Twin Research and Human Genetics
Volume 20 ▌ Number 5 ▌ pp. 425–445

Abstracts for the 41st Human Genetics Society of Australasia Annual Scientific Meeting

Brisbane, Queensland

August 5–8, 2017

Plenaries and Orals

Plenary 1
SEARCHING FOR GENES INFLUENCING SUCCESSFUL BRAIN AGING

D. C. Glahn[1,2], J. E. Curran[3], E. E. Knowles[1], S. R. Mathias[1], R. L. Olvera[4,5], P. T. Fox[5], F. Chouinard-Decorte[6], A. C. Evans[6], L. Almasy[7,8], P. Kochunov[9], R. Duggirala[3], and J. Blangero[3]

[1] *Department of Psychiatry, Yale University School of Medicine, New Haven, CT, USA*
[2] *Olin Neuropsychiatric Research Center, Institute of Living, Hartford Hospital, Hartford, CT, USA*
[3] *South Texas Diabetes and Obesity Institute, University of Texas Rio Grande Valley School of Medicine, Brownsville, TX, USA*
[4] *Department of Psychiatry, University of Texas Health Science Center San Antonio, San Antonio, TX, USA*
[5] *Research Imaging Institute, University of Texas Health Science Center San Antonio, San Antonio, TX, USA*
[6] *McConnell Brain Imaging Centre, Montreal Neurological Institute, McGill University, Montreal, QC, CA*
[7] *Department of Genetics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA*
[8] *Department of Biomedical and Health Informatics, Children's Hospital of Philadelphia, Philadelphia, PA, USA*
[9] *Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, MD, USA*

Population projections suggest for the first time in humanhistory that there will be more individuals over the age of 65 years than below the age of 14 years by 2050. Indeed, the percentage of Americans over the age of 65 years is expected to increase from 13% in 2010 to over 20% in 2040. Thus, there is considerable interest in delineating the biological mechanisms that influence age-related changes to facilitate successful aging. As the brain appears to play a pivotal role in aging biology, one promising strategy is to define measures of brain structure and function that index concomitant aging outcomes. However, the biological bases of successful brain aging are poorly understood and there is considerable debate whether aging is intrinsically 'programmed' or incidental to cumulative environmental exposure. Yet, genes likely regulate both the developmental program and the robustness to environmental exposure, suggesting a role for genetic variation in brain aging. To establish phenotypes for gene discovery projects focused on brain aging, we utilized a quantitative gene-by-environment interaction analysis, where age is treated as an environmental factor, in a large cohort of randomly selected pedigrees (n = 1,129 subjects, age range 18–83 years). We found a heritable basis for neurocognitive and gray-matter deterioration as a function of age. In contrast, increasing white-matter incoherence with age appears to be non-genetic. Here we present linkage analyses, using phenotypes identified via the gene × age (G × A) interaction approach, to localize chromosomal regions involved in brain again. Results of these analyses suggest novel quantitative trait loci influencing successful brain aging.

Plenary 2
STAVING OFF DEMENTIA: WHAT HAVE WE LEARNED FROM MENDELIAN FAMILIES?

William S. Brooks[1,2]

[1] *Neuroscience Research Australia, Sydney, NSW, Australia*
[2] *Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia*

Families with dominantly inherited Alzheimer's disease (AD) and other forms of dementia have been recognized for over 50 years. In Australia, at least 25 families with familial AD and a similar number with familial non-Alzheimer dementia, each with an identified causative mutation, are now known. Predictive testing has been possible for familial AD since 1991, but with no definitive treatment, uptake has been low. In 2008, the U.S. National Institutes of Health provided funding for the Dominantly Inherited Alzheimer Network (DIAN), an international multi-center cohort study led by Dr John Morris and Dr Randall Bateman at Washington University in St Louis. DIAN aimed to recruit members of familial AD kindreds to discover biomarkers of disease progression. Australian families provided almost 90 of the first 400 participants, enrolled through centers in Sydney, Melbourne, and Perth. From DIAN, it was clear that brain amyloid deposition, as detected by PET scans using amyloid ligands, began as long as 20 years before the age at which symptoms develop, with rising levels of tau protein detectable in the spinal fluid about 10 years before symptoms. These findings raised the possibility of intervening to modify the disease process during this long presymptomatic period. This work has now progressed to include prevention trials, in which monoclonal antibodies are given to lower brain amyloid deposition in the hope that this will prevent loss of neurons and symptoms of cognitive decline. There are plans to continue studying these and other drugs in this high risk but highly motivated group of people

https://doi.org/10.1017/thg.2017.46 Published online by Cambridge University Press

until a disease-modifying treatment is discovered. A similar cohort study in the area of familial frontotemporal dementia (FTD), the Genetic FTD Initiative (GENFI), was established in 2011 and is headed by Dr Jonathan Rohrer of University College, London.

