Westmead, with responsibility for the whole of NSW and the ACT.
- From 2000-2007, I undertook research in cardiac genetics based at the Victor Chang Cardiac Research Institute, leading to the award of PhD by the University of New South Wales in 2008.
- I have continued as an active researcher and clinician in the field of cardiac genetics since completion of my PhD. I provide a cardiac genetics clinical service, mainly focused on adults and children with cardiomyopathies and disorders of cardiac rhythm.
- I have continued an active research interest in cardiac genetics. My other areas of research have included metabolic diseases, epileptic encephalopathy and reproductive carrier screening.
- Commencing in August 2012, I trained in Genetic Pathology at the New South Wales Health Pathology Genetics Laboratory at Prince of Wales Hospital. I completed the Part I and Part II examinations of the Royal College of Pathologists of Australasia (RCPA) in 2015 and was admitted to Fellowship of the RCPA in February 2016.
- I have been employed as a Genetic Pathologist part time in the New South Wales Health Pathology Genetics Laboratory at Prince of Wales Hospital since August, 2016.
- I have been a Conjoint Appointee in the School of Women's and Children's Health since 1999. I was promoted to Conjoint Associate Professor in 2011 and Conjoint Professor in 2017.
- I was a member of the Specialist Advisory Committee in Clinical Genetics of the RACP (the committee responsible for the training of clinical geneticists) from 1999-2012, serving as Coordinator of Advanced Training from 2001-2006 and Chair from 2007-2012.
- I am currently the Chief Examiner in Genetic Pathology for the RCPA, having served in this capacity since December, 2017.
- I am compliant with the AHPRA requirements for Continuing Professional Development.

• My name is Alison Fiona COLLEY

• I have read the Expert Witness Code of Conduct provided to me, and I agree to be bound by it.

• I am employed by Liverpool Hospital, a public hospital under the NSW Ministry of Health, as a senior staff specialist Clinical Geneticist. I am the Director of Clinical Genetic Services for South Western Sydney Local Health District (LHD), Murrumbidgee LHD and Southern NSWLHD. My work address is: Liverpool Genetics service, Liverpool Hospital, Elizabeth Street, Liverpool NSW 2170

• I have the following training, qualifications, experience and continuing professional development in Medicine and in the specialist fields of Clinical Genetics:

• My qualifications are MBBS, FRACP MMedSc, Certified Clinical Geneticist HGSA.

I graduated from the University of NSW with MBBS in 1980; internship and resident medical officer years of 1981-2 were at Royal North Shore Hospital, St Leonards, Sydney. I started training in paediatrics at Prince of Wales Children's Hospital (now Sydney Children's Hospital) in 1983 and obtained my Fellowship of the Royal Australasian College of Physicians, in paediatrics in 1988. In 1986 and 1987 I began training in clinical genetics and in 1988 I did a fellowship at Royal Children's Hospital in Melbourne in genetic medicine. In 1989 and 1990 I was a research fellow in clinical genetics

at St Mary's Hospital, Manchester UK, under Professor Dian Donnai one of Europe's premier dysmorphologists and clinical geneticists.

In 1991 I was appointed as a staff specialist clinical geneticist in Hunter Area Health Service, Newcastle NSW. I worked full time in the Hunter Genetics Service and did a Masters in clinical epidemiology and biostatistics in University of Newcastle Centre for Epidemiology. I obtained a project grant with NHMRC to investigate children with developmental anomalies associated with chromosome 22q11.2 deletions.

In 1996 I accepted the role of staff specialist Clinical Geneticist to set up a genetic service at Liverpool Hospital, the premier teaching hospital for the population of South Western Sydney. Over the following 22 years I have developed and directed the Department of Clinical Genetics with various enhancements. A comprehensive clinical service is provided including fetal examination, reproductive genetics, paediatric and adult services with specialised multidisciplinary clinics in neurogenetics, immunogenetics, lipid disorders clinic, transition care for young people and in cardiac genetics. The Department includes staff specialist clinical geneticists, associate and certified genetic counselors, database managers and administrative officers and is in the Division of Medicine in the stream of Complex Care and Internal Medicine. There are 2 RACP college accredited training positions in clinical genetics and the only NSW Hospital to have a PGY2/JMO position in Clinical Genetics

I was a member of the NSW Ministry of Health, Genetics Services Advisory Committee (GSAC) from 1991 until 2016 when I became a member of the Clinical Genetics Executive Committee in The Agency for Clinical Innovation, MOH Health.

In 2014 I was invited to join the newly created NSW Genomics Think Tank, NSW Health Pathology, and participated meetings to help develop a framework to progress genomic testing and service delivery in NSW. Following that I have been a member of committees to progress the NSW Health Genomics Strategy published in 2017. I have supported Liverpool Hospital and SWSLHD becoming involved in various projects and grants, including the Australian Genomics Health Alliance (AGHA) under which the Department of Clinical Genetics has been included in 4 AHGA research flagships

I have been a member of the Human Genetics Society of Australasia (HGSA) since 1990 and I have served a term on its executive committee. I was the inaugural Chair of the Australasian Association of Clinical Geneticists, a special interest group of the HGSA.
I am a conjoint Senior Lecturer, University of New South Wales
Former editorial board member of the journal Clinical Dysmorphology
I have 50 papers in peer reviewed journals.
I am compliant with the AHPRA requirements for Continuing Professional Development.

1. Examinations Performed

Michael Buckley and Alison Colley were present at a directions meeting convened on Monday 10 December 2018 to discuss genetic analyses for the Inquiry.

Michael Buckley and Alison Colley have provided a separate statement that there is compelling evidence that changes in genomic knowledge, technologies and regulatory environment have the potential to provide information to the Inquiry that was not available in 2003.

At that meeting Prof Vinuesa provided information that the Victorian Clinical Genetics Service (VCGS) in Melbourne was establishing a technology to perform genomic studies on Guthrie cards. Michael Buckley contacted Prof Kathryn North (CEO and Director of the VCGS) by telephone during that meeting and established that VCGS would be in a position to assist with genomic analyses from Guthrie cards, but that that service had yet to be accredited by NATA.

Further investigations over following days determined that additional tissue and cells were available from two other siblings in the Folbigg family that might permit genetic testing to proceed.

The genomic analyses were split between two laboratories. DNA extracted by Prof Vinuesa's laboratory (KF), DNA from fibroblasts (SF) and DNA extracted from a frozen tissue block (PF) were analysed at the Australian Genome Research Facility (AGRF) in Melbourne as that laboratory holds NATA accreditation for whole genome sequencing (WGS) and chromosomal microarray (CMA) testing but does not have a validated protocol of WGS on DNA extracted from archival Guthrie cards.

Separately, two Guthrie cards from were provided to the VCGS for testing by WGS as this is a NATA accredited laboratory that had partially validated WGS on DNA extracted from archival Guthrie cards, and no other options for genomic testing existed in Australia. One Guthrie card yielded sufficient human DNA for WGS (CF). The other Guthrie card was found to have extensive microbial contamination and the DNA was unsuitable for WGS (LF), but the human DNA component of that mixture could be enriched and would be suitable for Whole Exome sequencing (WES).

2. Clinical Assumptions

The frequency of SUDI is currently in the range 1:2,000 to 1:5,000 livebirths in most countries (Duncan JR, Byard RW 2018, Univ of Adelaide Press) with point estimates of 1:2,000 in the US and 1:2,500 in the UK. The incidence of SUDI in Australia in 2016 was 94 out of 311,104 registered births (~1:3,300). SIDS represents 70%-80% of all SUDI.

Investigations of the percentage of SUDI cases aged under 1 year that can be attributed to monogenic causes are in the range 2-20% (PMIDs: 30268395, 30139991, 29544605, 29247119, 30086531, 29915097). In the majority of cases of a SUDI a genetic cause is not found.

Any putative genetic condition that resulted in four deaths in such young siblings would by definition have to be unusually severe. This implies either a recessive condition or gonadal mosaicism for autosomal dominant disorder in an unaffected parent. It is hard to reconcile such a severe phenotype with an individual being alive and well in their 50s; this goes far beyond the variability that we do observe in dominant conditions.

3. Phenotype in the sibship

Section 3 of this report relating to the phenotype of the 4 Folbigg children is based on the following information and documents, and was prepared by Dr Alison Colley.

A characteristic of genomic testing in complex disease is that the laboratory data must be interpreted in the context of the clinical presentation. The clinical phenotype and the laboratory results together can be considered to form a single testing process.

1 I (Dr Alison Colley) did not see any of the Folbigg children personally

2 I did meet Mrs Kathleen and Mr Craig Folbigg in 1991

3 Notes in the Hunter Genetics file HG-1564

4 Medical records on Patrick Folbigg, HAHS, Newcastle Western Suburbs Hospital 5-8/6/90, including ECG and echocardiogram 16/11/90
5 Letter to Dr Thompson from Dr Wilkinson 19/3/91, reply from Dr Thompson 25/3/91, reply from Dr Wilkinson 2/4/91
6 Cytogenetic report on Patrick Folbigg 8/4/91
7 Letter to Dr Colley from Dr Wilkinson 28/11/91
8 Letter from Dr Colley to Dr Wilkinson 27/2/92
9 Letter to Professor Bridget Wilcken from Dr Colley 4/12/91
10 Letter to Dr Colley from Professor Wilcken 10/12/91
11 Letter to Professor Wilcken from Dr Colley 27/2/92
12 Letter from Professor Wilcken 31/12/99
13 Report from professor Wilcken 14/1/00
14 Report by professor Berry 11/00
15 Report from Dr Brian Bailey, cardiologist 26/3/03
16 Report on Laura by Dr Chris Seton 4/3/03
17 Statement by Dr Hawker, aediatric cardiologist, 6/3/03
18 Statement of Jason Bendall on Laura 8/4/03
19 Report of Dr Owen Hugh Jones 15/4/03
20 Report by Professor Berry 29/4/03
21 Newborn screening reports for 4 children
22 Post mortem reports of 4 Folbigg children
23 Photographs of 4 Folbigg children
24 Letter from Dr Colley to the Inquiry 26/11/18
25 Documents produced by Justice Health on Kathleen Folbigg
26 Echocardiogram report Kathleen Folbigg 22/2/19

The below pertains to each of the 4 children, including Patrick prior to his initial unexpected event at 4 months, so I will report collectively:

1. There was no evidence of pregnancy related complications; all children had good Apgar scores at birth and normal birth weights
2. There were no congenital malformations noted at birth
3. Each child had newborn screening reported as normal
4. There were no dysmorphic features noted at birth or subsequently by any medical officer, including paediatrician and paediatric specialists when examination occurred.
5. Development was reported as normal for age for each child
6. Photographs on children were noted not to show dysmorphic features
7. All children were thriving at the time of their unexpected event (at 4 months for Patrick)
8. All of the children had normal growth parameters for their ages; there is no mention of small size or short stature
9. None of the children had a surgical operation or procedure
10. None of the children were admitted to hospital with a significant medical problem
11. None of the children were on continuous medication
12. None of the children were documented to have more than 8 respiratory infections a year
13. The retrieved blood spots on all the children were subject to tandem mass spectrometry with normal results, and negative for MCAD mutation testing.
14. Paediatric metabolic specialists, concluded that all children did not have evidence of an inborn error of metabolism
15. All children had autopsy examinations with no medical cause of death determined

I met Kathleen and Craig Folbigg in 1991, following the death of their first 2 children, and both parents agreed that Caleb and Patrick were normal health children prior to their sudden unexpected event, which was lethal for Caleb and resulted in severe subsequent neurological damage for Patrick. I have not met the parents subsequently.

Kathleen Folbigg
I (Dr Alison Colley) have read the reports and file notes from Justice Health on Kathleen Folbigg.

Kathleen had well documented high blood pressure and high cholesterol and triglycerides when she entered the Justice system, that were treated with a combination of lifestyle changes – weight loss/diet/exercise – and medications. This is very common in the population and not expected to cause death in children. There was no evidence of coronary artery or other vascular disease in the children on autopsy.

Kathleen had an ECG in 2011 and more recently in 2018 are both were normal– including normal QT measurements.

An echocardiogram in 2011was reported as normal as was a recent echocardiogram in February 2019

Only one EEG in 1989 which was reported as normal - I cannot read these myself so cannot comment on accuracy

I did not find any documentation of an episode of syncope with loss of consciousness, however, there was a report of Kathleen having an episode of dizziness and chest pain following an emotional episode. The Justice Health file mentions the possible diagnosis of the Takotsubo cardiac condition to explain her symptoms. This rare cardiac condition is not inherited and does not have a known genetic cause and does not cause death in childhood.

4. Variant Analysis

The data provided by AGRF and VCGS were: genome Variant Call Files (gVCF) based on genome sequence data mapped to the human reference genome build GRCh37, Binary Alignment Map (BAM) and Binary Alignment Index (BAI) files from a total of 5 individuals, 4 of which were whole genome sequencing and 1 of which was whole exome sequencing. Four analyses were performed at the Randwick Genetics Laboratory of NSW health Pathology on the data provided by the AGRF and VCGS.

The files were introduced without joint calling into the Genomic Annotation & Interpretation Application (GAIA) which is the Randwick laboratory's genomic analysis pipeline based on the open-source software Gemini developed by Prof Aaron Quinlan.

GAIA's standard settings were used to identify rare nonsynonymous heterozygous, homozygous, compound heterozygous and X-linked variants in the coding regions of any known gene (exons ±10bp of flanking DNA). The standard settings are based on Gemini impact (High and Medium impact variants), on allele frequencies of <1:50 in the ExAC/gnomAD, 1000 Genomes and NSWHP internal databases for homozygous and compound heterozygous models, <1:100 for X-linked models and <1:1000 for heterozygous models together with a threshold CADD score of 10. Variants were excluded if there were 3 or more records in the gnomAD database of the variant being present in homozygous or hemizygous form.

The normal population nucleotide variant frequency cut-offs used for this analysis of 1:50 for Autosomal Recessive - with up to 2 homozygote records; 1:100 for X-linked with up to 2 hemizygote records; and 1:1,000 for Autosomal Dominant with up to two heterozygous records are therefore very conservative in relation to the known frequency of SIDS in Australia of 1:3,300. The exclusion of variants with higher allele frequencies will not affect the sensitivity of the test to detect rare alleles causative of SUDI.

Each identified variant was viewed on two separate occasions in the Integrated Genomes Viewer (IGV) to determine whether it was likely to be a true variant or a sequencing artefact. Analysis was limited to those variants that were determined to be valid DNA sequence variants.

The evidence that a gene was able to cause the sudden death phenotype was evaluated according to laboratory criteria (Strande NT et al. (2017) PMID: 28552198).

Variant pathogenicity was assessed and categorised according following the joint consensus recommendations of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology for the interpretation of sequence variants (Richards et al. 2015 Genet Med. 17(5):405-24 PMID: 25741868); including some modifications specified in Amendola LM et al. 2016 (PMID: 27181684), Nykamp K et al. 2017 (PMID: 28492532), Tavtigian S et al 2018 (PMID: 29300386) and Abou Tayoun AN et al. 2018 (PMID: 30192042).

5. Limitations

Interpretation of the genomic results is limited to the information that is currently available. In particular the reference genome used in these analyses (GRCh37/hg19) may not be correct in all details, for example exons may be misidentified or omitted from this reference genome sequence. The results are based on DNA isolated from a specific tissues of various ages and states of preservation under the assumption that this tissue reflects the patient's germline DNA. In specific instances this assumption may be only an approximation, or may be incorrect.

Neither whole genome nor whole exome sequencing sequence all bases in the human exome. The variants identified in this report are limited to variants of 1-10bp in extent. Triplet repeat expansions, translocations, GC-rich and other low complexity repeat regions, pseudogenes or genes that show reduced mappability due to duplicate copies, mosaic variants, methylation changes and balanced genomic rearrangement events are currently not reliably analysed by genomic sequencing. Synonymous and imprinted variants are not systematically analysed currently, although these are known to contribute to disease in some individuals.

Not all disease-associated genes have been identified and the clinical significance of variation in many genes is not well understood. Published data indicate that the use of ACMG-AMP Guidelines for the interpretation of sequence variant pathogenicity improves the consistency of interpretation of variant pathogenicity, however up to 30% of variant pathogenicity interpretations remain discordant between laboratories.

The terms likely pathogenic and pathogenic refer to 90% and 99% likelihoods that a variant can be pathogenic when present in the appropriate zygosity. The terms likely benign and benign similarly refer to a 90 and 99% likelihood of a correct call that a variant is benign at the appropriate zygosity.

Pathogenicity of a variant does not directly equate with the presence of disease as zygosity, gene copy number, mosaicism, methylation, patient age, environmental and age related factors also contribute to the likelihood of disease presence.

RESULTS OF ANALYSES

1. Hypothesis-free Whole Genome/Exome Analysis

A total of 279 unique high confidence variants were identified in the data from the 5 genomic studies.
Of these 21 were present in all four siblings, 84 were present in 3 of the 4 siblings, 73 were present in 2 of the four siblings, 87 in a single sib, and 14 were not present in any child but were only present in the mother of the 4 children.

The 14 variants that were present only in Kathleen and not transmitted to her children were excluded from further analysis. In order to identify gene:phenotype associations among the 265 remaining variants searches were performed of the OMIM database using the HGSA gene symbol of the gene containing the variant, together with the following Pubmed searches:

(*HGVS SYMBOL*) AND ((((((((((sudden infant death) OR sudden unexplained death) OR SUDI) OR SUDEP) OR SIDS) OR arrhythmia) OR long QT) OR Catecholaminergic polymorphic ventricular tachycardia) OR CPVT) OR cardiac arrest) OR AV block) OR atrioventricular block) OR conduction abnormalities)

(*HGVS SYMBOL*) AND (((((congenital central hypoventilation syndrome) OR central hypoventilation) OR CCHS) OR ondine) OR autonomic dysregulation)

(*HGVS SYMBOL*) AND ((((((((((((((((((((Cardiomyopathy) OR Channelopathy) OR Cardiac) OR Epilep*) OR Hippocamp*) OR Myotoni*) OR Periodic paralysis) OR Conduction defect) OR Conduction disorder) OR Conduction abnormalit*) OR Brugada) OR Arrhythm*) OR Heart block) OR Atrioventricular block) OR Sodium channel) OR Atrial fibrillation) OR Ventricular tachycardia) OR Left ventricular non-compaction) OR Left ventricular noncompaction) OR Hypotonia)

(*HGVS SYMBOL*) AND ((((((((((((((((((((((((((((((seizures) OR arrest) OR ventricular fibrillation) OR ICV) OR ICVD) OR defibrillator) OR resuscitat*) OR heart) OR myocyte) OR congenital heart disease) OR Cardiomyopathy) OR Channelopathy) OR Cardiac) OR Epilep*) OR Hippocamp*) OR Myotoni*) OR Periodic paralysis) OR Conduction defect) OR Conduction disorder) OR Conduction abnormalit*) OR Brugada) OR Arrhythm*) OR Heart block) OR Atrioventricular block) OR Sodium channel) OR Atrial fibrillation) OR Ventricular tachycardia) OR Left ventricular non-compaction) OR Hypotonia) OR Respiratory control).

Of the 265 high-confidence variants

- 167 were excluded as extensive Pubmed and OMIM searches did not identify evidence of a Mendelian disease associated with the gene.
- 3 variants were excluded from further analysis as they were variants in genes associated with X-linked disorders whose clinical features are unrelated to the clinical presentation of the 4 deceased children
- 58 variants were excluded from further analysis as they were heterozygous variants for autosomal recessive disorders whose clinical features were inconsistent with the clinical presentation of the 4 deceased children
- 28 variants were excluded from further analysis as they were heterozygous variants for autosomal dominant conditions where the clinical features of the disorder are inconsistent with clinical presentation of the 4 deceased children
- 9 variants were selected for further characterisation as they were in genes where sudden unexpected death might arise. A summary of the findings is given here, with more detail provided in Appendices 1-9.

Variant	ACMG Categorisation	Present in
NM 003636.3(*KCNAB2*):c.31G>A | p.(Ala11Thr)	Variant of Uncertain Significance	CF, SF, LF
NM 001743(*CALM2*):c.340G>A | p.Gly114Arg	Variant of Uncertain Significance	KF, SF, LF
NM 001267550.2(*TTN*):c.79226G>A | p.(Arg26409His)	Likely Benign	KF, CF, PF, SF, LF
NM 001267550.2(*TTN*):c.36509A>T p.(Glu12170Val)	Benign	
NM 015093.5(*TAB2*):c.1345A>G | p.(Thr449Ala)	Variant of Uncertain Significance	KF, CF, SF
NM 006766.4(*KAT6A*):c.1138 1139delinsTC | p.(Glu380Ser)	Benign	KF, CF, PF, LF
NM 001038.5(*SCNN1A*):c.709T>G | p.(Phe237Val)	Variant of Uncertain Significance	KF, PF
NM 002471.3(*MYH6*):c.244C>T | p.(Pro82Ser)	No definitive association with disease	KF, CF, LF
NM 002230.4(*JUP*):c.578T>C | (p.Met193Thr)	Variant of Uncertain Significance	SF

After detailed review, none of the variants identified were deemed causal for the phenotype in these children.

2. Gene Panel Analyses

The data were reanalysed using a panel of **421 cardiac/non-cardiac genes** that had been published in relation to sudden death in infancy/childhood. These studies used a reduced CADD filter stringency (CADD of 0).

32 variants were identified in this analysis which were reviewed from this study using IGV visualisation and OMIM, Pubmed, and gnomad database searches (Appendix 10).

After detailed review, none of the variants identified were deemed causal for the phenotype in these children

Separately the data were reanalysed using a list of **204 genes associated with childhood neurological disorders** provided by Dr Michael Fahey (with an emphasis on epileptic encephalopathy). These studies used a reduced CADD filter stringency (CADD of 0).

8 variants were identified in this analysis which were reviewed from this study using IGV visualisation and OMIM, Pubmed, and gnomad database searches (Appendix 11).

After detailed review, none of the variants identified were deemed causal for the phenotype in these children

3. Pathogenic Annotation Analysis

The unfiltered annotated VCF file was also examined for all instances of the term "**PATH**" in the ClinVar Significance column. This was to detect any variant that has been annotated as **path**ogenic or likely **path**ogenic irrespective of the standard analysis settings. 'Pathogenicity' in this instance relates to ANY phenotype, and is not restricted to the phenotype of interest: sudden unexplained death in infancy/childhood.

8 variants were identified in 7 genes that have been termed pathogenic or likely pathogenic for a rare Mendelian disorder. Variants were excluded if they were reported to risk factors for a disorder, quantitative trait loci, or had high allele frequencies (Appendix 12).

After detailed review, none of the variants identified were deemed causal for the phenotype in these children.

4. Chromosomal Microarray Analysis

Analysis and reporting of the chromosome microarray data that was provided by the AGRF was performed at the Sydney Genome Diagnostics laboratory at the Children's Hospital Westmead by the head of the cytogenetics department Mr Dale Wright FHGSA FFSc.

The chromosome microarray data and reports of those analyses are provided separately.

APPENDIX 1: KCNAB2 VARIANT

chr1(GRCh37):g.6100659G>A

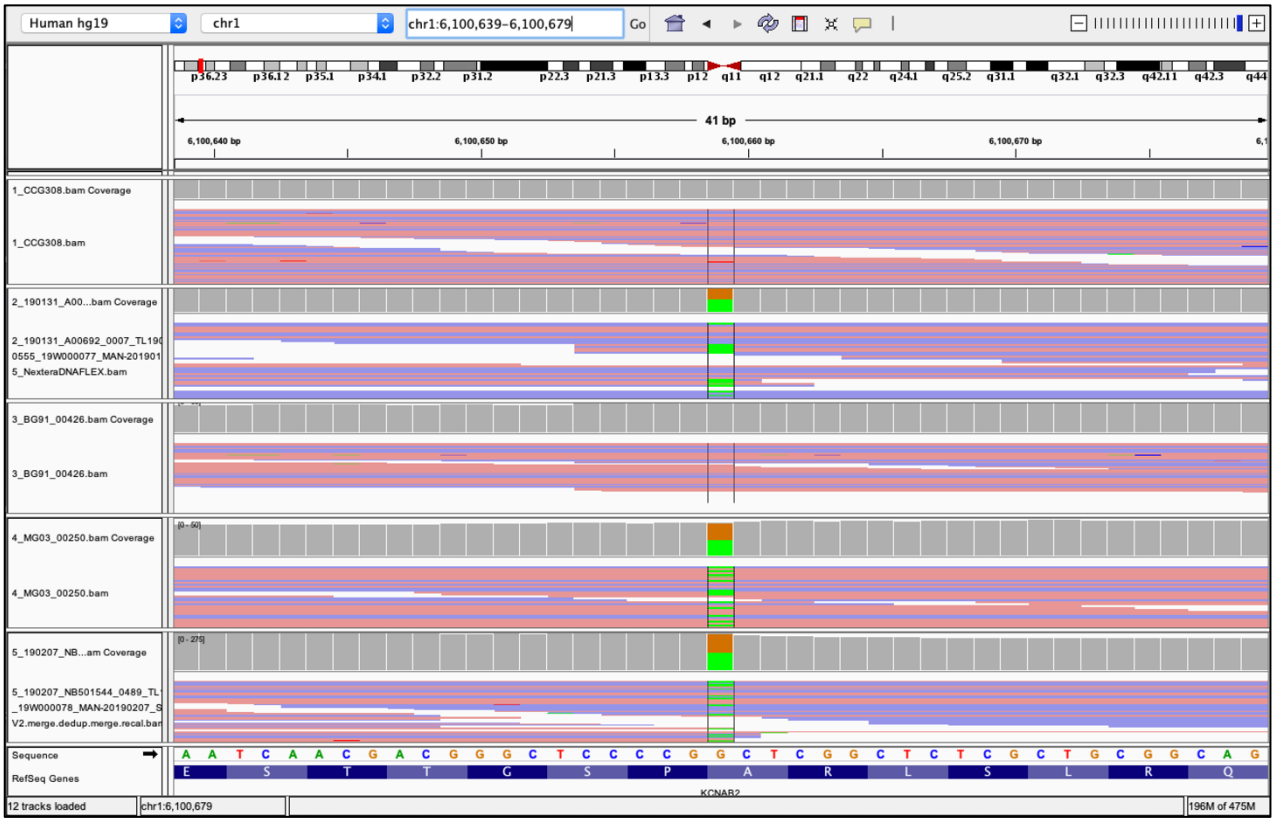
Canonical transcript: NM 001199862(KCNAB2):c.-5611G>A

Most expressed transcript: NM 001199861(KCNAB2):c.31G>A | p.(Ala11Thr)

Cardiac transcript: NM 003636.3(KCNAB2):c.31G>A | p.(Ala11Thr)

IGV Image

The KCNAB2 variant is present in Caleb, Sarah and Laura Folbiggs' samples. The KCNAB2 variant is not present in Kathleen or Patrick Folbiggs' samples. Based on these observations it is likely that this allele has been paternally inherited.



Gene: The Shaker voltage-gated K+ channels (Kv1 superfamily) control the efflux of K+ through cell membranes and, thereby, dampen membrane excitability. They are composed of KvAlpha and KvBeta2 subunits which associate in a hetero-octamer to form membrane pore. The regulatory subunit KvBeta2 subunit has sequence homology with aldoketo reductase enzymes and binds the nicotinamide cofactor. The beta subunit is known to modulate the channel's activity in a manner that depends on the redox state of the bound cofactor.

Clinical Review: Previously it was thought that deletion of KCNAB2 was the cause of epilepsy in the 1p36 deletion syndrome, but fine mapping of the region in affected individuals has consistently shown that loss of KCNAB2 is not necessary for epilepsy development. There is a single study of 2 families with Brugada syndrome where a p.(Arg12Gln) is documented. This association has not been replicated and the pathogenicity categorisation of the variant is overstated in the paper. Where an ECG had been performed, no member of the family had had a Brugada pattern.

Literature: The variant is absent from the ClinVar and HGMD (public) databases and does not appear to have been reported previously.

Population Frequency	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
European (Non-Finnish)	1	111366	0	1:111,366

Conservation

Alanine 11 is invariant among the 100 vertebrate genomes aggregated by UCSC Genome Browser.
The amino acid change is conservative, replacing a very small hydrophobic amino acid with a small amino acid with neutral hydrophobicity (Grantham score 58). KCNAB2 is tolerant to missense variation, with a gnomAD Z score for constraint being 2.6 (threshold value of Z=3).

In silico prediction tools are inconclusive regarding pathogenicity with 15/24 assessments calling the variant as likely deleterious (Varcards plus ClinPred).

SIFT	0.365	Tolerable	fitCons	0.632	Tolerable
Polyphen-2 HDIV	0.993	Probably damaging	GERP++	4.99	Conserved
DANN	0.996	Damaging	phyloP	7.861	Conserved
MutationTaster	0.992	Disease causing	phastCons	1.000	Conserved
MutationAssessor	0	Neutral	SiPhy	16.845	Conserved
FATHMM	0.78	Tolerable	REVEL	0.261	Tolerable
Eigen	0.475	Damaging	ReVe	0.541	Tolerable
VEST3	0.582	Damaging	GenoCanyon	1.000	Damaging
MetaSVM	-0.726	Tolerable	**ClinPred**	**0.813**	**Deleterious**
MetaLR	0.156	Tolerable	**CADD**	**24.4**	**Damaging**
M-CAP	0.068	Damaging	**Polyphen2 HVAR**	**.971**	**Probably damaging**
FATHMM MKL	0.960	Damaging	**PROVEAN**	**-0.58**	**Tolerable**

Protein Structure

The amino acid of interest (codon 11) does not lie in a known structural domain – the most amino terminal residue of the NADP-dependant oxireductase domains cited in Interpro is residue 26.

SUMMARY

The NM 003636.3(KCNAB2):c.31G>A | p.(Ala11Thr) is classified as a variant of uncertain significance as it has the following attributes:
PM2 - Absent from controls

APPENDIX 2: CALM2 VARIANT

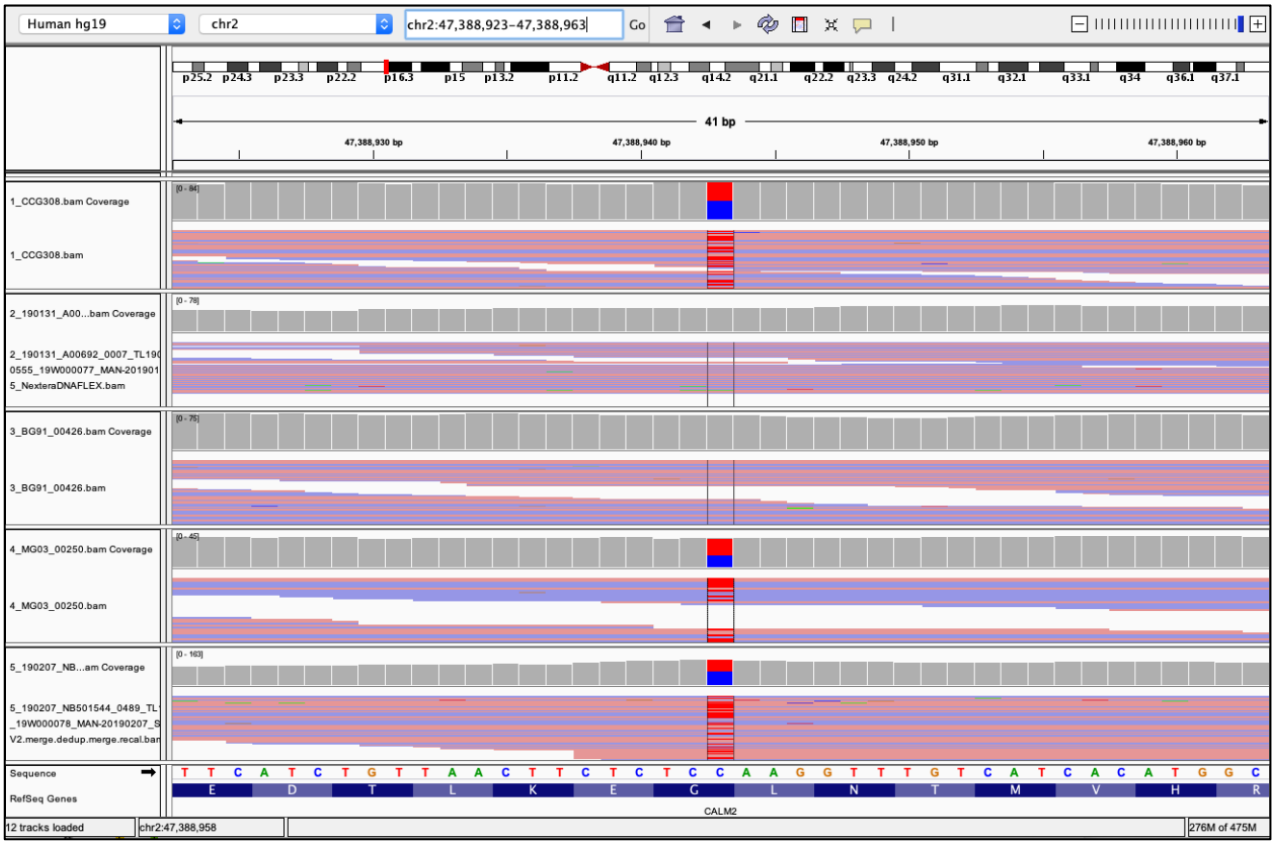
chr2(GRCh37):g.47388943C>T

Canonical transcript and transcript with highest expression:

NM 001743(*CALM2*):c.340G>A | p.Gly114Arg

IGV Image

The *CALM2* variant is present in Kathleen, Sarah and Laura Folbiggs' samples. The *CALM2* variant is not present in Caleb or Patrick Folbiggs' samples. This allele has been maternally inherited.



Gene: *CALM2* encodes calmodulin-2, which is one of three calmodulin genes that encode the same protein product. Calmodulin mediates the action of a variety of different enzymes, ion channels and other proteins via calcium-binding. In the context of cardiac rhythm disorders, the interactions with ion channels are particularly relevant. Evidence has been accumulating to support a relationship between variants in CALM1-3 and a severe form of long QT syndrome (LQTS), sufficient to meet the Clingen criteria for Strong evidence of gene-phenotype relationship (Strande et al, Am J Hum Genet 2017).

Clinical Review: CALM2-associated LQTS is an unusually severe form of LQTS. Where parental DNA has been available, all reported LQTS-associated variants have been shown to have arisen de novo.

The variant is absent from the gnomAD, ClinVar, HGMD (public) databases and does not appear to have been reported previously.

Glycine 114 is highly conserved in each of the 3 calmodulin genes, with no alternate amino acids among the 100 vertebrate genomes accessible through the UCSC genome browser.

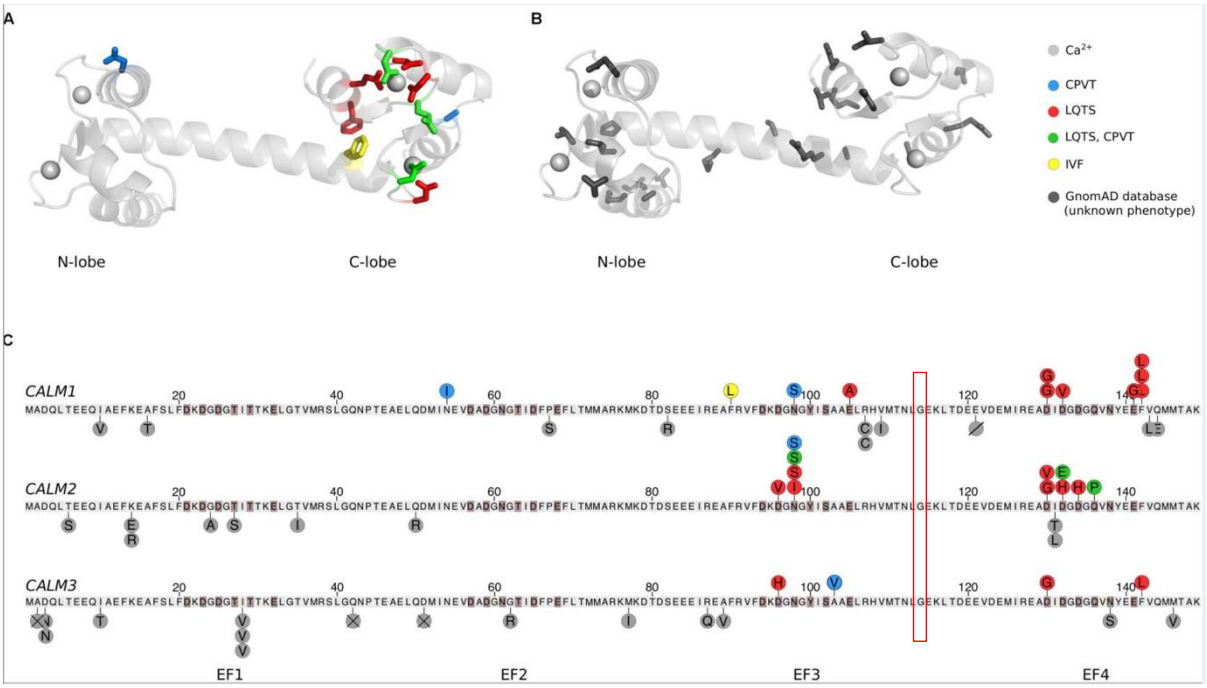
The amino acid change is moderately non-conservative (Grantham score 125), replacing a small, hydrophobic amino acid glycine with a large, charged amino acid arginine. CALM2 is relatively tolerant to missense variation, with a gnomAD Z score for constraint being 2.79 (threshold value of Z=3).

In silico prediction tools are supportive regarding pathogenicity with 21/24 assessments calling the variant as likely deleterious (Varcards plus ClinPred).