Plenary 3
SCANNING ULTRASOUND (SUS) AS A NOVEL TREATMENT MODALITY FOR ALZHEIMER'S DISEASE

Jürgen Götz

Queensland Brain Institute (QBI), The University of Queensland, Brisbane, QLD, Australia

Alzheimer's disease is characterized by the deposition of Aβ as extracellular plaques and hyperphosphorylated tau as intraneuronal tangles. As a potential treatment strategy, passive Aβ and tau immunotherapies are currently being explored; however, because only a small fraction of peripherally delivered antibodies crosses the blood-brain barrier and engages with its substrate, more efficient ways are warranted. To achieve this, we developed a novel method termed scanning ultrasound (SUS). By using repeated SUS treatments of mice with Aβ plaques, we achieved efficient Aβ removal without requiring an additional therapeutic agent. Aβ was internalized by microglia, and the treated mice displayed improved performance on three memory tasks. As far as the tau pathology is concerned, we face the additional challenge that it is intraneuronal and that microglia unlikely has a clearance role. We tested SUS on its own and in combination with a novel tau-specific single-chain antibody fragment. Surprisingly, even intraneuronal tau could be cleared by SUS. When administration of the antibody was combined with SUS, delivery into the brain and neuronal uptake were markedly increased, and efficacy was significantly enhanced. Together, our study presents SUS as a viable tool to improve therapeutic outcomes. As an outlook, I will discuss the challenges in developing SUS as a treatment strategy for human AD patients.

Genetics Education Day Plenary — Speaker 4
EDUCATIONAL RESOURCES FOR GPS IN GENOMIC MEDICINE

Syliva Metcalfe

Murdoch Childrens Research Institute and The University of Melbourne, Royal Children's Hospital, Melbourne, VIC, Australia

As genomics technologies advance, the impact on patients requires a healthcare workforce that is able to keep abreast of the latest changes while continuing to be grounded in the support they can provide to patients. Educational resources and training for GPs in genomics need to ensure that there is an appropriate balance between relevant information that is easily accessible and useful in daily practice yet ensures that GPs are adequately prepared to meet the challenges of genomic medicine. This presentation will discuss how the former *Genetics in Family Medicine: The Australian Handbook for General Practitioners*, a resource that was developed in 2007, has evolved into a point-of-care tool with a focus on practice points and includes current aspects related to genomics. The resource is due to be released in late 2017 through the Royal Australian College of General Practitioners. The usefulness of this updated educational resource will be demonstrated by case studies relevant to general practice. The presentation will also outline a range of other resources that are online, both within and external to Australia, that GPs can access for their educational support.

Plenary 4
CLINICAL APPLICATIONS OF PSYCHIATRIC GENETICS: FROM MOLECULAR GENETICS TO THE WORLDS FIRST SPECIALIST PSYCHIATRIC GENETIC COUNSELING CLINIC

Jehannine C. Austin

Canada Research Chair, Associate Professor, UBC Departments of Psychiatry and Medical Genetics, Vancouver, Canada

Psychiatric disorders (including depression, schizophrenia, and OCD) are common conditions affecting as many as one in five. Psychiatric disorders are etiologically heterogeneous and complex, involving interacting effects of genes and environmental factors. The first part of this presentation will trace the history of psychiatric genetics research, culminating in a review of current understanding of the genetics of these conditions. The second part of this presentation will focus on the intersection between clinical genetics practice and psychiatric disorders. Though psychiatric disorders are rare as primary indications for referral to genetic counseling, many patients referred for other indications will have psychiatric diagnoses, or family members with these diagnoses. The case will be made that it is important to ask people about personal or family history of psychiatric illness. Data and vignettes will be presented documenting the important improvements in patient outcomes that can be produced through the provision of genetic counseling for people with psychiatric disorders and their families. A brief overview of the world's first specialist psychiatric genetic counseling service that was established in 2012 in Vancouver, Canada, will be presented. There will be brief discussion of the potential for genetic counseling to provoke behavior change — specifically, engagement in health behaviors to reduce risk for common disease like psychiatric illness.