Pathogenicity/ Conservation Predictions: 21 out of 24 = supportive of pathogencity

SIFT	0.0	Damaging	fitCons	0.707	Damaging
Polyphen-2 HDIV	0.997	Probably Damaging	GERP++	5.74	Conserved
DANN	0.997	Damaging	phyloP	7.873	Conserved
LRT	0.000	Deleterious	phastCons	1.000	Conserved
MutationTaster	1	Disease causing	SiPhy	19.506	Conserved
Eigen	0.642	Damaging	REVEL	0.537	Damaging
FATHMM	0.47	Tolerable	ReVe	0.880	Damaging
VEST3	0.866	Damaging	GenoCanyon	1.0	Damaging
MetaSVM	-0.330	Tolerable	**ClinPred**	**0.996**	**Deleterious**
MetaLR	0.351	Tolerable	**CADD**	**31**	**Damaging**
M-CAP	0.236	Damaging	**Polyphen-2 HVAR 0.987**	**Probably Damaging**	
FATHMM MKL	0.988	Damaging	**PROVEAN**	**-5.8**	**Damaging**

Protein: The variant is located in the linker region between EF3 and EF4 and is not directly involved in coordinating Ca^{++} (see figure, Glycine 114 boxed in red). There is a very clear phenotype:genotype correlation with all but 1 reported pathogenic variant being located in the C domain of the CALM proteins and clustered within the EF hand structural motifs. Conversely variants observed in the normal population database gnomAD do not involve the EF hand motifs. The variant identified in Mrs Folbigg is located adjacent to variants present in unaffected individuals in the gnomAD database (see figure below) and lies outside the conserved EF hand domain in paralogous proteins.



Phenotype: The clinical features of affected patients reported to date are described below.
Note that normal QTc is <440ms in men and <460ms in women. QTc>480 at rest is considered strong evidence of long QT syndrome (LQTS), >500 is considered diagnostic if there is no secondary cause for prolonged QTc such as medications. Mean QTc in childhood is around 410ms.

Crotti et al 2013 [PMID: 23388215] describe 4 infants with recurrent cardiac arrest and 'dramatically prolonged QTc interval', three of whom had de novo variants in CALM1 and one of whom had a de novo variant in CALM2. This latter infant had fetal bradycardia observed during pregnancy, at 21 weeks of gestation, and an episode of 2:1 AV block observed at 28 weeks. Two hours following a normal delivery, the baby was noted to have sinus bradycardia, T-wave alternans, 2:1 AV block and markedly prolonged QTc (690ms). This patient then suffered cardiac arrest and multiple episodes of ventricular fibrillation (VF) from 3 weeks of age. An implantable defibrillator (ICD) was inserted and over the first two years of life she had numerous appropriate shocks from the defibrillator in response to episodes of VF.

Makita et al 2014 [PMID: 24917665] describe 5 individuals with de novo variants in CALM2, associated with LQTS in three and features of both CPVT and LQTS in the other two. Age of onset of symptoms was later in these children, with first major incident (syncope or cardiac arrest) from 1 – 9 years; some had documented ECG abnormalities from or before birth. Three had episodes of cardiac arrest. All had abnormal ECGs with markedly prolonged QTc, with the shortest measured in any of them while not on treatment being 478ms; the others who had ECGs off treatment all had QTc of at least 500ms. By contrast, it should be noted that although first symptoms in other forms of LQTS may occur at any age, cardiac events are most common in the second and third decades of life. For the most common forms of LQTS a substantial proportion of individuals with the condition never have any clinical manifestations as a result, and the lifelong risk of sudden death is generally <10%. So, although the phenotypes in the children reported in the Makita et al paper are overall less severe than in the other two publications, they are still much more severe than is typical for LQTS.

Boczek NJ et al 2016 [PMID: 26969752] report 3 individuals with CALM2 variants. One was found prenatally to have LQTS. Shortly after delivery, she had a QTc of 690ms, 2:1 AV block and T-wave alternans. Despite treatment with beta blockers she had a cardiac arrest aged 1 month, and had an ICD implanted. There was no family history of arrhythmias or sudden death; parental DNA was unavailable so it was not possible to determine whether the variant was de novo or inherited.

A second infant was noted to have bradycardia at birth. ECG at 12 hours showed QTc of 740ms and 2:1 AV block. She had multi-agent medical therapy, and later an ICD was implanted which subsequently discharged appropriately twice, despite ongoing medical treatment. There was no family history of arrhythmias or sudden death; parental DNA was unavailable so it was not possible to determine whether the variant was de novo or inherited.

A third infant was found to have 2:1 AV block in utero. QTc prolongation (QTc 800ms (!)) was documented at birth. Beta-blockers were started. He developed a restrictive cardiomyopathy in the second month of life; then developed torsades de pointes (an abnormal ECG pattern associated with CPVT and often leading to VF); he had sympathetic denervation, a treatment for CPVT, and insertion of an ICD. He also had two appropriate shocks in response to VF, one after missing a single dose of beta blocker. The variant was found to have arisen de novo.

SUMMARY

Variant Review: the CALM2:p.Gly114Arg is classified as a Variant of Uncertain Significance as it has the following attributes:

PM2 - Absent from controls
PP3 - Multiple lines of computational evidence support a deleterious effect on the gene or gene product
BS2 - Observed in a healthy adult individual

N.B. It is not considered appropriate to use the rule “PM1 - located in a mutational hot spot” as this variant is located outside of the EF-hand motifs where pathogenic variants cluster and is in a region where variants exist in normal populations.

APPENDIX 3: TTN VARIANT 1

chr2(GRCh37):g.179431633C>T (meta transcript)

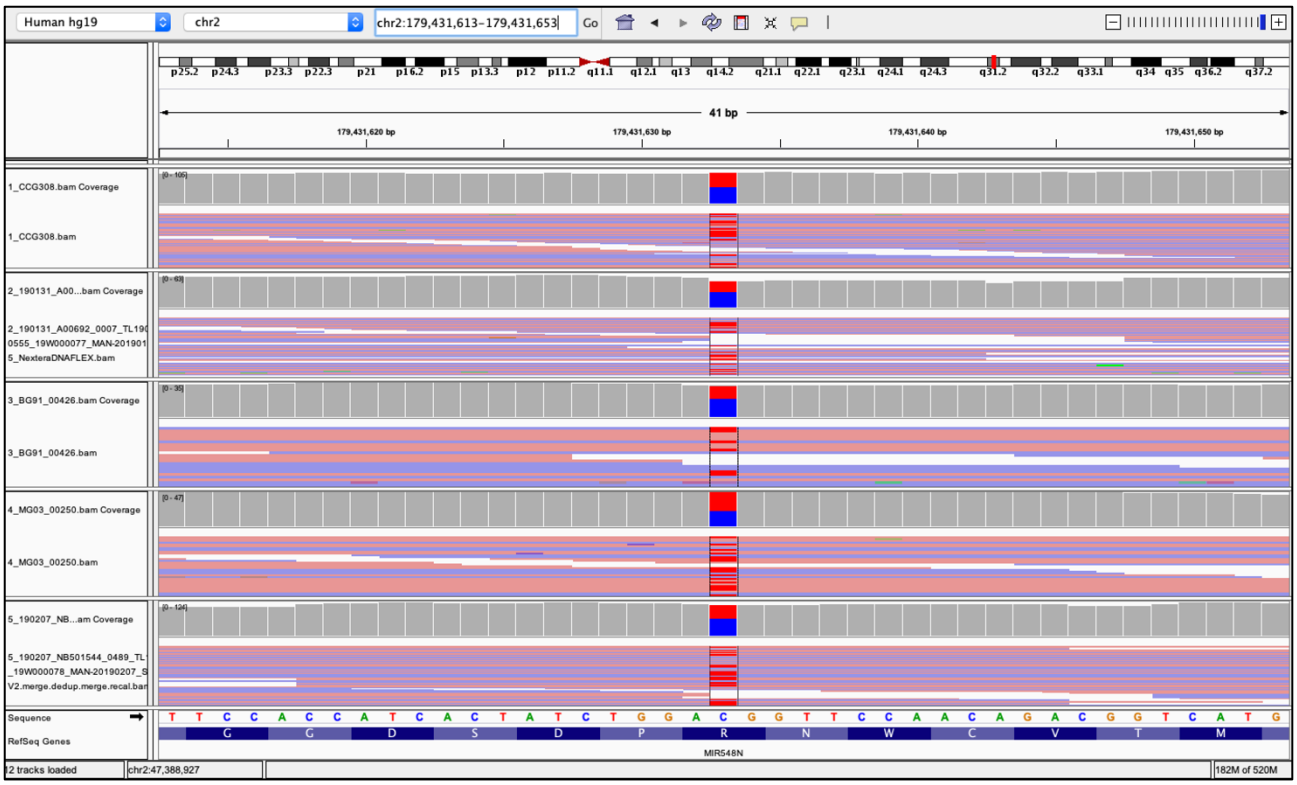
NM 001267550.2(TTN):c.79226G>A p.(Arg26409His)

N2BA (cardiac): NM 001256850.1:c.74303G>A | p.Arg24768His
N2B (cardiac): NM 003319.4:c.52031G>A | p.Arg17344His
Novex-1 (cardiac): NM 133432.3:c.52406G>A | p.Arg17469His
Novex-3 (cardiac): 3' non-coding
N2A (Muscle): NM 133378.4:c.71522G>A | p.Arg23841His

Exon 327 of 364, DCM % spliced in 100%, Average Exon % spliced in 95% [PMID 25589632 (Suppl Table 7)]

IGV Image

The variant is present in all individuals studied, Kathleen, Caleb, Patrick, Sarah and Laura Folbiggs' samples. It has therefore been maternally inherited.



Gene: Titin is a highly modular protein with ~90% of its mass composed of repeating immunoglobulin and fibronectin III modules that are interspersed with nonrepetitive sequences with phosphorylation sites, PEVK motifs, and a terminal kinase. The TTN gene encodes 364 exons that undergo extensive alternative splicing to produce many isoforms ranging in size from 5604 to 34,350 amino acids.

Clinical Review: Titin-truncating variants (TTNtv) are associated with a range of clinical disorders of skeletal and cardiac muscle. Heterozygous mutations that truncate full-length titin (TTNtv,) are the most common genetic cause of severe and familial DCM, accounting for about 25% of cases. TTNtv also occur in about 2% of individuals without overt cardiomyopathy, a value that exceeds the prevalence of nonischemic DCM by fivefold and poses significant challenges for the interpretation of TTNtv variants in the era of accessible genome sequencing. Critical parameters that distinguish pathogenic TTNtv and their mechanisms of disease remain unknown.

Literature: This variant has multiple entries in ClinVar with the following pathogenicity predictions

Clinvar entry	Phenotype	Categorisation
SCV000051444	Not provided	Likely benign
SCV000700929	Not provided	Uncertain significance
SCV000421614	Distal myopathy Markesbery-Griggs type	Uncertain significance
SCV000735882	Cardiovascular phenotype	Uncertain significance

SCV000542684	Multiple conditions	Uncertain significance
SCV000421609	Hypertrophic cardiomyopathy	Uncertain significance
SCV000421612	Myopathy, early-onset, with fatal cardiomyopathy	Uncertain significance
SCV000421611	Dilated Cardiomyopathy, Dominant	Uncertain significance
SCV000421610	Limb-Girdle Muscular Dystrophy, Recessive	Uncertain significance
SCV000421613	Hereditary myopathy with early respiratory failure	Uncertain significance

Population Frequency	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
European	127	127572	0	1:1004
Total	159	279566	0	1:1758

Conservation
Arginine 26409 is almost completely invariant in the 100 vertebrate genomes aggregated at the UCSC Genome Browser (two substitutions by Alanine).

There is a small physicochemical difference replacing the large, hydrophilic, amino acid arginine by histidine which is moderately sized and of neutral hydrophobicity (Grantham: 29). TTN is tolerant to missense variation, with a gnomAD Z score for constraint being -1.1.

In silico prediction tools are inconclusive regarding pathogenicity with 12/24 assessments calling the variant as likely deleterious (Varcards plus ClinPred).

SIFT	0.038	Damaging	fitCons	0.487	Tolerable
Polyphen-2 HDIV	1.0	Probably damaging	GERP++	4.87	Conserved
ReVe	0.548	Tolerable	phyloP	3.947	Conserved
Eigen	0.647	Damaging	phastCons	0.998	Nonconserved
MutationTaster	0.998	Disease causing	SiPhy	17.018	Conserved
MutationAssessor	2.03	Medium	REVEL	0.355	Tolerable
FATHMM	0.41	Tolerable	GenoCanyon	1.000	Damaging
DANN	0.895	Tolerable	FATHMM MKL	0.964	Damaging
VEST3	0.416	Tolerable	**CADD**	**23.4**	**Damaging**
MetaSVM	-0.303	Tolerable	**PROVEAN**	**-3.29**	**Damaging**
MetaLR	0.337	Tolerable	**Polyphen-2 HVAR**	**0.966**	**Probably damaging**
M-CAP	0.023	Tolerable	**ClinPred**	**0.0638**	**Tolerated**

SUMMARY
This variant is not a protein truncating variant and occurs at a significantly higher frequency in the general European population than the phenotype of Sudden Unexplained Death in infancy. No clinvar record indicates this is pathogenic, 1 says likely benign.

This variant is categorised as Benign as it has the following attributes:
BP1 - Missense variant in a gene for which primarily truncating variants are known to cause disease
BP6 - Reputable source recently reports variant as benign, but the evidence is not available to the laboratory to perform an independent evaluation
BS1 - Allele frequency is greater than expected for disorder
BS2 - Observed in healthy adult individuals

APPENDIX 4: TTN VARIANT 2

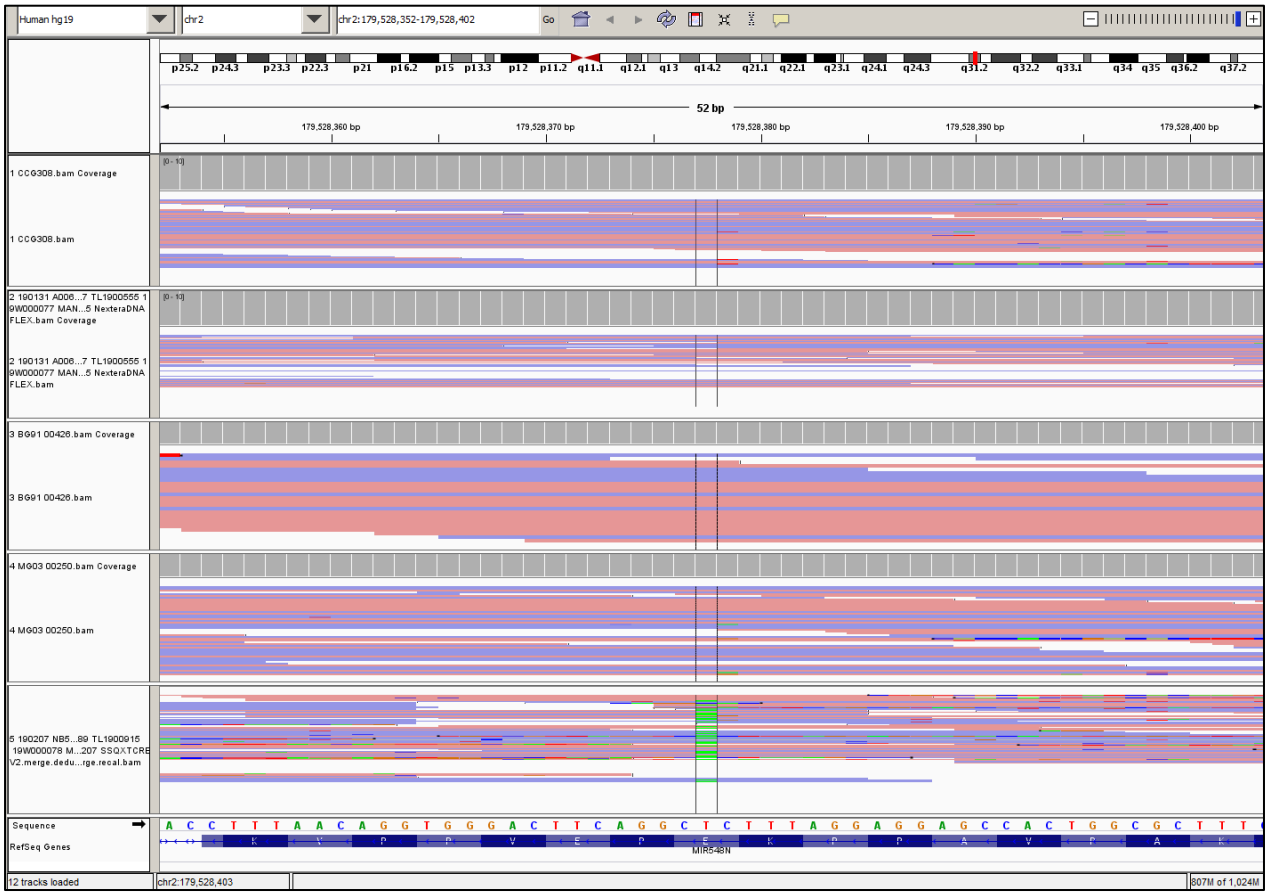
chr2(GRCh37):g.179528377T>A (meta transcript)

NM 001267550.2(TTN):c.36509A>T p.(Glu12170Val)

N2BA (cardiac): NM 001256850.1:c.34265-595A>T | p.(?)
N2B (cardiac): NM 003319.4:c.13283-21333A>T | p.(?)
Novex-1 (cardiac): NM 133432.3:c.13658-21333A>T | p.(?)
Novex-3 (cardiac): 3' non-coding
N2A (Muscle): NM 133378.4:c.31484-595A>T | p.(?)

IGV Image

The variant is present in Laura Folbigg's sample. The variant is not present Kathleen, Caleb, Patrick, Sarah Folbiggs' samples.



The variant is in the Exon 172 of 364 in the Titin meta transcript. This is a variably spliced exon with the DCM % spliced in being 7%, and the average Exon % spliced in is 28% [PMID 25589632 (Suppl Table 7)]

Population	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
Total	559	244120	1	1:436

The variant is recorded in Clinvar

ClinVar Record	Phenotype	Pathogenicity
RCV000172677.2	(not Provided)	Likely Benign/VUS
RCV000517437.1	(not provided)	Benign
RCV000231058.4	multiple conditions	Benign

SUMMARY

This variant is non-coding for all relevant transcripts. This variant is categorised as Benign as it has the following attributes:

BP6 - Reputable source recently reports the variant as benign
BS1 - Allele frequency is greater than expected for the disorder
BS2 - Observed in healthy adult individuals

APPENDIX 5: TAB2 VARIANT

chr6(GRCh37):g.149700396A>G
NM 015093.5(TAB2):c.1345A>G
p.(Thr449Ala)

IGV Image

The TAB2 variant is present in Kathleen, Caleb and Sarah Folbiggs' samples. The TAB2 variant is not present in Patrick or Laura Folbiggs' samples. This allele has been maternally inherited.

Loss of function pathogenic variants or haploinsufficiency of TAB2 can result in congenital heart defects (Thienpont et al., 2010). TAB2 deficiency can present in various degrees of severity and at different stages of life, even within the same family. People with TAB2 deletions also have a typical range of non-cardiac findings including: characteristic dysmorphic facial features, intrauterine growth restriction and/or postnatal proportionate short stature, hypotonia, developmental delay and/or intellectual disability, and connective tissue abnormalities. No-one in this family has evidence of structural congenital heart disease.

Gain of function missense variants in TAB2 are a cause of frontometaphyseal dysplasia, which is a sclerosing skeletal dysplasia clinically characterized by prominent supraorbital ridges, sclerosis of the skull, and dense, undermodelled cortices of the long bones and phalanges. A range of extraskeletal manifestations, such as progressive joint contractures, genitourinary tract defects, laryngeal stenosis, and hearing loss, significantly impact the health and wellbeing of affected individuals over their lifetime. No-one in this family had features of frontometaphyseal dysplasia.

Population Frequency	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
Total	3	246220	0	1:82,000

The variant is absent from Clinvar, HGMD (public) and has not been published in the medical literature

Threonine 449 is moderately conserved amino acid and is substituted by serine in several species in the 100 vertebrate genomes aggregated by the UCSC Genome Browser.