Plenary 5
PREPARING HEALTH PROFESSIONALS FOR THE RAPIDLY CHANGING FIELD OF GENOMICS — ARE WE MOVING FAST ENOUGH?

Kate Dunlop

Northern Sydney Local Health District, Centre for Genetics Education NSW Health, Sydney, NSW, Australia

Genomic testing is potentially disruptive and is rapidly moving into clinical care. The National Genomic Strategy identifies that a skilled and literate genomic workforce is a key priority in the integration of genomics into our health system. Program 4 of the Australian Genomic Health Alliance has created a database of current education programs in genomics and is developing an evaluation framework to assist with the identification of successful approaches. In addition, the HGSA is moving to update competencies. Yet, a recent needs assessment by the Centre for Genetics Education NSW Health suggests there is a perception among non-genetics trained health professionals that the need for genomics education is not urgent. Engaging our current workforce in education is challenging particularly in this complex field. This paper presents a number of education strategies underway and considers the next step. Preparing health professionals requires new thinking with a different focus if we are going to match this rapid pace.

Plenary 6
GENETIC RISK PREDICTION IN COMMON DISEASES

Matthew A. Brown

Institute for Health and Biomedical Innovation, Queensland University of Technology, Translational Research Institute, Princess Alexandra Hospital, Brisbane, Australia

One of the potential applications of genetic data is to predict the likelihood of development of common diseases, potentially enabling

https://doi.org/10.1017/thg.2017.46 Published online by Cambridge University Press

identification of subjects either prior to development of the disease or early in the disease course. This could enable targeted preventative medicine or early disease intervention approaches. The failure of GWAS studies to date to identify more than generally a small minority of definitely disease-associated loci has precluded this approach being sufficiently informative to be of clinical utility. However, the development of whole of GWAS approaches has enabled far more of the overall heritability of diseases to be captured, raising the possibility of the use of genetic risk prediction in the clinic, as well as in improving disease classification. While this will not work for all diseases, there are some early examples where the performance of this approach is sufficiently good to warrant its clinical application.

Plenary 7
THE IMPACT OF DNA DAMAGE ON AGING, SUSTAINING HEALTH, AND LONGEVITY

Jan H. J. Hoeijmakers

Erasmus University Medical Center Rotterdam, Department of Molecular Genetics, Netherlands

Virtually, all progeroid syndromes in man relate to genome instability. We generated mouse models which strikingly mimic human DNA repair deficiencies and display extensive accelerated aging; for example, $Ercc1^{\Delta/-}$ mice defective in ≥3 repair pathways show premature multi-morbidity in virtually all post-mitotic and proliferative tissues, limiting lifespan to 4–6 months. Simultaneously, these mice exhibit an anti-aging 'survival response' that suppresses growth and enhances maintenance, resembling the longevity response by dietary restriction (DR). Remarkably, subjecting these mutants to 30% DR tripled(!) remaining lifespan, and drastically retarded numerous accelerated aging features; for example, they retained 50% more neurons and delayed motor decline ~30(!)-fold. Repair-deficient progeroid $Xpg^{-/-}$ mice responded similarly. Interestingly, ad libitum $Ercc1^{\Delta/-}$ liver expression profiles showed declining expression of long genes, consistent with genome-wide accumulation of stochastic, transcription-blocking lesions that affect long genes more than short ones. Similar findings were made in human brain profiles upon aging, demonstrating relevance for normal aging in humans. DR in repair-deficient mice alleviated this decline, indicating that DR prolongs genome function. We will present phenotypes of conditional DNA repair models targeting aging to selected organs and connections with the unfolded protein response and proteinopathies (Alzheimer's and Parkinson diseases). Our findings strengthen the link between DNA damage and aging, establish $Ercc1^{\Delta/-}$ mice as powerful model for identifying interventions to promote healthy aging, reveal untapped potential for reducing endogenous damage, provide new venues for understanding the molecular mechanism of DR, and suggest a counterintuitive DR-like therapy for human progeroid genome instability syndromes and DR-like interventions for preventing neurodegenerative diseases.

Plenary 8
GENOMIC INSTABILITY: SENSING DNA DAMAGE

Derek Richard[1], Emma Bolderson[1], Mark Adams[1], Syed Ali Naqi Raza Jaffary[1], Nicolas Paquet[1], Nicholas Ashton[1], Liza Cubbedu[2], Roland Gamsjaeger[2], and Ken O'Byrne[1]

[1] *Queensland University of Technology, Brisbane, QLD, Australia*
[2] *Western Sydney University, Sydney, NSW, Australia*

Introduction: DNA damage is the underlying cause of cellular aging and diseases of age such as cancer and neuro-degeneration. The cell posesses a large number of proteins that function to detect, signal, and repair specific DNA lesions within the genome. One such protein, hSSB1, functions to detect double-strand DNA breaks. One critical pathway responsible for the removal of oxidized nucleotides from the genome is the Base Excision Repair pathway (BER). This relatively simple pathway requires a DNA glycosylase to excise the base and an AP nuclease to cleave the phosphate backbone, allowing the incorporation of the correct nucleotide. *Results:* It was previously thought that 8-oxoG lesions (the most commonly oxidized nucleotide) were detected by the DNA glycosylase hOGG1; however, our data now indicates that hSSB1 is the cellular sensor of 8-oxoG containing double-stranded DNA. hSSB1 binds to duplex DNA containing 8-oxoG with high affinity and recruits the DNA glycosylase hOGG1 to the site of damage. hSSB1 further stimulates the activity of hOGG1, allowing the removal of the base. Interestingly, hSSB1 has an oxidation-sensing cysteine (C81) that detects oxidized conditions and stimulates dimerization of hSSB1, with this event being required for recognition of the 8-oxoG lesion but not DNA double-strand breaks. *Conclusions:* We have now identified the sensor of oxidized guanines nucelotides within the genome. hSSB1 is overexpressed in most solid malignancies and may function to allow the cell to tolerate high levels of 8-oxoG generation. This could make hSSB1 an attractive drug target.

Plenary 9
CANCER GENOMICS AND ITS CLINICAL POTENTIAL

Nic Waddell

QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia

Genome sequencing has made great advances in our understanding of tumor development and progression. The genome data is being used to classify tumors into significant subtypes, discover driver mutations, identify the mutational processes that underlie tumor development and find alternative therapeutic targets. These are important steps toward 'personalized medicine' where the diagnosis, management, and treatment of patients are based on an individual's clinical and genomic data. This talk will describe some of the key findings from whole genome sequencing of a variety of cancer types. There will be a particular emphasis on the clinical utility of cancer sequencing for the identification of therapeutic targets and germline genetic causal variants.

Plenary 11
MUTATIONAL MECHANISMS AND ONCOGENIC SWITCHES IN SOLID TUMORS

Sean M. Grimmond

University of Melbourne Centre for Cancer Research, Victorian Comprehensive Cancer Centre, Melbourne, VIC, Australia

It is now well established that a cancer's mutational burden drives tumor formation, influences disease progression, and can dictate sensitivity to chemotherapy. Professor Grimmond's laboratory has pioneered large-scale cancer genome sequencing of >1,000 patients, primarily as part of the International Cancer Genome Consortium (ICGC). These efforts have addressed three core questions: (1) what are the root causes of DNA damage, (2) what are the genetic events that lead to tumor formation and disease progression, and (3) how can personalized cancer-genome analysis improve treatment selection and patient outcome? These studies have provided tools to readily detect DNA damage repair deficiencies causing accumulated somatic mutation across all common malignancies (e.g., deficiencies in homologous recombination, mismatch repair, base excision repair, nucleotide excision repair, trans-lesional repair). Furthermore, these studies have also highlighted a range of oncogenic events capable of driving tumorigenesis far beyond simple point mutations in coding sequences. Taken together, these insights are redefining our understanding of solid tumorigenesis and provide opportunities

https://doi.org/10.1017/thg.2017.46 Published online by Cambridge University Press

for improved clinical intervention based on personal cancer genome information.