The amino acid does not lie in a recognised structural motif of the TAB2 protein. The mutant amino acid is smaller than the wild-type. The mutant residue is more hydrophobic than the wild-type. Overall there is a small physicochemical difference between threonine and alanine (Grantham dist.: 58 [0-215]).

TAB2 is tolerant to missense variation, with the gnomAD Z score for constraint being 1.61 (threshold value of Z=3).

In silico prediction tools do not support pathogenicity with only 7/25 assessments calling the variant as likely deleterious (Varcards plus ClinPred).

SIFT	0.293	Tolerable	fitCons	0.707	Damaging
Polyphen-2 HDIV	0.0	Benign	GERP++	3.05	Conserved
REVEL	0.090	Tolerable	phyloP	4.382	Conserved
LRT	0.000	Neutral	phastCons	1.000	Conserved
MutationTaster	1.000	Disease causing	SiPhy	10.336	Nonconserved
FATHMM	1.98	Tolerable	VEST3	0.111	Tolerable
MetaSVM	-0.995	Tolerable	MetaLR	0.010	Tolerable
M-CAP	0.007	Tolerable	ReVe	0.174	Tolerable
DANN	0.945	Tolerable	Polyphen-2 HVAR	0.001	Benign
FATHMM MKL	0.948	Damaging	CADD	11.68	Tolerable
Eigen	-0.208	Tolerable	PROVEAN	-0.07	Tolerable
GenoCanyon	1.000	Damaging	ClinPred	0.206	Tolerated
MutationAssessor	1.39	Low			

SUMMARY

This variant is categorised as Likely Benign as it has the following attributes:
PM2 Absent from controls
BP4 Multiple lines of computational evidence suggest no impact on gene or gene product
BS2 Observed in healthy adult individuals

APPENDIX 6: KAT6A VARIANT

Chr8(GRCh37):g.41834750 41834751delinsGA
NM 006766.4(KAT6A):c.1138 1139delinsTC
p.(Glu380Ser)

IGV Image

The KAT6A variant is present in Kathleen, Caleb, Patrick and Laura Folbiggs' samples. The KAT6A variant is not present in Sarah Folbigg's sample. This allele has been maternally inherited.

Lysine (K) acetyltransferase 6 A (KAT6A, a.k.a. MOZ, MYST3) belongs to the MYST family of histone acetyltransferases that are defined by the presence of a highly conserved MYST domain consisting of acetyl-CoA binding motif and a zinc finger. The MYST family of proteins (KAT6A, KAT6B, KAT5, and KAT7) take part in a wide range of core cellular functions, such as chromatin remodelling, gene regulation, protein translation, metabolism, and cellular replication. KAT6A and KAT6B each function in a multi-subunit complex with three other proteins: BRPF1/2/3, ING5, and hEAF614. These proteins form a complex to acetylate lysine residues on histone H3 tails, thereby promoting a wide range of developmental programs.

Decreased expression due to haploinsufficiency of KAT6A is pathogenic and causes a neurodevelopmental syndrome termed mental retardation autosomal dominant 32 (MRD32) (OMIM 616268). This syndrome has a phenotypic profile that commonly includes intellectual disability, neonatal hypotonia, speech delay and behavioural problems. Feeding issues, gastrointestinal problems (reflux and constipation), ophthalmology issues, cardiac malformations (atrial septal defect), and behavioural issues have also been reported. Dysmorphic features are also reported with a broad nasal tip and thin tented upper lip being the most consistent facial features. The majority of reported variants are truncating frameshift or nonsense variants predicted to result in a loss of protein function.

The mutational mechanism for KAT6A is loss of function variants (47:50 records in Clinvar). Review of the three missense changes in Clinvar p.R427L (SCV000583086.3), p.E1071A (SCV000582283.3) and p.G1549S (SCV000567550.3) shows that in each case the reviews were submitted by a single laboratory. Based on the supporting evidence provided in each record the variants are more appropriately reclassified as Variants of Uncertain Significance.

Variant p.(Glu380Ser) leads to the introduction of a new serine residue immediately adjacent to a short region of compositional bias with 4 serines – essentially an in-frame expansion of the polyserine tract from 4 to 5 residues.

The mutant residue is smaller than the wild-type residue. The wild-type residue charge was NEGATIVE, the mutant residue charge is NEUTRAL. The mutant residue is more hydrophobic than the wild-type residue. Together these differences account for a modest physicochemical Grantham score of 80. KAT6A is tolerant to missense variation, with a gnomAD Z score for constraint being 2.07 (threshold value 3).

gnomAD review shows that 70 among 282668 alleles have the p.(Glu380Ser) polyserine expansion variant (1:4000), a number which greatly exceeds the frequency of KAT6A related disorders.

SUMMARY

The NM 006766.4(KAT6A):c.1138 1139delinsTC | p.(Glu380Ser) variant is categorised as BENIGN as it has the following attributes

BS1 - Allele frequency is greater than expected for disorder

BS2 - Observed in a healthy adult individual for a dominant (heterozygous) variant with full penetrance expected at an early age

BP3 - It is an in-frame insertion/ deletion in a repetitive region without a known function

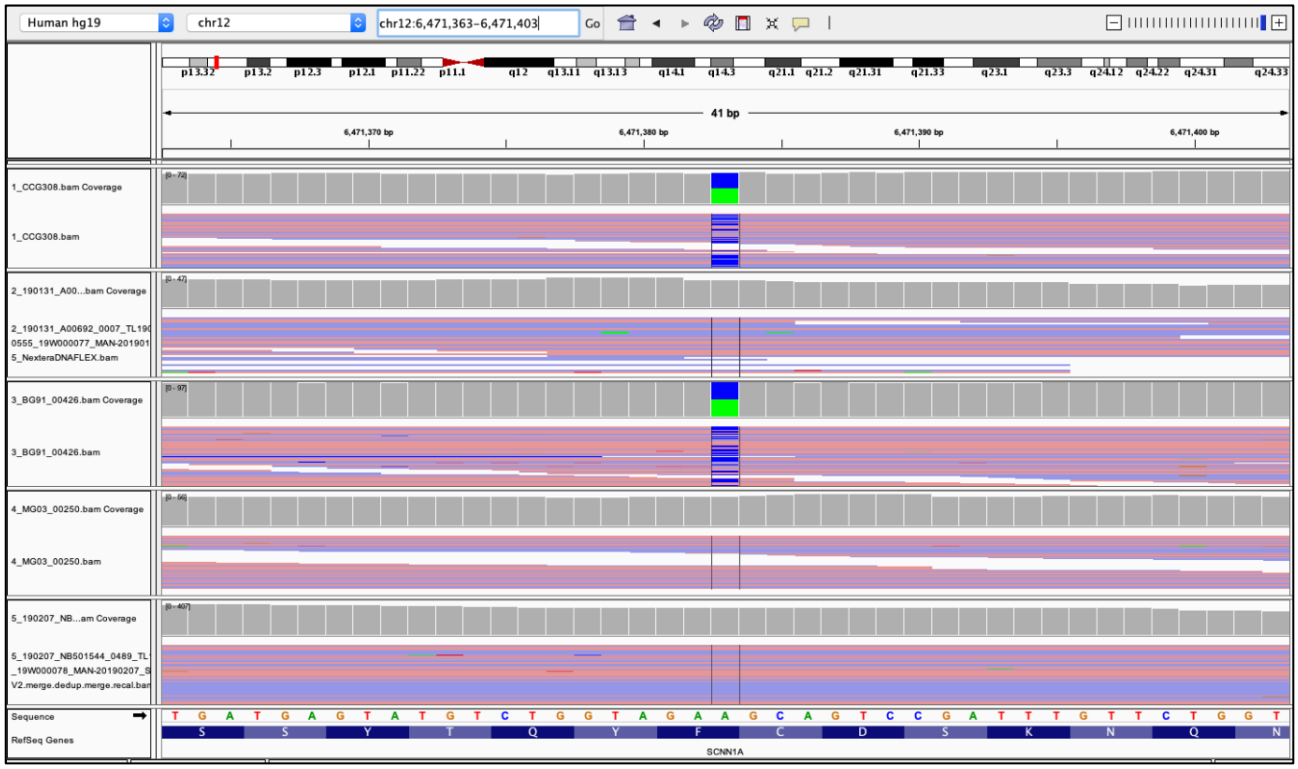
BP1 - Missense variant in a gene for which primarily truncating variants are known to cause disease

APPENDIX 7: SCNN1A VARIANT

chr12(GRCh37):g.6471383A>C
NM 001038.5(SCNN1A):c.709T>G
p.(Phe237Val)

IGV Image

The SCNN1A variant is present in Kathleen and Patrick Folbiggs' samples. The SCNN1A variant is not present in Caleb, Sarah or Laura Folbigg's samples. This allele has been maternally inherited



The amiloride-sensitive sodium channel, is localised in the apical portion of epithelial cells of distal nephron, distal colon, lung and ducts of exocrine glands. This channel is crucial, together with renal outer medullary K+ channels and Na+/K+ ATPase, for Na+ reabsorption and, thus, for electrolyte homeostasis. The channel is a heteromeric complex constituted of three homologous subunits, α, β and γ encoded by the SCNN1A, SCNN1B and SCNN1G genes, respectively.

Pathogenic variants in SCNN1A are a cause of Liddle syndrome – a clinical presentation that mimics primary aldosteronism. The typical clinical features are resistant, early onset salt-sensitive arterial hypertension, severe hypokalaemia (2.8 mmol/L) and metabolic alkalosis, often associated with a family history for early onset hypertension and sudden death. There is significant variability in clinical features (including the severity of hypertension, age at onset, plasma potassium concentration, and urinary aldosterone excretion levels).

The SCNN1A:c.709T>G variant is absent from the gnomad population database, Clinvar, and the HGMD (public) database. It has not been reported in the medical literature.

The SCNN1A Phe237 is invariant in the 100 vertebrate genomes aggregated by the UCSC Genome Browser.

The mutant residue is smaller than the wild-type residue, this physicochemical difference accounts for the very low Grantham score of 22. SCNN1A is tolerant to missense variation, with the gnomAD Z score for constraint being slightly negative at -0.49 (threshold value 3).

In silico prediction tools are supportive regarding pathogenicity, with 19/25 assessments calling the variant as likely deleterious (Varcards plus ClinPred).

SIFT	0.084	Tolerable		fitCons	0.672	Tolerable
Polyphen-2 HVAR	0.811	Possibly damaging	GERP++	5.05	Conserved	
LRT	0.000	Deleterious		SiPhy	12.753	Conserved
MutationTaster	1	Disease causing		phyloP	6.757	Conserved
MutationAssessor	2.085	Medium		phastCons	1.000	Conserved
FATHMM	-0.1	Tolerable		REVEL	0.635	Damaging
VEST3	0.876	Damaging		ReVe	0.908	Damaging
MetaSVM	-0.210	Tolerable		MetaLR	0.430	Tolerable
DANN	0.990	Damaging		**Polyphen-2 HDIV**	**0.923**	**Possibly damaging**
FATHMM MKL	0.876	Damaging		**CADD**	**25.8**	**Damaging**
Eigen	0.566	Damaging		**PROVEAN**	**-4.93**	**Damaging**
GenoCanyon	1.000	Damaging		**ClinPred**	**0.991**	**Deleterious**
M-CAP	0.069	Damaging				

SUMMARY

The NM 001038.5(SCNN1A):c.709T>G | p.(Phe237Val) variant is categorised as a VARIANT OF UNCERTAIN SIGNIFICANCE as it has the following attributes:

PM2 - Absent from controls in the gnomAD Consortium database

PP3 - Multiple lines of computational evidence supportive of a deleterious effect on the gene or gene product

BS2 - Observed in a healthy adult individual for a dominant (heterozygous) variant with full penetrance expected at an early age

APPENDIX 8: MYH6 VARIANT

chr14(GRCh37):23874937G>A
NM 002471.3(MYH6):c.244C>T
p.(Pro82Ser)

IGV Image

The MYH6 variant is present in Kathleen, Caleb and Laura Folbiggs' samples. The MYH6 variant is not present in Sarah Folbigg's sample. This allele has been maternally inherited.

Gene: MYH6 encodes cardiac alpha-myosin heavy chain. This protein is a major part of the cardiac sarcomere, the part of the cardiac muscle cell which provides contractile force. Variants in MYH6 have been associated with cardiomyopathies and with congenital heart disease. The fact that alpha-myosin is a sarcomeric protein is relevant, because although variants in sarcomeric proteins have been associated with cardiomyopathy, which can cause arrhythmias as a secondary phenomenon, there are no other sarcomeric genes known to be associated with primary disorders of cardiac rhythm and conduction (eg LQTS, CPVT); all of the genes associated with those phenotypes either encode cardiac channels, or proteins important for the normal function of channels.

The Proline affected by the variant is highly conserved, with no alternate amino acids among the 100 vertebrate genomes accessible through the UCSC genome browser. Pro82 is located in the myosin head motor domain of the protein in a relatively highly conserved region of the protein, although some nearby amino acids vary in birds, reptiles and fishes relative to mammalian protein sequence.

The variant is present in gnomAD, represented by 4 alleles (of 251,492 alleles, i.e. 4 individuals out of 124,746); there are a number of other missense variants in this region and there are also 28 alleles of Pro82Leu.

Population	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
Total	4	251492	0	1:62,873

MYH6 is tolerant to missense variation, with the gnomAD Z score for constraint of 0.86 (threshold score = 3).

Of the in silico prediction tools queried by the Varcards website plus ClinPred, 19/24 assess the variant as likely to be deleterious, i.e. pathogenicity predictions are supportive.

SIFT	0.0	Damaging	fitCons	0.497	Tolerable
Polyphen-2 HDIV	0.705	Possibly damaging	GERP++	3.91	Conserved
MutationTaster	1.000	Disease causing	phyloP	9.826	Conserved
MutationAssessor	2.795	Medium	phastCons	1.000	Conserved
FATHMM	-0.63	Tolerable	SiPhy	16.039	Conserved
VEST3	0.618	Damaging	ReVe	0.778	Damaging
MetaSVM	-0.105	Tolerable	MetaLR	0.405	Tolerable
M-CAP	0.047	Damaging	REVEL	0.532	Damaging
DANN	0.999	Damaging	**Polyphen-2 HVAR**	**0.584**	**Possibly damaging**
FATHMM MKL	0.996	Damaging	**PROVEAN**	**-6.12**	**Damaging**
Eigen	0.552	Damaging	**CADD**	**27.4**	**Damaging**
GenoCanyon	1.000	Damaging	**ClinPred**	**0.95**	**Deleterious**

Even if there were persuasive evidence for gene-phenotype relationship in relation to MYH6, the absence of a clear fit with any of the 28 ACMG rules for pathogenicity assessment variant would mean this variant must be classified as a Variant of Uncertain Significance (Class 3).

By the Clingen criteria, the evidence for a relevant gene-phenotype association is classified as Limited. The observations of Lam et al and Bowles et al (see below) may prove to be spurious, although it is still possible that additional evidence will emerge supporting an association. It is important to understand that there are very numerous examples in the medical literature of similar observations which seemed to indicate association between variants in a particular gene and a phenotype, only for subsequent evidence to emerge which shows that this apparent association was spurious.

Where there is only Limited evidence for gene-phenotype association, it is not possible to classify a variant in that gene as Likely Pathogenic or Pathogenic in relation to the phenotype in question. Further information is provided below for completeness.

Evidence for involvement of MYH6 in monogenic disorders of cardiac rhythm and conduction is very limited. We can find only two papers suggesting that this may be the case, relating to different cardiac conditions. One has significant methodological flaws (see below) and the other describes a single small family, including a clinically normal 64-year old woman who is heterozygous for the variant reported in the paper. The only other evidence for a role for an MYH6 variant in cardiac conduction disease comes from a study of sick sinus syndrome (SSS) in Iceland (Holm et al, Nature Genetics 2011;43(4):316-320) in which a variant in MYH6 was shown to be a risk factor for SSS. This is a condition which mainly affects adults, with the main effect of the variant being observed in people aged >70.

Literature: Lam et al 2015 [PMID: 28491533] describe a family in which the proband suffered a VF arrest aged 24. An ICD was implanted and did not deliver any shocks over the following 4 years of follow-up. ECG showed right bundle branch block and monomorphic ventricular ectopy. His three children had cardiac phenotypes. A daughter had sinus node dysfunction and had episodes of syncope from 9 months; a loop recorder found junctional bradycardia with periods of asystole lasting as long as 13 seconds. She had a pacemaker implanted aged 3 years and had no subsequent events. The son had episodes of syncope from 12 months; Holter monitoring recorded an episode of 11 seconds of asystole. He had a pacemaker inserted but continued to have brief episodes of unconsciousness. A younger daughter also had several episodes of unconsciousness from 3 months, lasting 5-10 seconds. A pacemaker was implanted when she was 11 months old because of the episodes and family history.

Exome sequencing was performed in the proband, identifying a missense variant, p.Arg654Trp. There are 6 alleles for this variant in the gnomAD database (which was not available at the time of publication of this paper). The variant was identified in all three affected children, but also in the mother of the proband, who had no history of syncopal events and no abnormalities found on cardiac evaluation. It should be noted that variable expression and nonpenetrance are common in dominant cardiac conditions. Nonetheless, the observation of a clinically unaffected individual with the

variant, plus 6 individuals from an admittedly large population dataset, raise doubts over the association between this variant and the phenotype in the family.

No functional data were presented to support a possible functional impact of the variant.

Bowles et al 2015, [PMID: 26284702] report a family with Wolff-Parkinson-White syndrome and a missense variant in MYH6, p.Glu1885Lys. Wolff-Parkinson-White syndrome is a condition in which there is a risk of episodes of raised heart rate (tachycardia); it is generally less severe than the other conditions discussed above, and does not usually cause sudden death. Bowles and colleagues performed exome sequencing in five affected family members, finding several hundred variants shared by all five that were rare or novel, predicted by at least one algorithm to be deleterious to gene function, and were in genes with a potential role in cardiac development or function. Ten of these were prioritised for further assessment, with the MYH6 variant and a variant in LAMB2 having the highest combined scores from two prioritization algorithms.

Segregation was carried out in 10 unaffected family members. However, for reasons not explained, these included unrelated spouses of family members, as well as unaffected children of unaffected family members. The paper states that only MYH6 was absent from all unaffected family members, but in fact this amounted to two informative individuals for that variant, not of itself strong additional evidence of pathogenicity. The p.Glu1885Lys variant is present in 4 alleles in the gnomAD database; given the less severe phenotype described in this paper this could still be consistent with pathogenicity. No functional data were presented in relation to the variant.

The approach to filtering and segregation used in this paper is unusual and leaves room for doubt regarding the pathogenicity of the MYH6 variant.

SUMMARY

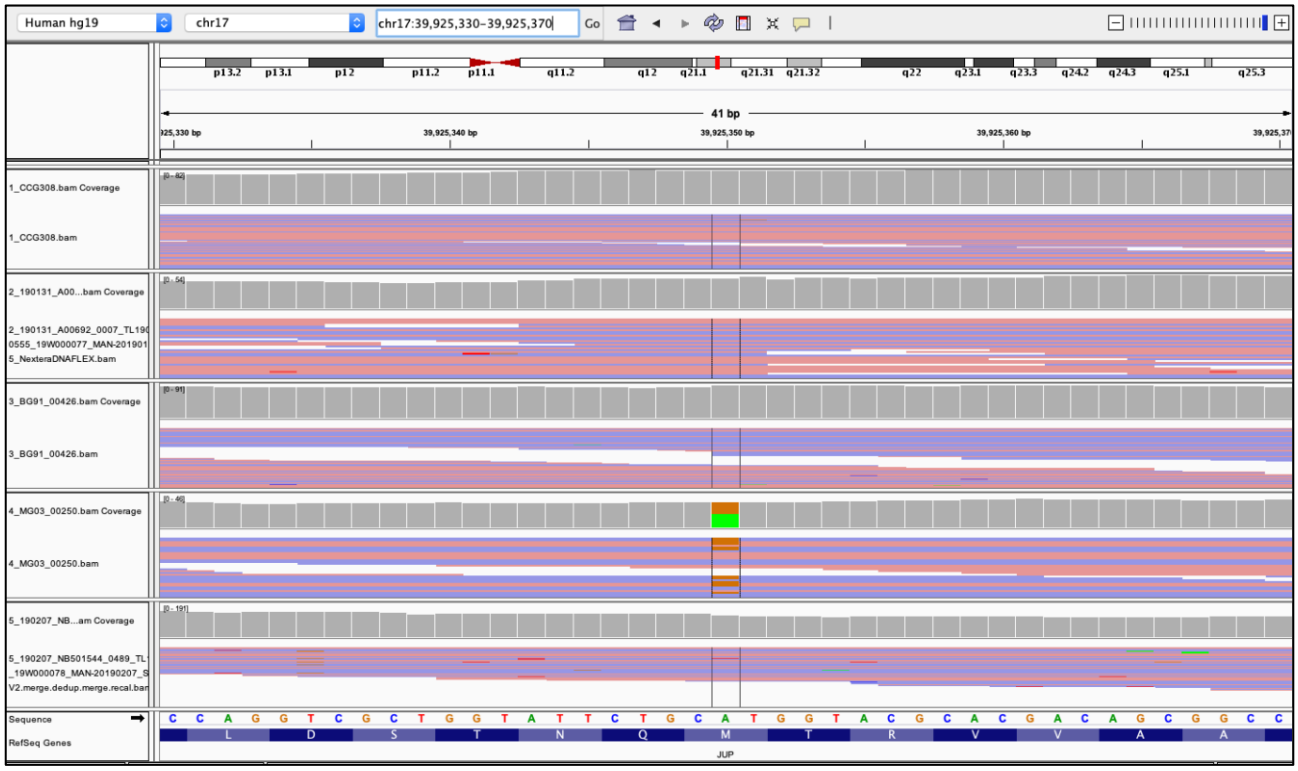
The MYH6 gene does not show a robust association with disease therefore it is not appropriate to classify variant pathogenicity using the ACMG framework

APPENDIX 9: JUP VARIANT

chr17:39925350A>G
NM 002230.4(JUP):c.578T>C
(p.Met193Thr)

IGV Image

The JUP variant is present in Sarah Folbigg's sample. The JUP variant is not present in Kathleen, Caleb, Patrick or Laura Folbiggs' samples. This allele has either been paternally inherited or is a de novo event.



The membrane-associated plaques are architectural elements in an important strategic position to influence the arrangement and function of both the cytoskeleton and the cells within the tissue. The presence of plakoglobin in both the desmosomes and in the intermediate junctions suggests that it plays a central role in the structure and function of submembranous plaques.

JUP is associated with an autosomal recessive disorder NAXOS syndrome, and rare autosomal dominant cases of arrhythmogenic right ventricular dysplasia-12. Polivka et al [PMID 26399581] identified 82 published patients, all with biallelic variant in JUP. Among them, 74 patients carry the Naxos homozygous deletion (c.2157del2, exon 14). The Naxos phenotype is characterised by diffuse Palmoplantar keratoderma, woolly hair and classic AD arrhythmogenic right ventricular cardiomyopathy in all reported patients. Two Turkish related patients carried a homozygous missense mutation (c.794G>A, exon 4) with a phenotype close to Naxos syndrome and characterised by the association of cardiomyopathy (classic AD arrhythmogenic right ventricular cardiomyopathy), alopecia (atrichia) and PPK (CAPK syndrome). In patients with Naxos and CAPK syndromes, symptomatic cardiac involvement started during the second decade (13–43 years).

Haggerty et al 2017 [PMID: 28471438] identified 5 missense variants of uncertain significance in the JUP gene in 20 subjects from a cohort of 30,716 patients, none of whom had evidence on ECG of ARVD. These data indicate that variants that are not loss of function variants have a low likelihood of pathogenicity, and the ARVD12 clinical disease has a frequency less than 1:2,0000.

Population	Allele Count	Allele Number	Number of Homozygotes	Allele Frequency
European (Non-Finnish)	17	128176	0	1:7,540

African	3	24766	0	1:8,255

The JUP:c.578T>C variant has not been reported in the medical literature.

Clinvar entries for this variant

RCV000656166	Wolff-Parkinson White pattern	Uncertain significance
RCV000468133	Arrhythmogenic right ventricular cardiomyopathy, type 12	Uncertain significance
RCV000208130	Primary Dilated Cardiomyopathy	Uncertain significance

The variant is almost invariant among the 100 vertebrate genomes aggregated by the UCSC Genome Browser and lies in Armadillo protein structural motif, but is not a conserved element among paralogous ARM domains.

The mutant residue is smaller than the wild-type residue and is neutral in terms of hydrophobicity. This physicochemical difference accounts for the moderate Grantham score of 81. JUP is tolerant to missense variation, with the gnomAD Z score for constraint being 1.32 (threshold value 3).

In silico prediction tools are inconclusive regarding pathogenicity, with 16/24 assessments calling the variant as likely deleterious (Varcards plus ClinPred).

SIFT	0.174	Tolerable	fitCons	0.719	Damaging
Polyphen-2 HDIV	0.993	Probably damaging	GERP++	5.79	Conserved
LRT	0.000	Deleterious	phastCons	1.000	Conserved
MutationTaster	0.999	Disease causing	SiPhy	15.315	Conserved
MutationAssessor	1.955	Medium	FATHMM MKL	0.965	Damaging
FATHMM	2.26	Tolerable	Eigen	0.597	Damaging
VEST3	0.904	Damaging	GenoCanyon	1.000	Damaging
REVEL	0.462	Damaging	ReVe	0.745	Damaging
MetaSVM	-0.798	Tolerable	**Polyphen-2 HVAR**	**0.987**	**Probably damaging**
MetaLR	0.227	Tolerable	**CADD**	**23.5**	**Damaging**
M-CAP	0.020	Tolerable	**PROVEAN**	**-3.79**	**Damaging**
DANN	0.943	Tolerable	**ClinPred**	**0.339**	**Tolerated**

SUMMARY

This variant is categorised as a Variant of Uncertain Significance as it has the following attributes:
PP3 - Multiple lines of computational evidence support a deleterious effect on the gene

APPENDIX 10: Variants identified in 421 genes reported to be associated with SUDI +/- cardiac or non-cardiac disease pathways (including ~170 from Prof Vinuesa)

Gene:VEP HGVS cDNA	VEP HGVS Protein	Impact	Observations
ALG14:c.289-14357dup		intronic variant	deep intronic in both isoforms
ANK3:c.10055A>G	p.Glu3352Gly	missense variant	likely benign | AR 4 normal homozygotes in gnomad
CACNA1B:c.2093-4C>A		splice region variant	no effect on splicing, 1% of Dutch genomes, 11 homozygotes in gnomad
CACNA1E:c.29C>A E	p.Ala10Asp	missense variant	unrelated severe disorder | PMID: 30849329, 30343943
CACNA1E:c.4735-6 4735-4del		splice region variant	likely benign | 417 Heterozygotes and 1 homozygote in gnomad
CACNA1G:c.1450C>T	p.Arg484Cys	missense variant	unrelated severe disorder | PMID 29878067 | 15 heterozygotes in gnomad, de novo mutations.
CALM2:c.340G>A	p.Gly114Arg	missense variant	See Appendix 2
COX14:c.-9+25 -9+44dup		splice region variant	intronic variant no splice effect predicted
COX14:c.-9+40 -9+44del		splice region variant	intronic | 5'UTR in 3 transcripts
CTNNA3:c.1900G>A	p.Glu634Lys	missense variant	147 heterozygotes in gnomad for an AD disease | 2 likely benign, 1 VUS
DMD:c.1313A>G	p.His438Arg	missense variant	XLR | likely benign | de novo or paternally inherited
DOCK7:c.4675A>T	p.Ile1559Leu	missense variant	Heterozygous Ile => Leu, Met, Val, Thr substituted rarely here | Varcards 11:23; ClinPred 0.58
DTNA:c.1219C>T	p.His407Tyr	missense variant	intronic variant | AD 409 heterozygotes | likely benign
ECE1:c.1376G>A	p.Ser459Asn	missense variant	Benign/Likely benign in Clinvar
ETFA:c.40-16 40-5dup		splice region variant	non coding in both transcripts
FBN2:c.976C>T	p.Pro326Ser	missense variant	Benign/Likely benign in Clinvar
HLCS:c.-1066-5del		splice region variant	High frequency del at -5 | 2026 homozygotes in gnomAD
HTT:c.102 110dup	p.Gln36 Gln38dup	inframe insertion	unrelated severe adult onset disorder | polymorphism in CAG repeat
JUP:c.578T>C	p.Met193Thr	missense variant	See Appendix 9
MIB1:c.1092+3A>G		splice region variant	Likely benign in Clinvar
MYH6:c.244C>T	p.Pro82Ser	missense variant	See Appendix 8
MYLK:c.2107C>G	p.Gln703Glu	missense variant	unrelated disorder | AD aortic aneursym
MYPN:c.2510C>T	p.Pro837Leu	missense variant	AD 865 records in gnomad Benign/LB in Clinvar
PRICKLE2:c.788-6T>C		splice region variant	Benign/LB | deletion A in the middle of a poly-A splice region sequence
PSEN2:c.211C>T	p.Arg71Trp	missense variant	likely benign | 6 normal homozygotes, 1049 heterozygotes in gnomad
RYR2:n.2284-5C>T		splice region variant	deep intronic variant
SSTR2:c.-93+43 -93+48del		splice region variant	deletion in a 20 TG dinucleotide repeat region
TPH2:c.540A>G	p.Pro180=	splice region variant	Likely benign
TTN:c.79226G>A	p.Arg26409His	missense variant	See Appendix 3
TTN:c.36509A>T	p.Glu12170Val	missense variant	See Appendix 4
ZFPM2:c.89A>G	p.Glu30Gly	missense variant	AD Tetralogy Fallot 754 heterozygotes in gnomad
ZFPM2:c.1480G>A	p.Val494Ile	missense variant	this variant associated with sex reversal

APPENDIX 11: Variants identified in 204 genes reported to be associated with neurological disorders in children provided by Dr Fahey

Gene:VEP HGVS cDNA	VEP HGVS Protein	Impact	Observations
ABCD4:c.1099C>T	p.Arg367Trp	missense variant	435 Heterozygotes and 5 homozygotes in gnomad aged 50-80 years
ATP1A3:c.3252 3253del	p.Pro1085Ilefs*125	frameshift variant	non coding in 3 transcripts | 11 heterozygotes aged 35 and over
DBT:c.940-2A>G		splice acceptor variant	minor transcript | deep intronic in all major protein coding transcripts in Alamut
DOCK7:c.4675A>T	p.Ile1559Leu	missense variant	Heterozygous Ile => Leu; Met, Val, Thr substituted rarely here | Varcards 11:23; ClinPred 0.58
ETFA:c.40-16 40-5dup		splice region variant	Non coding in 2 transcripts
HLCS:c.-1066-5del		splice region variant	High frequency del at -5 2026 homozygotes in gnomAD
MTR:c.-360		5'UTR variant	Non coding 5'UTR c.-360 in the major ttanscripts
TPP1:c.101G>A	p.Gly34Asp	missense variant	Heterozygous | 10:23 varcard score, ClinPred 0.178 | likely rare benign variant

APPENDIX 12: Reported pathogenic or likely pathogenic variants identified in 5 genomic studies (any disorder).

KIAA0586:c.392del	p.Arg131LysfsTer4	frameshift variant	Pathogenic	RCV000652578, RCV000186590, RCV000255927, RCV000612898	
Joubert syndrome 23, 616490 (3);Short-rib thoracic dysplasia 14 with polydactyly, 616546 (3)				Autosomal recessive	Present in: KF, CF
SERPINA1:c.863A>T	p.Glu288Val	missense variant	Pathogenic	RCV000148878, RCV000177031	
Emphysema due to AAT deficiency, 613490 (3) Hemorrhagic diathesis due to antithrombin Pittsburgh, 613490 (3)				Autosomal recessive	Present in: PF, SF, LF
ABCC6:c.4254G>A	p.Arg1418=	synonymous variant	Pathogenic	RCV000499190	
Pseudoxanthoma elasticum, 264800 (3);Pseudoxanthoma elasticum, forme fruste, 177850 (3)				Autosomal recessive	Present in: KF, CF, PF, LF
NOD2:c.2798+158C>T		intron variant	Pathogenic, risk factor	RCV000004962, RCV000416486, RCV000416489	
Inflammatory bowel disease 1, Crohn disease				Multigenic	Present in: KF, CF, PF
C9:c.162C>A	p.Cys54Ter	stop gained	Pathogenic/Likely pathogenic	RCV000018569	
C9 deficiency, 613825 (3);{Macular degeneration, age-related, 15, susceptibility to}, 615591 (3)				Autosomal recessive	Present in: KF, CF, SF
PRSS1:c.86A>T	p.Asn29Ile	missense variant	Pathogenic	RCV000012652, RCV000506924	
Pancreatitis, hereditary, 167800 (3)				Autosomal dominant	Present in: KF, PF
PRSS1:c.161A>G	p.Asn54Ser	missense variant	Pathogenic	RCV000012656	
Pancreatitis, hereditary, 167800 (3)				Autosomal dominant	Present in: KF, SF
PRKDC:c.1777-710dup		intron variant	Pathogenic	RCV000142391	
Immunodeficiency 26, with or without neurologic abnormalities, 615966 (3)				Autosomal recessive	Present in: CF

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EDUCATION

Secondary	1980-83	Scotch College, Perth, Western Australia (General Exhibition, Tertiary Entrance Examinations 1983)
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1999	Royal Children's Hospital Foundation Fellowship (Brisbane) (declined)
2002	National Heart Foundation PhD Scholarship
2004	Ralph Reader Prize, Clinical Section (Cardiac Society of Australia and New Zealand)
2016	Karen Snow-Bailey Award (best scientific presentation at Human Genetics Society of Australasia ASM by a member of ASDG)
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PhD thesis: **The genetics of atrial septal defect and patent foramen ovale (UNSW, 2008)**

PUBLICATION METRICS (Google Scholar, March 2019)

h-index 28 (24 since 2014)

i10-index 52 (39 since 2014)

Citations 3,265 (2,002 since 2013)

10 publications with at least 100 citations each; a further 11 with at least 50 each.

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BOOK CHAPTERS

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GOVERNMENT REPORT

95. **Kirk EP** for the Human Genetics Society of Australasia: The Scope and Purpose of Genetic Testing. Report to the Health Insurance Commission, May 1999 (146 pages)

EDITORIAL CORRESPONDENCE

96. **Kirk EP.** Zika virus: accurate terminology matters. *Nature* 2016;531:173
97. **Kirk EP.** “Nasal” speech – hyper or hypo? *Eur J Hum Genet* 2012;20(4):367
98. Marsh DJ, Trahair TN, **Kirk EP**. Mutant AKT1 in Proteus syndrome *New Eng J Med* 2011;365:2141-2142
99. **Kirk EP**. Classification of stillbirth: classification is not explanation. *BMJ* 2005;331:1269
100. **Kirk EP**. Ethics of therapeutic cloning. *Int Med J* 2005;35 (8):500
101. **Kirk EP**, Hattam A, Turner A. Genetic risk estimation by health care professionals. *Med J Aust* 2005;182(11):596-597

102. **Kirk EP**, Smith JM, Field M, Marshall GM, Marsh DJ. Diagnosis of Proteus syndrome was correct. *Am J Med Genet*. 2004;130A(2):214.
103. **Kirk EP**. Treatment by deception is bad medicine (letter). *Lancet* 2003;362:668
104. **Kirk EP**. To live or let die? (letter). *J Paed Child H* 2003;39:480
105. **Kirk EP**. Embryo selection for complex traits is impracticable (letter). *BMJ* 2003;326:53

HIGHER DEGREE SUPERVISION

Dr Lisa Worgan – MSc, awarded 2005 (primary supervisor). *The role of nuclear-encoded subunit genes in mitochondrial complex I deficiency*
Dr Ingrid Sinnerbrink, M Med awarded 2011 (primary supervisor). *The health and developmental outcomes of children with a de novo apparently balanced chromosomal rearrangement identified at prenatal diagnosis and the associated psychosocial impact on parents*
Dr Dr Mahdi Moradi, PhD, awarded 2013 (co-supervisor with Prof Richard Harvey). *The genetics of congenital heart disease.*
Dr Albert Lam, MD, awarded 2013 (primary supervisor). *Human subtelomeric aberrations in the Hong Kong population*
Dr Gillian Blue, PhD, awarded 2015 (Sydney University), (associate supervisor with A/Prof David Winlaw). *The genetics of congenital heart disease: new genes, mechanisms and attitudes*

Dr Emma Palmer, PhD candidate (primary supervisor), 2013 - continuing

POSTDOCTORAL SUPERVISION

Dr Nadine Kasparian – NHMRC postdoctoral fellow, 2008 – 2012. *Following her postdoctoral studies, Dr Kasparian was the recipient of an NHMRC Career Development Fellowship for 2013-2016: "Developing an evidence base for the psychological care of children and families affected by congenital heart disease" ($397,724).*

OTHER SUPERVISION

Ms Jacqui Robinson - Master of Nursing (Nurse Practitioner), awarded 2012 (primary supervisor)
Ms Catherine Spinks – Master of Genetic Counselling, awarded 2012 (primary supervisor)
Mr Mike Gibbs **–** Master of Genetic Counselling, 2016 – (primary supervisor)
Mr Benjamin Challis – BmedSci(Hons), 2017. *Preconception screening by whole genome sequencing*

ILP STUDENTS (UNSW)

Mr Ritik Kaul – ILP student, ILP completed 2009. *A survey of the information and support needs of families affected by childhood heart disease*
Mr Blake Fidock – ILP student, ILP completed 2010 *A cross–sectional retrospective analysis of the utilisation of genetics services by parents of children with congenital heart disease*

ACTIVITIES AS CONJOINT STAFF MEMBER, UNSW

Coordinator of medical student teaching for clinical genetics (Phase 3 students) 2008-

Medical student selection interviewer 2003- 2011

Research Student Progress Reviews: panel member for School of Women's and Children's Health student reviews, 2009- present (currently chairing two panels)

Longstanding role in medical student teaching; examiner in 5th year exams in the previous curriculum; teaching and examining for the Diploma of Paediatrics while it operated. Assessor of ILP abstracts for ILP awards (School of Women's and Children's Health). Numerous lectures and tutorials since 1999.