Plenary 12
MENDELIAN DISTURBANCES OF AGING

Raoul C. M. Hennekam

Department of Pediatrics, Academic Medical Center, UVA, Amsterdam, Netherlands

Aging can be defined as 'a progressive functional decline' or as 'the intrinsic inevitable and irreversible age-related process of loss of viability and increase of vulnerability'. We age more than ever before. This is because our Initial Mortality Rate is decreasing — for instance, by our abilities to decrease mortality by infectious diseases, and not because the Mortality Rate Doubling Time has changed, as that is based on a large number of basic, intrinsic processes in the human body, and likely has remained unchanged over many millennia. These latter processes are almost invariably genetically determined. Mutations occur in all genes, so also in genes involved in aging. This offers unequaled insight in a process that happens to all of us. External physical characteristics that give away an existing disturbed aging process are a thin, atrophic skin with loss of elasticity, deficient adipose tissue, premature loss of teeth, sparse and early greying hair, and skin pigmentations, but also cataract, early arteriosclerosis, early osteoporosis, and early cancer may indicate this. Early loss of cognitive abilities (i.e., dementia) is the major mental clue. No Mendelian entity is demonstrating all these processes, but there is a series that shows a large number of the aging signs and symptoms. The prototype of the entities caused by Mendelian disturbances of aging is Hutchinson–Gilford progeria. In this lecture, this and a series of other Mendelian entities, such as Nestor–Guillermo syndrome, Wiedeman–Rautenstrauch syndrome, Ehlers–Danlos syndrome progeroid type, Penttinen syndrome, Fontaine–Petty syndrome, and SHORT syndrome will be described. The DNA repair disorders Werner syndrome and Cockayne syndrome will be discussed elsewhere (lecture by Dr J. H. Hoeijmakers). A comparison of phenotypes, present knowledge of the etiologies and pathogeneses, and the insight of these combined data in processes involved in aging will be provided.

Plenary 13
GENETICS OF REPRODUCTIVE LIFESPAN

Grant W. Montgomery

Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, Australia

The onset of menarche and menopause are important life events linked to fertility and a range of other conditions. Large genome-wide association studies have been conducted for the timing of menarche and menopause. They shed new light on the mechanisms of reproductive aging and other diseases associated with variation in reproductive lifespan. The most recent genome scan for age at menarche in ~370,000 women identified 389 independent signals, and associations between puberty timing and risks for breast and endometrial cancer in women and prostate cancer in men. Forty-four genomic regions have been associated with age at natural menopause, including two regions with additional rare missense alleles of large effect. Genomic regions associated with age at natural menopause include signals in or near genes associated with delayed puberty and DNA damage response genes. Genome-wide association studies are also conducted for related traits. These genetic studies are useful to gain better understanding of the biology underlying variation in reproductive lifespan and identifying shared biological pathways linking puberty timing, cancer risk, and reproductive aging.

HGSA Oration
A FORTUITOUS METABOLIC PATHWAY

Jim McGill

Department of Metabolic Medicine, Lady Cilento Children's Hospital, Brisbane, QLD, Australia

I have been very fortunate to be involved in clinical and metabolic genetics during a period of such rapid growth and change. My entry into the field was accidental when, during my pediatric training, I diagnosed the first recognized Victorian patient with MCADD. I have had the advantage of excellent teachers headed by David Danks, John Rogers, and Charles Scriver. While training, I experienced the excitement of the formation of the Murdoch Institute, revolutionary in its concept. With so few in the field, I also had the opportunity to be on many committees and became involved in the formation of the ASIEM, the introduction of metabolic nurses, the formation of the Queensland Clinical Genetics Service, the introduction of genetic counseling to Queensland and, more recently, the formation of the Queensland Lifespan Metabolic Medicine Service and the blueprint for a national newborn screening program. During my 32 years of involvement in the field, I have seen the emergence of new metabolic conditions including mitochondrial, carbohydrate deficient glycoprotein, and peroxisomal disorders. The rapid progression of molecular genetics and the development of tandem mass spectroscopy has revolutionized metabolic diagnoses, particularly in the field of newborn screening. I have also had the opportunity to influence government funding of therapies for lysosomal enzymes, particularly for MPS I, (II), VI, and IV, Fabry, and Pompe diseases. The future of genetics looks equally exciting as molecular diagnoses lead to new therapies. The challenge will be how to finance these therapies as they emerge, particularly those that require recurrent funding. Currently, therapies exist for only 2% of rare diseases, but some of them have lifetime costs in excess of $40million/patient. Other challenges will include funding for molecular genetic testing, balanced education of the public on the utility of genetic testing, and avoiding the deskilling of the roles of genetic clinicians and counselors.

Plenary 15
DEVELOPING PRECISION MEDICINE APPROACHES TO DEAL WITH THE BURDEN OF GLAUCOMA BLINDNESS IN AN AGING AUSTRALIAN POPULATION

Jamie Craig

Eyemedics Ophthalmologists, Adelaide, SA, Australia

Glaucoma is a common complex genetic disease manifesting as a progressive optic neuropathy that can cause blindness at any age. Positive family history, raised intraocular pressure, and advancing age are major risk factors. There are mechanistic similarities to other complex degenerative diseases of aging such as age-related macular degeneration and Alzheimer's disease. In this presentation, a national disease registry approach to understanding glaucoma blindness is outlined that has enabled the discovery and quantification of numerous genetic loci increasing susceptibility to glaucoma blindness. The approach to translating these discoveries to more efficient diagnostic and monitoring strategies is discussed in the context of a national longitudinal study of glaucoma progression in early and glaucoma suspect cases. New approaches to treatment of established disease based on genetic discovery will also be addressed.

https://doi.org/10.1017/thg.2017.46 Published online by Cambridge University Press

Plenary 16
ASSOCIATION OF AD RISK GENES AND MRI MARKERS OF BRAIN AGING

Margie Wright[1] and Michelle Lupton[2]

[1] *Queensland Brain Institute and Centre for Advanced Imaging, University of Queensland, Brisbane, QLD, Australia*
[2] *QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia*

Brain imaging studies have identified MRI markers associated with brain changes characterizing Alzheimer's disease (AD). Multiple studies, ranging in size and significance, show that brain atrophy and altered brain activity is associated with the apolipoprotein E (APOE) ε4 genotype. In addition to APOE, recent GWAS have identified common variants that jointly make a contribution to the risk of developing AD, with others identifying rare variants. Because neuropathological features of AD can present several decades before disease onset, we investigated whether effects of increased genetic risk for AD are detectable by neuroimaging in a population sample and AD case-control cohort (total $N = 2{,}100$). We examined the association between AD polygenic risk scores (PRSs) constructed from 20 AD risk loci and a single nucleotide polymorphism in TREM2 on imaging measures using T1-weighted structural scans. Through stratification into AD, mild cognitive impairment (MCI), and healthy older groups, we show at which disease stage associations can be identified. We found an association between AD PRSs and hippocampal volume in healthy older adults and those with MCI, with higher risk associated with lower hippocampal volume. APOE4 was associated with hippocampal volume in those with AD and MCI but not healthy older individuals. TREM2 was associated with reduced hippocampal volume in MCI and healthy older adults. We found no evidence for effects of AD risk variants on brain structure in young adults. While reproducibility of results remains crucial, these investigations show the potential for combining genotypic and brain imaging phenotypes to assist in risk prediction.

Concurrent Session 1 — Australasian Society of Genetic Counselors

ASGC Oral 1
SO WHAT DO WE THINK? A PROFESSIONAL STATUS SURVEY OF GENETIC AND GENOMIC HEALTH PROFESSIONALS

Amy Nisselle[1,2,3,4], Ivan Macciocca[3,5], Fiona McKenzie[6,7], Kate Dunlop[1,8], Sylvia Metcalfe[1,2,4], and Clara Gaff[1,3,4,9]

[1] *Australian Genomics Health Alliance, Australia*
[2] *Murdoch Children's Research Institute, Melbourne, VIC, Australia*
[3] *Australasian Society of Genetic Counsellors, Australia*
[4] *The University of Melbourne, Melbourne, VIC, Australia*
[5] *Victorian Clinical Genetics Service, Melbourne, VIC, Australia*
[6] *Australasian Association of Clinical Geneticists, Australia*
[7] *Genetic Services of Western Australia, Department of Health, Perth, WA, Australia*
[8] *Centre for Genetics Education, NSW Health, Sydney, NSW, Australia*
[9] *Walter & Eliza Hall Institute for Medical Research, Melbourne, VIC, Australia*