RESEARCH GRANT SUPPORT - AS CHIEF INVESTIGATOR ($23,930,000 total)

2018 **Kirk EP**, Delatycki M, Laing N. Mackenzie's Mission – the Australian Reproductive Carrier Screening Project. Genomics Health Futures Mission Grant - $19,982,540 over three years

2017 Schofield D, Laing N, Delatycki M, Dinger M, Roscioli T, **Kirk E**, Field M, Shrestha R, Bruno D, Kelly S. Preconception carrier screening: providing genetically at risk families with a chance to have healthy children. NHMRC Partnership Grant AP1146134. $845,827

2016 Roscioli T, Sachdev R, **Kirk EP**, Palmer E, Bye A, Schofield D, Dinger M, Cowley M. Drug-resistant childhood onset epilepsy with intellectual disability: leveraging genomic sequencing to identify novel genes and neurodevelopmental pathways and determine optimal diagnostic paradigm. NSW Genomics Collaborative Grant. $180,000

2015 Dunwoodie S, Ho J, Winlaw D, Harvey R, Giannoulatou E, **Kirk E**. Discovering the genetic causes of inherited heart diseases in babies. NSW Genomics Collaborative Grant. $370,000

2014 Kasparian N, Austin M-P, Glover V, Sholler G, Winlaw D, **Kirk E**, Barnett B, Swinsburg D, Badawi N, Grant K-A, Walker K, Bauman A and Sherlock K. Biomarkers of parental stress after fetal diagnosis of complex congenital heart disease. Heartkids Australia. $50,000.

2014 **Kirk E**, Barlow-Stewart K, Roscioli T, Meiser B, Buckley M, Mahmoud I, Burnett L. Exome sequencing for pre-conception counselling in consanguineous couples. **Apex Foundation for Research Into Intellectual Disability**. $40,000.

2013 Roscioli T, Zhou J, Cox T, Buckley M, van Bokhoven H, **Kirk E.** Gene identification in familial orofacial clefts by next generation sequencing of exomes and p63

regulatory elements. **National Health and Medical Research Council** (APP1045465). $565,181.18. (5 year grant)

2012 Roscioli T, Buckley M, Cox T, Zhou J, van Bokhoven H, **Kirk E**.**UNSW Goldstar Award** Gene Identification in Familial Orofacial Clefts by Next Generation Sequencing of Exomes and p63 Regulatory Elements. $40,000.

2012 Kasparian N, Sholler G, **Kirk E**, Barnett B, Winlaw D. **Perpetual.** Congenital heart disease and psychological care: A program for translational research. $225,000 (3 year grant)

2011 Kasparian N, Austin M-P, Glover V, **Kirk E**, Sholler G, Barnett B, Winlaw D. **Heartkids Australia Project Grant** (Assessed by the NHMRC). Parental response to fetal or postnatal diagnosis of congenital heart disease and subsequent infant developmental outcomes: A unique test of the fetal programming hypothesis. (3 year grant; 2011-2013), $300,000.

2010 Kasparian N, Sholler G, **Kirk E**, Barnett B, Winlaw D. Psychological aspects of congenital heart disease: A program for translational research. **Adolph Basser Trust Award** (3 year grant; 2010-2013), $225,000.

2010 Kasparian N, Austin M-P, Glover V, **Kirk E**, Sholler G, Barnett B, Winlaw D. Testing the fetal programming hypothesis in the context of major congenital heart disease: A series of preliminary studies. **Malcolm Alan Burgess and Julia Burgess Trust Award**, $75,000.

2009 **Kirk EP,** Kasparian NA, Camphausen C, Murphy D. A prospective study of psychological outcomes following prenatal or postnatal diagnosis of congenital heart disease: Does timing of diagnosis make a difference? **Sydney Children's Hospital Foundation**. $15,000.

2007 Harvey RP, **Kirk** EPE, Moran C. Identifying common alleles underlying polygenic congenital heart disease. **National Heart Foundation**. (2 year grant) $123,000.

2006 **Kirk EPE**, Meiser B, Halliday J. Follow up of children with prenatally detected de novo apparently balanced chromosomal rearrangements. **UNSW Faculty Research Grant**, $20,000.

2006 **Kirk EPE**. Follow up of children with prenatally detected de novo apparently balanced chromosomal rearrangements. **Sydney Children's Hospital Foundation**, $15,000.

2006 **Kirk EP,** Halliday J, Amor D, Meiser B, Waters E. Follow up of children with prenatally detected de novo apparently balanced chromosomal rearrangements. **Apex Foundation for Research into Intellectual Disability Limited**, $25,000.

2002 Harvey RP, **Kirk EPE**, Biben C, Buckley M, Moran C. Genetic Modifiers of congenital heart disease. **National Institutes of Health**, Grant number R01 HL68885 (5 year grant),
$950,355.

2001 **Kirk EPE**, Buckley M. Fine mapping of an autosomal dominant ASD locus. **Sydney Children's Hospital Foundation**, $12,000.

2001 Harvey RP, **Kirk EPE**, Buckley M. Mapping of modifier loci for patent foramen ovale (PFO) and atrial septal dysmorphogenesis in mice. **National Heart Foundation**, grant number G00S0738 (2 year grant), $72,600.

2001 **Kirk E,** Worgan L, Thorburn D. The role of nuclear genes in disorders of childhood due to complex I deficiency. **United Mitochondrial Diseases Foundation (US),** $22,200.

2000 **Kirk EPE**, Buckley M, Jones O. Genes and environment in the causation of cardiac septal defects. **Sydney Children's Hospital Foundation**, $45,000.

2000 Buckley M, McKenzie F, **Kirk E**, Glass I. Molecular genetic basis of an autosomal dominant syndrome characterised by atrial and ventricular septal defects. **Royal College of Pathologists of Australasia, Technical Assistance Grant**, $2,800.

RESEARCH GRANT SUPPORT - AS ASSOCIATE INVESTIGATOR

2004 Graham R, Allen D, Fatkin D, Feneley M, Harvey R, Chief Investigators (**Kirk E – Principal Investigator G) NHMRC Program Grant** - Victor Chang Cardiac Research Institute. 2004.
$7,724,725 over 5 years.

2004 Lindeman R, Roscioli T, Buckley M, Donald J, Ziegler J, (AIs Wong M, **Kirk E**)**.** Genetic basis of veno-occlusive disease. NHMRC 300462 (3 year grant), $220,500.

2015 Dunwoodie S, Ho Joshua, Thomas P, Kikuchi K (AIs Mowat D, Krishnan U, Kirk E, Belessis Y, Chapman G, Enriquez A, Giannoulatou E, Guillemin G. Identifying genes required for vertebral column and heart formation. NHMRC APP1102373 (3 year grant), $950,417.50

MEETING ORGANISER

Convenor, 2nd Australasian Clinical Metabolic Meeting, Sydney, March 5-6, 2010

Member, Australian Clinical Genomics Update Steering Committee, 2016-

INTERNATIONAL CONSORTIUM MEMBER

Member of International CantuTreat Consortium – a group of clinicians and researchers studying Cantú syndrome. Attended inaugural CantuTreat meeting, Utrecht, The Netherlands, September 2015; attending CantuTreat meeting in St Louis, USA in June 2017 (both as invited participant)

CONFERENCE PRESENTATIONS (INVITED SPEAKER)

Preconception Carrier Screening: the New Frontier. Kidgen Renal Genetics Symposium. Sydney, 2018

Mackenzie's Mission – Plenary Session. Human Genetics Society of Australasia. Sydney, 2018

Talk Like a Geneticist. International Clinical Cardiovascular Genetics Conference. Brisbane, May 2018

Conference Debate: "Direct to consumer testing in cardiac genetics". International Clinical Cardiovascular Genetics Conference. Brisbane, May 2018.

The Clinical Utility of Exome and Whole Genome Sequencing. Pathology Update, Sydney, March 2017 *(This meeting is the annual scientific meeting of the Royal College of Pathologists of Australasia. This was the closing talk of the meeting)*

Preconception carrier screening for consanguineous communities in New South Wales. Australian Genomic Health Alliance Workshop, Perth, November 2016 *(In addition to presenting recent research into preconception screening, I was asked to join a small group who met to plan preconception screening in Western Australia in a symposium held after the meeting)*

Genomic Medicine - Current status of genetic testing. Australian Clinical Genomics Update, Sydney, November 2016 *(Recently established genomics meeting with wide attendance from people working in the field from around Australia)*

Conference debate: "You only treat the phenotype, not the genotype". International Clinical Cardiovascular Genetics Conference. Brisbane, August 2016.

Challenging variant interpretation in cardiac genetics – Pathology Update, Melbourne, March 2016

Cantu Syndrome and its Cardinal Features – American College of American Genetics, Salt Lake City, Utah, March 2015 *(key clinical session at major international meeting)*

Congenital Heart Disease Genetics – Seminar series, HudsonAlpha Institute for Biotechnology, Huntsville, Alabama, March 2015 *(in conjunction with the ACMG meeting, I was invited to visit this major genomics institute and present recent cardiac genetics research)*

Conference debate: "Targeted genetic testing is a better approach than testing the whole exome or genome". International Clinical Cardiovascular Genetics Conference. Brisbane, August 2014.

Genetics of CHD and the Role of Genetic Testing. International Clinical Cardiovascular Genetics Conference. Brisbane, August 2014.

Investigating Cardiac Death – How Far (Technically) Can You Go? – Pathology Update, Melbourne 2014 *(combined genetics/forensic pathology session*)

Interpreting ENCODE from a clinical perspective. Short Course in Medical Genetics and Genetic Pathology (RCPA). Gold Coast, June 2013

Congenital Heart Disease – Are We There Yet? Human Genetics Society of Australasia Annual Scientific Meeting, Gold Coast, August 2011

Genetics of Congenital Heart Disease. Physicians Week, Sydney, May 2009

Overview of Monogenic Congenital Heart Disease. Cardiac Society of Australasia and New Zealand ASM, Adelaide, August 2008

Tinman, TBX and Holes in the Heart. Conjoint Scientific Meeting, Hong Kong Society of Cytogenetics and Hong Kong Society of Medical Genetics. Hong Kong, April 2008 *(invited to address leading genetics body in Hong Kong regarding congenital heart disease research)*

Opportunities for Cardiovascular Disease in a Genetics Service Business Plan. Cardiac Society of Australia and New Zealand – Cardiac Genetics satellite meeting. Sydney, March 2006

Genetic Modifiers of Patent Foramen Ovale and Atrial Septal Defect. Cardiac genetics symposium, Children's Hospital at Westmead, Sydney, October 2004.

PROFESSIONAL ACTIVITIES

Paediatric Physician Training Council of NSW	Member, 2007-2013
NSW Newborn Screening Advisory Committee	Member, 2008 –
NSW Adult Genetic Medicine Governance Committee	Member, 2011-
Community Genetics Program	Advisory Committee Member, 2016 – Medical Director, 2016-
Australian Cardiac Genetic Testing Network Steering Committee	Member, 2016-
NSW Agency for Clinical Innovation – Clinical Genetics Executive Committee	Member, 2016-2019
NSW Health Pathology Rare Diseases Working Group	Member, 2017-
Co-Head, Centre for Clinical Genetics, SCH	2016-2019
NSW Health Genomics Translational Medicine Committee	Member, 2018-

ROYAL AUSTRALASIAN COLLEGE OF PHYSICIANS

Specialist Advisory Committee in Clinical Genetics	Member, 1999-2001 Coordinator of Advanced Training, 2001-2006 Chair, 2007 – 2012
Written Examination Committee (Paediatrics)	Member, 2002 - 2007
Network Director of Paediatric Education, Greater Eastern and Southern NSW Child Health Network	2007 - 2013
Examiner (clinical examination)	2004-
College Education Committee	Member, 2009 – 2012
National Convenor, Australian Directors of Paediatric Physician Training	2010 - 2013
Paediatric Division Education Committee	Member, 2010 – 2013
College Council	Member, 2016 -

EDITORIAL PANEL MEMBERSHIP

Journal of Paediatrics and Child Health	Associate Editor, 2009-2015 Editor 2015-

EXTERNAL REVIEW OF GENETICS SERVICE

In June, 2008 I was a member of the credentialing committee which reviewed the Northern Regional Genetics Service in Auckland, and drafted the committee's report.

REVIEWER

Journals: *Birth Defects Research Part A: Clinical and Molecular Teratology*, *Journal of the American College of Cardiology, European Journal of Human Genetics, American Journal of Medical Genetics, Journal of Medical Case Reports, Clinical Genetics, Australasian Journal of Dermatology, Twin Research and Human Genetics, Australian Medical Students Journal, Journal of Pediatric Genetics, AIMS Genetics, Animal Genetics, Circulation, Circulation: Cardiovascular Genetics, Circulation: Genomic and Precision Medicine, Heart Lung and Circulation, BMC Research Notes, Endocrine, Molecular Genetics and Metabolism*

Grant reviews: NHMRC; Netherlands Health Care Efficiency Research Programme; Todd Foundation, New Zealand; National Medical Research Council, Singapore; Women's and Children's Hospital Foundation

Other: Charles Sturt University (honours thesis, 2005)
UNSW Press (editorial review of a book, 2005)
Sydney University (PhD thesis, 2014, PhD thesis, 2015)

External reviewer for Professorial appointments, University of Bristol, UK (2012); University of Adelaide (2012)

External reviewer for appointment to the academic status of “Privat-docents”, Université de Genève, Switzerland (2015)

HUMAN GENETICS SOCIETY OF AUSTRALASIA

Board of Training in Clinical Genetics	Member, 1999-2001 Chair, 2001-2004
Australasian Association of Clinical Geneticists	Member of Executive, 2007-2012

SYDNEY CHILDREN’S HOSPITAL/ SYDNEY CHILDREN’S HOSPITAL NETWORK

Network Clinical Education Committee	Member, 2011-2013
Tow Prize Committee	Member, 2000-2004
Research Committee	Member, 2004-2012
SCHN Scientific Advisory Committee	Member, 2012-2017
Junior Medical Staff Advisory Committee	Member, 2007-2013
Annual course in paediatrics	Lecturer, 2000-
Diploma in paediatrics	Lecturer, 2000-2012

SCIENCE COMMUNICATOR

Radio broadcasts – *Self-Improvement Wednesday,* ABC Radio (702) – four broadcasts 2015-2016

Several television appearances including on *Insight* SBS

Mackenzie’s Mission October 2018 – Channel 7 news, Channel 9 news. ABC 24, Radio National

Name: Dr Alison Colley
Qualifications: MBBS University of NSW in 1980 and paediatrics at the Sydney Children's Hospital to obtain her FRACP in 1989. MMedSc (epidemiology) 1990 Uni of Newcastle
Current position(s): Director, Department of Clinical Genetics, SWSLHD
Senior Staff Specialist, Clinical Geneticist, Senior Clinical Lecturer UNSW

Areas of research excellence related to OneGenome Theme: Alison is a Clinical Geneticist with a particular interest in children with undiagnosed intellectual disability, dysmorphic syndromes and neurological phenotypes- in the setting of consanguinity. She is actively recruiting patients with undiagnosed intellectual disability syndromes for genomic testing through the Kinghorn Centre of Clinical Genomics, as part of a philanthropic grant.

Dr Colley trained in genetics at Sydney Children's Hospital and Royal Children's Hospital, Melbourne before going to Manchester, UK, for two years for genetic research and further clinical training. In 1991 Dr Colley took up a staff specialist clinical geneticist position in Hunter Genetics, Newcastle NSW, where she was Chief Investigator on NHMRC project grant (950320) (*Molecular Characterisation of Birth Defects on Human Chromosome 22*), before coming to Liverpool as the founding geneticist in 1996. In 2001 Dr Colley was awarded her Masters in Medical Science in Epidemiology and biostatistics from the University of Newcastle Centre for Epidemiology.
Dr Colley is a member of the NSW Ministry of Health Genetics Services Advisory Committee. Dr Colley is a past president and secretary of the Australasian Society of Clinical Geneticists which is a subgroup of the Human Genetics Society of Australasia.

Total Publications: Alison has 39 peer reviewed papers, 6 in last 5 years
Key Research Papers Last 5yrs years
Muhn F, Klopocki E ...Colley A... et al Novel mutations of the PRKARIA gene in patients with acrodysostosis. Clinical Genetics 84(6) 531-8 2013
Roscioli T,...Colley A... et al. Genotype and clinical care correlations in craniosynostosis AJMG C 163:259-270 2013
Goldlust I,...Colley A et al Mouse model implicates GNB3 duplication in a childhood obesity syndrome PNAS 110(37) 14990-4 2013
Dellabona C ...Colley A et al Novel ovario leukodystrophy related to AARS2 mutations . Neurology 82(23) 2063-71 2014
Chaoui A,...Colley A et al Subnuclear re-localisation of SOX10 and p54RB correlates with a unique neurological phenotype associated with SOX10 missense mutations. Hum Mol Gen 24(17) 4933-47 2015
Todd E,...Colley A et al Next generation sequencing in a large cohort of patients presenting with neuromuscular disease before or at birth. Orphanet Journal of Rare Diseases 10:148 2015
In 2014 Dr Colley joined the NSW Genomics Think Tank, NSW Health Pathology, and participated in meetings to develop a framework to progress genomic testing and service delivery in NSW. Dr Colley is an Associate Investigator on the NHMRC CRE grant APP1061507 2014 *Transforming the Diagnosis and Management of Intellectual Disability through Genomics*. Dr Colley is a co-investigator on NHMRC Project grant APP1099731 *New Genetic Testing for Couples who are Related and planning a Pregnancy*. Dr Colley has been granted a philanthropic donation of $300,000 from the Garvan Institute Foundation for genomic sequencing of 100 children with intellectual disability and a health economic study looking at the feasibility of genomic sequencing becoming the first line investigation of the genetic cause of intellectual disability.

Evidence of Excellence in Teaching/Training:
She has mentored 10 genetic counsellors to obtain certification, supervised 4 RACP fellows through advanced training and is a dedicated teacher for UNSW and WSU medical courses.

Awards and Appointments (Last 5 years)
Dr Colley is the Director, Department of Clinical Genetics for SWSLHD. The Department is based in Liverpool Hospital with clinics in Liverpool, Bankstown, Camden/Campbelltown and in Bowral. A clinical genetics service is also provided to Murrumbidgee and Southern NSW LHDs through outreach clinics, thus the department provides genetics services to a total population of nearly 1.5 million.

A. PERSONAL DETAILS

Name: **Michael Francis Buckley**
BHB MBChB PhD FRCPA FHGSA FRCPath FFSc

Address: Randwick Genetics laboratory, NSW Health Pathology
Prince of Wales Hospital, Barker Street
Randwick, NSW 2031
Sydney, AUSTRALIA

Tel: (+61-2) 938 29125 (business hours)
Mob: (+61) 0466 11 3738
Email1: michael.buckley@health.nsw.gov.au
Email2: phenocopy69@gmail.com

Date of Birth: 27th December, 1959
Citizenship: Australia & New Zealand
ORCID: 0000-0002-8298-8758

Summary

Dr Buckley is the Clinical Director of the Genetics Laboratory on the Randwick campus of NSW Health Pathology, Sydney, with appointments as Consultant Genetic Pathologist at ACT Pathology, Canberra. He leads a team of 4 genetic pathologists, 3 pathology trainees and 40 scientific and technical staff involved the genetic and genomic diagnosis of disease. Dr Buckley is currently the President of the Human Genetics Society of Australasia.