Background: Work practices of genetic health professionals are changing rapidly in response to increased availability of, and demand for, genomics in healthcare, prompting a census by the ASGC, AACG, and HGSA, managed by the Australian Genomics Health Alliance (AGHA). *Aim:* To capture demographics, practice and work conditions, current and anticipated training and practice in genomics, and solicit AACG and ASGC feedback. *Methods:* An online survey developed, piloted, and deployed February–April 2017 to members of the ASGC, AACG, and HGSA, and alumni of Australian genetic counseling (GC) and clinical genetics (CG) training programs. *Results:* Three-hundred-four surveys were completed: 230 GCs and 70 CGs (50.7% response rate). A total of 73.8% work for publicly funded genetics/pathology services, 26.2% have multiple jobs and 83.8% do unpaid overtime. A total of 86.7% work in clinical roles, also doing research (47.1%), education (36.1%), or policy (11.0%). 74.2% of GCs and 85.7% of CGs recently attended genomics training. Overall, more CGs (80.9%) currently incorporate genomics into their practice than GCs (29.7%); however, many GCs feel they should perform a broader range of steps involved in whole exome/genome sequencing, including testing-related steps (creating gene lists, providing phenotypic information, and variant curation) and pre- and post-test counseling. Conversely, the majority of both groups felt the testing-related steps were not the remit of non-genetic health professionals. *Conclusion:* These data provide critical insight for workforce planning into the education, training, and work practices of Australian genetic health professionals, and a baseline for longitudinal comparisons as genomics becomes part of routine healthcare.

ASGC Oral 2
THE EVOLVING LANDSCAPE OF GENETIC COUNSELING IN THE GENOMIC ERA

Tanya Dwarte,[1] Kristine Barlow-Stewart,[1] Rosie OShea,[1] Marcel Dinger,[2] and Bronwyn Terrill[2]

[1] *Discipline of Genetic Medicine, Sydney Medical School — Northern, University of Sydney, Sydney, NSW, Australia*
[2] *Kinghorn Centre for Clinical Genomics, Garvan Institute of Medical Research, Sydney, NSW, Australia*

Background: Facilitating informed decision making regarding genetic testing is a core component of genetic counseling practice. Internationally, and more recently in Australia, genetic testing is moving from single genes to genomic testing (including gene panels, whole-exome or whole-genome sequencing). The rationale is improved diagnostic yield and cost-effectiveness. *Aim:* To explore genetic counseling practice in the UK and Australia in the context of genomic testing. *Method:* An invitation was purposively sent to 14 genetics practitioners residing in Australia or the UK who were known to have experience with the offer and delivery of panel and/or genomic results. Additionally, a request to snowball to colleagues was included in the invitation. A total of 12/17 practitioners who have consented to participate have been interviewed to date. Semi-structured telephone interviews were used to explore their experiences and practice. Interviews were transcribed verbatim, deidentified, coded with concordance from two coders, and analyzed using an inductive thematic approach. *Results:* Three themes have emerged to date: (1) role delineation: current and future and the influence of increasing complexity; (2) the evolving spectrum of practice: building on core skills; blurred boundaries between research and clinical services, consent processes and streamlining based on experience; and return of results strategies; and (3) policy and governance needs: access to testing; achieving consistent variant interpretation, reporting and responsibility for review; managing incidental findings; and professional registration for Australian genetic counselors. *Significance:* These exploratory data highlight that genetic counseling practice in the genomic era is evolving but remaining patient-centered, with core skills underpinning practitioners' capacity to adapt.

https://doi.org/10.1017/thg.2017.46 Published online by Cambridge University Press

ASGC Oral 3
THEORY VERSUS REALITY: REFLECTIONS ON THE GENOMIC CONSENT PROCESS

Kirsten Boggs[1,2], Mary-Anne Young[1,3,4], and Ainsley Newson[1,4,5]
[1] *Australian Genomics Health Alliance, Australia*
[2] *Sydney Children's Hospital Network, Sydney, NSW, Australia*
[3] *Genome.One, Sydney, NSW, Australia*
[4] *Garvan Institute of Medical Research, Sydney, NSW, Australia*
[5] *Centre for Values, Ethics and the Law in Medicine; Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia*

Numerous advances in genomic technology have meant there is continuing debate about how to best facilitate the informed consent process for families undergoing genomic testing. The aim of this presentation is to bring together the theory around the genomic consent process as well as practical experiences from a genetic counselor working on the frontline of genomics. This will be achieved through personal reflection informed by the current literature. The qualitative method of narrative inquiry into the practice of genetic counselors in genomics has been developed. This will be used to critically reflect on common themes identified throughout the literature regarding consent to genomic testing. The purpose of this reflection is to provide clarity on the differences between day-to-day genomics and the literature. Themes identified to date include: determining the barriers to informed consent, motivated participants, paternalism, discordance in values, and timing of the consent process. This has enabled reflection on the challenges of the genomic consent process in reality, while also celebrating the successes. This critical reflection will prepare and educate the genetic counseling workforce around approaches to informed consent, while providing key insights into the forefront of genomic practice. This will therefore contribute to determining and evaluating best practice for genetic counseling in the genomic era.