As one of Australia's leading Genetic Pathologists he has held the positions of Chief Examiner in Genetics and Registrar for the RCPA Board of Censors and as Chief Examiner in Molecular Genetics for the Human Genetics Society of Australasia (HGSA). In addition he has held positions on Federal and State Government committees such as the National Pathology Accreditation Advisory Council (NPAAC) and the NSW Genetic Services Advisory Committee. Between 2008-2011 he was awarded a Marie Curie International Fellowship in the Department of Human Genetics at Radboud University Nijmegen Medical Centre, the Netherlands. He has a career total of 47 publications, including 14 in the five year period between 2010-2014. His two most cited articles on the identification of Cyclin D1 in breast cancer have together been cited more than 1000 times and are Citation Classics. He has been a co-investigator on $5.4 million in funded national and international competitive grants in the last 5 years, of which $900K has been as CI-A. This has included a Marie Curie International Fellowship (Craniotechgene), an NHMRC Targeted Call in genomics (APP1113531), NHMRC Centres for Research Excellence (APP1117394 and APP1031893), NHMRC Partnership Grant (APP1113895) and 3 NHMRC Project Grants (APP1024364; APP1022707; APP1045465) and 3 Research Infrastructure Grants.

Dr Buckley is an authority on the application of genome diagnostics in healthcare and its use in the identification of new disease genes. He has a long standing interest in the field of neurocognitive disorders with 4 papers on the population genetics of Fragile X and other trinucleotide repeat disorders associated with neurodevelopmental disorders. In two recent papers his group quantified the clinical utility of combined screening techniques for Duchenne muscular dystrophy, and determined the contribution to the intellectual disability component of this multisystem disorder attributable to mutation heterogeneity.

Dr Buckley has also made significant discoveries in the molecular genetic basis of Mendelian disorders including the roles of ENPP1 in Infantile Arterial Calcification, SP110 in hepatic veno-occlusive disease with immunodeficiency syndrome, SLC29A3 in Histiocytosis-Lymphadenopathy Plus syndrome, and FREM1 in metopic craniosynostosis. In addition he has played key roles in collaborative efforts to identify disease genes such as ISPD in Walker Warburg syndrome, and IL11RA in recessive forms of Crouzon syndrome.

Since 2000, Dr Buckley has supervised to completion 7 PhD and 2 Master students. He has also been the trainee supervisor of 7 Fellowship candidates with The Royal College of Pathologists of Australasia (RCPA).

Dr Buckley has been a member of the International Craniofacial Consortium since its inception and has contributed patients to its effort to map common variants that influence craniofacial diseases. This led

to the publication in Nature Genetics in 2012 of the first GWAS in craniofacial disease which showed that common variants in two genes, BMP2 and BBS9 influence the risk of craniosynostosis. This paper is the most prominent of eight studying the genetics of craniosynostosis, including the first publication of a disease gene in Metopic craniosynostosis,

Current Appointments: (* indicates a non-salaried appointment)

1997-date	Clinical Director, SEALS Genetics, NSW Health Pathology Prince of Wales Hospitals, Sydney.
2017-2019	*President, Human Genetics Society of Australasia
2017	Visiting Medical Officer, Supervising Genetic Pathologist ACT Pathology, Canberra

Previous Appointments:

2015-2017	Vice-President Human Genetics Society of Australasia
2014-2017	Consultant Genetic Pathologist The Kinghorn Centre for Clinical Genomics, Garvan Institute of Medical Research
2008-2011	Marie Curie International Incoming Fellow, Department of Human Genetics, Radboud University Medical Centre, Nijmegen, the Netherlands.
2002-2009	*Chief Examiner in Genetics, Royal College of Pathologists of Australasia.
2007-2008	*Chief Examiner in Molecular Genetics, Human Genetics Society of Australasia.
2001-2004	*Registrar, Board of Censors, Royal College of Pathologists of Australasia
1993-1997	Fellow in Genetics, Department of Haematology & Genetics, Sydney Children's and Prince of Wales Hospitals, Sydney.
1992-1993	NHMRC Australian Postdoctoral Fellow, Cancer Biology Division, Garvan Institute, Sydney.
1990-1991	Victorian Medical Board Pathology Training Fellowship, Victorian Cancer Cytogenetics Service, Melbourne.
1986-1989	Anti-cancer Council of Victoria Medical Postgraduate Fellow, Monash Medical School, Melbourne.
1984-1985	House Surgeon, Auckland District Hospitals Board, Auckland, NZ.

Association with Hong Kong

2015	NATA auditor for Queen Elizabeth hospital genetic services
2016	Sydney host for a planning delegation for genetic laboratory services of the Hong Kong Children's Hospital
2016	Genetic and genomics laboratory 3 month placement for visiting pathologists Dr Jason So and Dr KF Wong
2017	Lead pathologist, Hong Kong Health Authority commissioned training in Clinical Genomics
2017	Laboratory host for Dr Mary Tang, a 1 week attachment in prenatal genomics

B. EDUCATION, TRAINING AND AWARDS

Secondary

1973-1977	St Paul's Collegiate School, Hamilton, New Zealand

Tertiary

Undergraduate: School of Medicine, University of Auckland, New Zealand

1978-1980	BHB (Course content: Human Anatomy, Physiology, Biochemistry, Psychology)
1981-1983	MBChB (Course content: Medicine, Surgery, Paediatrics, Pathology, ObGyn, Psychiatry)

Graduate School

Dept of Pathology and Immunology, Monash University, Melbourne Australia

1986-1990	Anti-Cancer Council of Victoria Medical Postgraduate Fellowship. PhD Thesis Topic: The human plasma cell antigen, PC1. Supervisor: Prof James W. Goding.

Postgraduate

Medical Postgraduate: Fellowship of the Royal College of Pathologists of Australasia

1987-1991	RCPA Training programs in Immunopathology and in Genetics Supervisors: Prof James McCluskey and A/Prof O. Margaret Garson

Postdoctoral

Garvan Institute for Medical Research, Sydney (Australia)

1992-1993	NHMRC Australian Postdoctoral Fellowship. Postdoctoral Research Topic: Cell cycle regulation in breast cancer. Supervisor: Prof Robert Sutherland (Head of Division).

Prizes and Awards

1980-1983	Maurice and Phyllis Paykel Scholarship for Medical Research
1986-1989	Anti-Cancer Council of Victoria Medical Postgraduate Fellowship
1990-1991	Victorian Medical Board Training Fellowship
1992-1993	NHMRC Australian Postdoctoral Fellowship
1991 (declined)	Sydney University Faculty of Medicine Postdoctoral Fellowship
1999	University of NSW Teaching Award in Pathology
2008-2010	Marie Curie International Incoming Fellowship, European Union

Degrees and Fellowships

1981 BHB	Bachelor of Human Biology (University of Auckland)
1984 MBChB	Bachelors of Medicine and Surgery (University of Auckland)
1991 PhD	Doctor of Philosophy (Monash University Melbourne)
1991 FRCPA	Fellowship (Genetics), Royal College of Pathologists of Australasia
1994 MHGSA	Membership (Cytogenetics), Human Genetics Society of Australasia
2000 FHGSA	Fellowship (Molecular Genetics), Human Genetics Society of Australasia
2010 FFSc	Foundation Fellow, Faculty of Science (Royal College of Pathologists of Australasia)
2012 FRCPath	Fellowship Royal College of Pathologists (United Kingdom)

Medical and Scientific Registrations

1984-2000	Medical Board of New Zealand
1985-1995	Medical Board of Victoria
1991-date	Specialist Registration in Pathology, Medicare Australia
1992-2010	New South Wales Medical Board (MPO 281514)
1996-date	General Medical Council of UK (4342687)
1998-date	Approved Pathology Practitioner, Medicare Australia (APP 21779W)
2010-date	Australian Health Practitioner Registration (MED0001160804)
2013-date	Registered Clinical Scientist, Health & Care Professional Council, UK (CS18472)

C. COMMITTEES

A. International Committees

2013	EurogenTest, Best Practice Working Party in Next Generation Sequencing
2006	Organisation for Economic Cooperation and Development Quality Assurance in Molecular Genetics

B. Australian Federal Government Committee Memberships

2012	Genetics Working Party, "Development of a National Framework for Genetic Testing"
2005-2008	Pathology Services Advisory Committee, Genetics Working Party
2005-2007	NPAAC Cytogenetics subcommittee
2000	NPAAC Quality Systems subcommittee
2000	Medical Services Advisory Committee, Fragile XA subcommittee
1999-2003	National Pathology Accreditation Advisory Council, RCPA nominee
1999	NPAAC Nucleic Acid Amplification subcommittee (chair)

C. New South Wales State Government Committee Memberships

2018-ongoing	Member, NSW Health's Genomics Framework Translational Medicine Committee
2017- ongoing	Chair, NSW Health Pathology's Rare Disease Genomics Committee
2012- ongoing	NSW Clinical Genetics Executive Committee
2005-2008	Genetics Services Advisory Committee, NSW Dept of Health
2005-2008	Cancer Institute of NSW, Cancer Genetics Working Group,
1997-2008	NSW Dept of Health, DNA Working Party

D. Professional Bodies

2008 - ongoing	Examiner in Molecular Genetics, Human Genetics Society of Australasia
2008 - ongoing	Examiner in Genetics, RCPA
1997-2009	Board of Censors, RCPA
1997-2009	Genetics Advisory Committee, RCPA
1995-1998	NSW Branch Committee, HGSA

D. SUPERVISION

Graduate students

Completed:

1996-2000	Dr Sultana Faradz PhD 1999
1999-2000	Can-Hong Zhao BSc (Hons 1st Class) 2001
2000-2008	Dr Peter Taylor PhD 2009
2002-2005	Dr Lisa Worgan MMedSc 2006*
2003-2005	Glenda Mullan MSc 2006
2003-2006	Dr Carol Cheung PhD 2005
2003-2008	Dr Edwin Kirk PhD 2007*
2004-2007	Dr Tony Roscioli PhD 2007
2007-2009	Corinna Walsh BSc (Hons 1st Class) 2009*
2005-2011	Melody Caramins PhD 2011 (part time)
2005-2012	Simon Cliffe PhD 2012 (part time)
2012	Nila Quayam Grad Dip Biochem Mol Gen

(* indicates secondary supervisorship)

Postgraduate medical fellows:

2004-2005	Dr Adetola Daramola (cytogenetics)
2005-2006	Dr Christopher Bell FRCPA (molecular genetics)
2005-2006	Dr Elizabeth Tegg FRCPA (cytogenetics)
2005-2006	Dr Melody Caramins FRCPA (molecular Genetics)

2013-2013	Dr Meaghan Wall FRCPA (cytogenetics)
2013-2015	A/Prof Edwin Kirk FRCPA (medical genomics)
2014-2018	Dr Eric Lee FRCPA (medical genomics)
2016-	Mrs Fiona Webb (RCPA FSc trainee in medical genomics)
2017-	Mrs Corinna Cliffe (RCPA FSc trainee in medical genomics)
2018-	Dr Marina Beric (RCPA trainee in medical genomics)
2018-	Dr Cheng-Yee Chan-Nixon (RCPA trainee in medical genomics)
2018-	Dr Samantha Sundercombe (RCPA trainee in medical genomics)

E. GRANTS

2018-2021 Mackenzie's Mission: The Australian Reproductive Carrier Screening Project
$20,000,000
PIA Kirk EP, PIB Delatycki M, PIC Pachter N
AIA Laing N, AIB Barlow-Stewart K, AIC Schofield D, AID Farrar M, AIE Bruno D, AIF Lunke S, AIG Beilby J, AIH Davis M, AII Fietz M, AIJ Newson A, AIK Amor D, AIL Robson S, AIM Emery J, AIN Buckley MF, AIO Roscioli T, AIP Braithwaite J, AIQ Massie J, AIR Archibald A, AIS Meldrum C, AIT McGaughran J, AIU Liebelt J, AIV Lau C, AIW Fletcher J, AIX Colley A, AIY Dunlop K, AIZ Shrestha R, AIZ1 Wilson M. Affiliates: Casella R, Casella J

2018-2023 APP1151906 NHMRC Partnership Project $1,144,787
The economic impact of providing precision medicine through whole genome sequencing
CIA Deborah Schofield CIB Tony Roscioli: CIC Dr Michael Field, CID Michael Buckley

2016-2020 APP1117394 NHMRC Centre of Research Excellence $2,499,330
Transforming the Genomic Diagnosis and Management of Severe Neurocognitive Disorders
CIA Tony Roscioli: CIB Prof Jozef Gecz: CIC Dr Michael Field, CID Deborah Schofield, CIE Michael Buckley, CIF Kathryn North, CIG Marcel Dinger, CIH John Christodoulou, CII David Amor, CIJ Gareth Baynam:

2017-2020 Sydney Partnerships for Health Education Research and Enterprise $ 500,000
Genome Connect: Translating Genomic Medicine to Clinical Care
CIA Tony Roscioli, CIB Michael Buckley, CIC Dr Michael Field, CID Deborah Schofield

2015-2019 APP1113895 NHMRC Partnership Project $1,263,576
The economic and social impacts of genetic sequencing for intellectual disability
CIA Deborah Schofield CIB Tony Roscioli: CIC Dr Michael Field, CID Michael Buckley

2013-2015 APP1045465 NHMRC Project Grant $565,181
Gene identification in familial orofacial clefts by next generation sequencing
CIA Tony Roscioli, CIB A/Professor Jo Huiqing Zhou, CIC Professor Timothy Cox
CID Michael Buckley, CIE Prof Hans van Bokhoven CIF A/Prof Edwin Kirk

F. PUBLICATIONS AND PRESENTATIONS

Thesis
The Plasma Cell Membrane Glycoprotein PC1 (1990). Monash University, Melbourne, Australia.

Original Research and Reviews
1. Buckley MF, Goding JW (1988). Preparation of bacteriophage lambda DNA using the TL-100 ultracentrifuge. Analytical Biochemistry 175(1):281-3.

2. Buckley MF, Loveland KA, McKinstry WJ, Garson OM, Goding JW (1990). Plasma cell membrane glycoprotein PC-1. Journal Biological Chemistry 265(29):17506-11

3. Bashford J, Szer J, Wiley JS, Buckley M, Garson OM, van der Weyden MB (1991). Treatment of acute promyelocytic leukaemia relapsing after allogeneic bone marrow transplantation with all-trans-retinoic acid. Br J Haematol 79:331-4

4. Buckley MF, Goding JW (1992). Plasma cell membrane glycoprotein Pca-1 linked to the proto-oncogene Myb on mouse chromosome 10. Immunogenetics. 36(3):199-201

5. Buckley MF, Sweeney KJE, Hamilton JA, Sini RL, Manning DL, Nicholson RI, deFazio A, Watts CKW, Musgrove EA, Sutherland RL (1993). Expression and amplification of cyclin genes in human breast cancer. Oncogene 8:2127-33

6. Musgrove EA, Lee CSL, Buckley MF, Sutherland RL (1994). Cyclin D1 Induction in Breast Cancer Cells Shortens G1. PNAS 91:8022-26

7. Musgrove EA, Buckley MF, de Fazio A., Watts CKW, Sutherland RL (1994). Expression and regulation of cyclin genes in breast cancer cells In: The Cell Cycle: Regulators, Targets, and Clinical Applications. Hu VW (Ed), Plenum Press NY

8. Rubinsztein DC, Leggo J, Coetze GA, Irvine RA, Sequence variation and size ranges of CAG repeats in the Machado-Joseph disease, spinocerebellar ataxia type 1 and androgen receptor genes. Hum Mol Genet 4(9); 1585-90

9. Faradz SM, Buckley MF, Lam-Po-Tang PR, Leigh DA, Holden JJA (1999). Molecular screening for fragile X syndrome among Indonesian children with developmental disability Am J Med Genet 83:350-1

10. Ryan MM, Taylor P, Donald JA, Ouvrier RA, Buckley MF, North KM (1999) A novel syndrome of episodic muscle weakness maps to Xp22. 3. Am J Hum Genet. 65(4):1104-13

11. Buckley MF, James JW, Brown DE, Whyte GS, Dean MG, Chesterman CN, Donald JA (2000). A novel approach to the assessment of variations in the human platelet count. Thromb Haemost. 83(3):480-4

12. Faradz SMH, Pattiiha MZ, Leigh DA, Jenkins M, Leggo J, Buckley MF, Holden JJA (2000). Genetic diversity at the FMR1 locus in the Indonesian population. Annals of Human Genetics 64(4):329

13. O'Toole G, MacKenzie D, Buckley MF, Lindeman R, Poole M (2001). A review of therapeutic angiogenesis and consideration of its potential applications to plastic and reconstructive surgery. Br J Plast Surg. 54(1):1-7

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Co-authored Laboratory Standards Publications

1. NPAAC Publication 2729 Laboratory Standards for Nucleic Acid Based Testing. First Edition (2001). (Subcommittee chairman and principal author)
2. NPAAC Publication 2882. Guidelines for Quality Systems in Medical Laboratories. First Edition (2001)
3. NPAAC Publication 2616. Standards for Pathology Laboratories Third Edition (2002).
4. NPAAC Publication 2316. Standards and Guidelines for Cytogenetics Laboratories. First Edition (2006)

Invited Oral Presentations

5. Buckley MF, Ryan MM, Taylor PJ, Donald JA, Ouvrier RA, Morgan G, Danta G, North KN (1999). A novel syndrome of episodic muscle weakness maps to Xp22.3. ASHG 1999 San Francisco Abstract 164. American Society of Human Genetics, San Francisco - 1999.
6. Buckley MF, High through-put technologies for aneuploidy screening. RCPA Pathology Update, Sydney - 2002.
7. Buckley MF. Genetic regulation of human platelet count. RCPA Pathology Update, Sydney - 2004
8. Buckley MF. Clinical utility of comprehensive mutation detection in DMD. RCPA Pathology Update, Sydney - 2008
9. Cliffe ST, Kramer J, Hussain K, Robben J, de Jong E, Nibbeling E, Kamsteeg E-J, Wong M, Prendiville J, James C, Padidela R, Becknell C, van Bokhoven H, de Brouwer AP, Deen PMT, Hennekam RCM, Lindeman R, Schenck A, Roscioli T, Buckley MF (2009) The SLC29A3 gene is mutated in pigmented hypertrichosis with insulin dependent diabetes mellitus syndrome and interacts with insulin signaling. European Society of Human Genetics, Vienna 2009 (Plenary 2- What's New in Genetics).
10. Hoischen A, Gilissen C, van der Vliet W, Arts P, Wieskamp N, Vermeer S, Meijer R, Buckley M, Kremer B, van Slobbe-Knoers N, Veltman J, Scheffer H (2009) Massive parallel sequencing of ataxia genes after array-based enrichment. European Society of Human Genetics, Vienna 2009 (Plenary 2- What's New in Genetics).
11. Buckley MF, Hoischen A, Arts P, van der Vliet W, Wieskamp N, Gilissen C, Anderson P, Veltman J, Scheffer H. A transcriptome snapshot of midline craniosynostosis. VKGN/VKGL/NVGC meeting Utrecht, June 18, 2009
12. Vissers L, Cox TC, Boyd S, Buckley MF, Roscioli T. FREM1 mutations in metopic craniosynostosis. European Society of Human Genetics, Goteburg, Sweden 2010
13. Buckley MF. DNA Sequencing in the genetics diagnostics laboratory. RCPA Pathology Update, 2011 Melbourne.
14. Buckley MF. Next generation Sequencing in Diagnostics - The promise and practicalities. RCPA Pathology Update, 2011 Melbourne.

15. Buckley MF. New research strategies in craniosynostosis. Royal Australasian College of Surgeons ASM 2011-Adelaide.
16. Buckley MF. Keynote Address: The Sutherland Lecture, HGSA Canberra 2012
17. Buckley MF. Plenary: Next Generation Sequencing in the Clinic, HGSA Canberra 2012
18. T. Roscioli, E.-J. Kamsteeg, K. Buysse, I. Maystadt, J. van Reeuwijk, C. van den Elzen, E. van Beusekom, M. Riemersma, R. Pfundt, L. E. L. M. Vissers, M. Schraders, M. F. Buckley, H. G. Brunner, H. Zhou, J. A. Veltman, C. Gilissen, G. M. S. Mancini, M. A. Willemsen, D. Petkovi Ramadža, D. Chitayat, C. Bennett, E. Sheridan, E. A. J. Peeters, G. M. B. Tan-Sindhunata, H. Kayserili, O. Abd El-Fattah El-Hashash, D. L. Stemple, D. J. Lefeber, Y.-Y. Lin, H. van BokhovenNext generation sequencing detects mutations in ISPD as a common cause of Walker-Warburg syndrome with defective glycosylation of α-dystroglycan.(Abstr 214, ASHG 2012, San Francisco)
19. Buckley MF. Keynote Address: ANZSCN, Sydney 2013
20. Buckley MF. Keynote: Next Generation Sequencing in the Clinic, ANN Sydney 2013
21. Buckley MF. Plenary: Exome Sequencing in the Clinic. Update in Medical Genetics and Genetic Pathology, 15-18 June 2013, Sanctuary Cove, QLD
22. Buckley MF et al. Plenary: Identification of a Novel Gene For Midline Craniosynostosis By Whole Exome Sequencing. 3rd Annual NGS Asia, Singapore, 8 October, 2013
23. Buckley MF. Keynote: Exome Sequencing in the Clinic. National Pathology Forum, Sydney. 14th October, 2013
24. Buckley MF. Keynote: Gene assay testing, what is being tested for, applicability and implications. Australian Institute of Medical Sciences Centenary Meeting, Sydney September 2015
25. Buckley MF. Keynote: Applications of Genomics. Australian Institute of Medical Sciences Centenary Meeting, Sydney September 2018

Invited Lectures (other than at conferences - last 5 years only)

26. Lecturer: Understanding Your Genome: Garvan Institute March 2014
27. Course Lecturer: Laboratory Practice and Next Generation Sequencing, RCPA, FScRCPA and HGSA course in genetics and genetic pathology, Sanctuary Cove, Australia
28. Garvan Institute of Medical Research, Sydney 2012. Leaders in Science Lecture Series
29. Royal College of Pathologists of Australasia, Sydney 2012. Research Involvement for Pathology Trainees

Inquiry into the convictions of Kathleen Megan Folbigg

21 December 2018

Conjoint Professor Edwin Kirk
Staff Specialist
Randwick Genetics Laboratory
Level 4, Campus Centre Building
Prince of Wales Hospital
RANDWICK NSW 2031

By email: Edwin.kirk@health.nsw.gov.au

Dear Professor Kirk

Letter of Engagement

Background

On 22 August 2018 the Governor of New South Wales directed that an inquiry be held into the convictions of Kathleen Megan Folbigg for three counts of murder, one count of manslaughter and one count of maliciously inflicting grievous bodily harm in respect of her four children on 21 May 2003 ("the Inquiry"). The Crown Solicitor is the Solicitor Assisting the Honourable Reginald Oliver Blanch AM QC ("the Judicial Officer") with the Inquiry.

The scope of the Inquiry includes consideration of expert medical evidence, including:

- any new research or advances in medical science relevant to the causes of death of each child and the cause of the apparent or acute life threatening event in respect of one child, Patrick.
- expert medical opinion as to the causes of death of each child and the cause of the apparent or acute life threatening event in respect of Patrick in light of any relevant new research or advances in medical science.
- any new research or literature concerning the incidence of reported deaths of three or more infants in the same family attributed to unidentified natural causes.
- any other related expert medical evidence.

Scope of engagement

As discussed you are engaged, as one of a team of experts, to interpret raw data produced as a result of genetic sequencing and testing arranged by the Inquiry in respect of the Folbigg family, and provide an expert report to the Inquiry regarding the presence of any

likely pathogenic genes, or pathogenic genetic variants in genes, that are known to be associated with sudden unexpected death in infancy.

As per our correspondence to you dated 20 December, we anticipate the data will be available by early February 2019.

We confirm the team of experts the Inquiry is engaging comprises:

- Dr Michael Buckley MBChB PhD FRCPA FHGSA FRCPath: senior staff specialist genetic pathologist employed by NSW Health Pathology and currently the President of the Human Genetics Society of Australasia

- Dr Alison Colley MBBS FRACP FRCPA: senior staff specialist clinical geneticist in specialist practice at Liverpool Hospital and Director of the Liverpool Genetics Service

- Professor Matthew Cook MBBS PhD FRACP FRCPA: clinical immunologist in specialist practice employed by ACT Health at Canberra Hospital and the ACT pathologist service.

It is possible that you will be required to give oral evidence at the public hearings of the Inquiry. It is expected the hearing relevant to genetics will be held in March 2018. We will advise you as soon as the hearing dates have been listed.

Preparation of your report

The Inquiry would be assisted if you could interpret the results of the genetic testing and prepare a report which identifies and explains whether any of the results of that testing are relevant to the causes of death of each of the children.

Your report should only offer opinions to the extent those opinions are based upon your knowledge, training and fields of specialist expertise.

In preparing your report, please:

i. identify (and reference as appropriate) any facts and assumptions from materials upon which you rely;

ii. show how those facts and assumptions relate to your opinions;

iii. provide an explanation of your reasons for each of your opinions;

iv. define and explain any technical terms; and

v. if necessary, set out any qualification or reservations you have about the opinions expressed in your report (for instance, because of reservations you hold about a fact, or if further information is required, or for any other reason).

Documents with which you are briefed

As you know, in advance of the meeting of geneticists on 10 December, we provided you with a set of briefing documents. For your reference, the index to this set is set out below in **Annexure A**. We will provide you with any other necessary documents as they come to hand.

Expert code of conduct and curriculum vitae

At **Annexure B** to this letter I set out the Expert Witness Code of Conduct and ask that you read it carefully. In your report you should acknowledge that you have read the Code and agree to be bound by it. I suggest the following form of words be included in the body of the report:

> "I, Professor Edwin Kirk, acknowledge that for the purpose of Rule 31.24 of the Uniform Civil Procedure Rules 2005 that I have read the Expert Witness Code of Conduct in Schedule 7 to the said rules and agree to be bound by it."

I also request that you please attach a copy of your curriculum vitae to your report.

Confidentiality

Please ensure you keep your engagement, the documents with which you are briefed, and your report **confidential**.

Conclusion

Please do not hesitate to contact Amber Richards, Senior Solicitor, on (02) 9258 0832 or amber.richards@cso.nsw.gov.au if you have any queries or require anything further to assist in the preparation of your report.

Kind regards

Amber Richards
Senior Solicitor
for Crown Solicitor

Encl. (1)

ANNEXURE A

Index to briefing material

Tab	Document	Date	Source
1.	Medical testing of Patrick Folbigg	13 February 1991	ODPP Volume 1 of 7, Tab 29
2.	Letter to Doctor Wilcken regarding newborn blood sample	11 October 1999	ODPP SYD02582197, Tab 168
3.	Genetics report regarding death of Caleb Folbigg	13 January 2000	SC054200, Tab 211
4.	Genetics report regarding death of Patrick Folbigg	13 January 2000	SC054200, Tab 212
5.	Genetics report regarding death of Sarah Folbigg	13 January 2000	SC054200, Tab 213
6.	Genetics report re death of Laura Folbigg	13 January 2000	SC054200, Tab 214
7.	Expert Certificate / Statement of Doctor Bridget Wilcken and exhibits 7a – 7c	14 January 2000	ODPP SYD02583893, Tab 98
7a.	Letter from Doctor Alison Colley to Doctor Bridget Wilcken regarding Caleb and Patrick Folbigg	4 December 1991	ODPP SYD02583893, Tab 100
7b.	Letter from Doctor Bridget Wilcken to Doctor Alison Colley regarding Caleb and Patrick Folbigg	10 December 1991	ODPP SYD02583893, Tab 101
7c.	NSW Newborn Screening Programme Report regarding Caleb, Patrick, Sarah and Laura Folbigg	13 January 2000	ODPP SYD02583893, Tabs 103-106
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ANNEXURE B

Uniform Civil Procedure Rules 2005, Sch 7: Expert Witness Code of Conduct

1 Application of code

This code of conduct applies to any expert witness engaged or appointed:

(a) to provide an expert's report for use as evidence in proceedings or proposed proceedings, or

(b) to give opinion evidence in proceedings or proposed proceedings.

2 General duties to the Court

An expert witness is not an advocate for a party and has a paramount duty, overriding any duty to the party to the proceedings or other person retaining the expert witness, to assist the court impartially on matters relevant to the area of expertise of the witness.

3 Content of report

Every report prepared by an expert witness for use in court must clearly state the opinion or opinions of the expert and must state, specify or provide:

(a) the name and address of the expert, and

(b) an acknowledgement that the expert has read this code and agrees to be bound by it, and

(c) the qualifications of the expert to prepare the report, and

(d) the assumptions and material facts on which each opinion expressed in the report is based (a letter of instructions may be annexed), and

(e) the reasons for and any literature or other materials utilised in support of each such opinion, and

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(g) any examinations, tests or other investigations on which the expert has relied, identifying the person who carried them out and that person's qualifications, and

(h) the extent to which any opinion which the expert has expressed involves the acceptance of another person's opinion, the identification of that other person and the opinion expressed by that other person, and

(i) a declaration that the expert has made all the inquiries which the expert believes are desirable and appropriate (save for any matters identified explicitly in the report), and that no matters of significance which the expert regards as relevant have, to the knowledge of the expert, been withheld from the court, and

(j) any qualification of an opinion expressed in the report without which the report is or may be incomplete or inaccurate, and

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(1) Where an expert witness has provided to a party (or that party's legal representative) a report for use in court, and the expert thereafter changes his or her opinion on a material matter, the expert must forthwith provide to the party (or that party's legal representative) a supplementary report which must state, specify or provide the information referred to in clause 3 (a), (d), (e), (g), (h), (i), (j), (k) and (l), and if applicable, clause 3 (f).

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Inquiry into the convictions of Kathleen Megan Folbigg

21 December 2018

Doctor Alison Colley
Senior Staff Specialist Geneticist, Director of Clinical Genetics
Department of Clinical Genetics
Liverpool Hospital
Locked Bag 7279
LIVERPOOL BC NSW 1871

C/-
Deanne Tadros
Senior Legal Officer
NSW Ministry of Health
73 Miller Street
NORTH SYDNEY NSW 2060

By email: Deanne.tadros@health.nsw.gov.au

Copied to: Ian.fraser@fjc.net.au; Blaise.lyons@health.nsw.gov.au

Dear Dr Colley

Letter of further engagement

Engagement to date

On 13 November 2018 we engaged you to prepare a report for the Inquiry which:

1. identified and explained any new research or medical advances in your area of expertise since 2002 relevant to the causes of death of any of the Folbigg children and/or the cause of the apparent or acute life threatening event in respect of Patrick; and

2. provided your view as to whether, and if so what, further genetic testing can now be performed relevant to the causes of death of any of the Folbigg children and/or the cause of the apparent or acute life threatening event in respect of Patrick.

You accordingly provided a report to the Inquiry dated 26 November 2018, and attended a meeting of geneticists on 10 December 2018 to assist in identifying the types of genetic testing that can be performed on appropriate samples from the Folbigg family.

Scope of further engagement

As discussed you are now engaged, as one of a team of experts, to interpret raw data produced as a result of genetic sequencing and testing arranged by the Inquiry in respect of the Folbigg family, and to provide an expert report to the Inquiry regarding the presence of any likely pathogenic genes, or pathogenic genetic variants in genes, that are known to be associated with sudden unexpected death in infancy.

As per our correspondence to you dated 20 December, we anticipate the data will be available by early February 2019.

We confirm the team of experts the Inquiry is engaging comprises:

- Dr Michael Buckley MBChB PhD FRCPA FHGSA FRCPath: senior staff specialist genetic pathologist employed by NSW Health Pathology and currently the President of the Human Genetics Society of Australasia.

- Professor Edwin Kirk MBBS PhD FRACP FRCPA: senior staff clinical geneticist and genetic pathologist employed by NSW Health Pathology and Chief Examiner in Genetics for the Royal College of Pathologists of Australia.

- Professor Matthew Cook MBBS PhD FRACP FRCPA: clinical immunologist in specialist practice employed by ACT Health at Canberra Hospital and the ACT pathologist service.

It is possible that you will be required to give oral evidence at the public hearings of the Inquiry. It is expected the hearing relevant to genetics will be held in March 2018. We will advise you as soon as the hearing dates have been listed.

Preparation of your further report

Your report should only offer opinions to the extent those opinions are based upon your knowledge, training and fields of specialist expertise.

In preparing your report, please:

i. identify (and reference as appropriate) any facts and assumptions from materials upon which you rely;

ii. show how those facts and assumptions relate to your opinions;

iii. provide an explanation of your reasons for each of your opinions;

iv. define and explain any technical terms; and

v. if necessary, set out any qualification or reservations you have about the opinions expressed in your report (for instance, because of reservations you hold about a fact, or if further information is required, or for any other reason).

Documents with which you are briefed

As you know, to assist in the preparation of your previous report, we provided you with a set of briefing documents. For your reference, the index to this set is set out below in **Annexure A**. We will provide you with any other necessary documents as they come to hand.

Expert code of conduct and curriculum vitae

At **Annexure B** to this letter I set out the Expert Witness Code of Conduct and ask that you read it carefully. In your further report you should acknowledge that you have read the Code and agree to be bound by it. I suggest the following form of words be included in the body of the report:

> "I, Dr Alison Colley, acknowledge that for the purpose of Rule 31.24 of the Uniform Civil Procedure Rules 2005 that I have read the Expert Witness Code of Conduct in Schedule 7 to the said rules and agree to be bound by it."

I also request that you please attach a copy of your curriculum vitae to your report.

Confidentiality

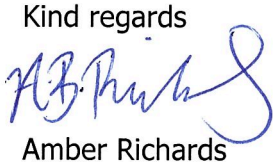
We note we intend to seek a non-publication order in respect of the data and the report(s) prepared by the data interpretation team.

Please ensure you keep your engagement, and any material received in respect of your engagement, **confidential**.

Conclusion

Please to not hesitate to contact Amber Richards on (02) 9258 0832 or amber.richards@cso.nsw.gov.au if you have any queries or require anything further to assist in the preparation of your report.

Kind regards



Amber Richards
Senior Solicitor
for Crown Solicitor

ANNEXURE A

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Inquiry into the convictions of Kathleen Megan Folbigg

21 December 2018

Dr Michael Buckley
Clinical Director
Randwick Genetics Laboratory
Level 4, Campus Centre Building
Prince of Wales Hospital
RANDWICK NSW 2031

By email: michael.buckley@health.nsw.gov.au

Dear Dr Buckley

Letter of Engagement

Background

On 22 August 2018 the Governor of New South Wales directed that an inquiry be held into the convictions of Kathleen Megan Folbigg on 21 May 2003 for three counts of murder, one count of manslaughter and one count of maliciously inflicting grievous bodily harm in respect of her four children ("the Inquiry"). The Crown Solicitor is the Solicitor Assisting the Honourable Reginald Oliver Blanch AM QC ("the Judicial Officer") with the Inquiry.

The scope of the Inquiry includes consideration of expert medical evidence, including:

- any new research or advances in medical science relevant to the causes of death of each child and the cause of the apparent or acute life threatening event in respect of one child, Patrick;
- expert medical opinion as to the causes of death of each child and the cause of the apparent or acute life threatening event in respect of Patrick in light of any relevant new research or advances in medical science;
- any new research or literature concerning the incidence of reported deaths of three or more infants in the same family attributed to unidentified natural causes; and
- any other related expert medical evidence.

Scope of engagement

As discussed you are engaged to:

- provide expert advice as to the type and nature of genetic testing which can and should be conducted in relation to the Folbigg family, having regard to the nature and extent of available samples and available testing;

- together with us, liaise with facilities such as the Australian Genome Research Foundation ("AGRF") and the Victorian Clinical Genetics Service ("VCGS") to identify the most appropriate samples on which the recommended testing is to be conducted and arrange for this testing to be completed and data produced in a timely manner; and

- as one of a team of experts, interpret raw data produced as a result of genetic sequencing and testing arranged by the Inquiry in respect of the Folbigg family, and provide an expert report to the Inquiry regarding the presence of any likely pathogenic genes, or pathogenic genetic variants in genes, that are known to be associated with sudden unexpected death in infancy.

As per our correspondence to you dated 20 December, we anticipate the data will be available by early February 2019.

We confirm the team of experts the Inquiry is engaging comprises:

- Professor Edwin Kirk MBBS PhD FRACP FRCPA: senior staff clinical geneticist and genetic pathologist employed by NSW Health Pathology and Chief Examiner in Genetics for the Royal College of Pathologists of Australia.

- Dr Alison Colley MBBS FRACP FRCPA: senior staff specialist and clinical geneticist in specialist practice at Liverpool Hospital, and Director of the Liverpool Genetics Service.

- Professor Matthew Cook MBBS PhD FRACP FRCPA: clinical immunologist in specialist practice employed by ACT Health at Canberra Hospital and the ACT pathologist service.

It is possible that you will be required to give oral evidence at the public hearings of the Inquiry. It is expected the hearing relevant to genetics will be held in March 2018. We will advise you as soon as the hearing dates have been listed.

Preparation of your report

Your report should only offer opinions to the extent those opinions are based upon your knowledge, training and fields of specialist expertise.

In preparing your report, please:

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Documents with which you are briefed

As you know, in advance of the meeting of geneticists on 10 December, we provided you with a set of briefing documents. For your reference, the index to this set is set out below in **Annexure A**. We will provide you with any other necessary documents as they come to hand.

Expert code of conduct and curriculum vitae

At **Annexure B** to this letter I set out the Expert Witness Code of Conduct and ask that you read it carefully. In your report you should acknowledge that you have read the Code and agree to be bound by it. I suggest the following form of words be included in the body of the report:

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I also request that you please attach a copy of your curriculum vitae to your report.

Confidentiality

Please ensure you keep your engagement, and any material received in respect of your engagement, **confidential**.

Conclusion

Please to not hesitate to contact Amber Richards on (02) 9258 0832 or amber.richards@cso.nsw.gov.au if you have any queries or require anything further to assist in the preparation of your report.

Kind regards

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(b) provide the court with a joint report specifying (as the case requires) matters agreed and matters not agreed and the reasons for the experts not agreeing, and

(c) abide in a timely way by any direction of the court.

6 Conferences of experts

Each expert witness must:

(a) exercise his or her independent judgment in relation to every conference in which the expert participates pursuant to a direction of the court and in relation to each report thereafter provided, and must not act on any instruction or request to withhold or avoid agreement, and

(b) endeavour to reach agreement with the other expert witness (or witnesses) on any issue in dispute between them, or failing agreement, endeavour to identify and clarify the basis of disagreement on the issues which are in dispute.