ASGC Oral 4
CLINICAL WHOLE EXOME SEQUENCING (WES): A MULTIDISCIPLINARY TEAM APPROACH

Justine Elliott[1], Tiong Tan[1,2], Zornitza Stark[1], Alison Yeung[1], Sebastian Lunke[1], Belinda Chong[1], and Susan White[1,2]
[1] *Victorian Clinical Genetics Services, Murdoch Children's Research Institute, Melbourne, VIC, Australia*
[2] *Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia*

Whole exome sequencing (WES) has the potential to diagnose patients with complex clinical presentations where traditional testing has failed. In March 2016, Victorian Clinical Genetics Services (VCGS) launched a diagnostic Clinical Exome service employing a phenotype-based approach ensuring reliable identification of disease-causing variants to maximize diagnostic yield. Precurated evidence-based gene lists facilitate prioritization of high-impact phenotype-associated variants with optional expansion of analysis to the 'Mendeliome'. An audit of the first 309 patient samples revealed common indications for testing included intellectual disability (35%), neurological phenotypes (23%), and multiple congenital abnormalities (11%). Funding was provided through various Victorian health services (38%), Melbourne Genomics Health Alliance (26%), patient self-funding (19%), interstate (12%), and international (5%) centers. Sixty-one diagnostic results were issued in 190 patients (32% diagnostic rate). Eighty-eight negative (46%) results and 41 (22%) cases of 'variants of unknown clinical significance' were reported. In addition, two secondary findings, requiring genetic counseling and medical follow-up, were identified; one in a patient with an otherwise negative result and one where a diagnosis was issued. Multidisciplinary team (MDT) collaboration involving comprehensive phenotyping by clinical geneticists and other specialists, and close dialog between clinicians and laboratory scientists is essential to support this complex testing approach. Genetic counselors play important coordination and educational roles to support patients and referrers. MDT meetings are essential aspects of the process to review phenotype and reach consensus on variant interpretation. Ongoing challenges include access to funding for patients and streamlining the request process to capture important clinical information from referrers.

ASGC Oral 5
A PILOT PROGRAM USING WHOLE GENOME SEQUENCING FOR PERSONAL HEALTH MANAGEMENT

Mary-Anne Young, Skye McKay, Marcel Dinger, Leslie Burnett, Bronwyn Terrill, Ben Lundie, Lisa Ewans, and Eric Lee
Genome.One, Sydney, Australia

Background: Whole genome sequencing (WGS) in healthy individuals, while controversial, is increasingly discussed as a tool to help individuals manage their health. The goal is to provide genetically informed predictions of disease risk, medication safety/efficacy and additional information so that individuals can take a more personalized and preventative approach to their health. *Aim:* (1) Undertake a pilot project in healthy individuals including pre- and post-test genetic counseling and WGS for personal health management (PHM) in partnership with their GP. (2) Develop a model of genetic counseling to support genomic testing in healthy individuals. *Methods:* Thirteen individuals were recruited to the pilot program and 11 underwent testing. Information (including information about risk-rated insurance) was sent to all participants prior to their pre-test genetic counseling appointment. Initial analysis of 228 genes and pharmacogenomic testing was undertaken. Qualitative analysis of participants' knowledge and attitudes was undertaken. *Results:* Participant motivations included curiosity about the technology and wanting to gain health information. Other factors identified that required consideration included participant desire for access to their raw data and a model of genetic counseling reflective of the predicted low rate of positive genomic findings. *Conclusions:* Lessons learned from these early adopters of genomic technology in Australia will inform the approach to WGS for PHM in Australia.

ASGC Oral 6
SCOPING THE SCENE: WHAT DO NURSES, MIDWIVES, AND ALLIED HEALTH PROFESSIONALS KNOW ABOUT GENETICS?

Mona Saleh[1], Romy Kerr[1,2], and Kate Dunlop[1]
[1] *Centre for Genetics Education, Sydney, NSW, Australia*
[2] *New Zealand Genetic Health Service, New Zealand*

Rapid changes in genomic technology are transforming healthcare delivery. Although it has been well established that many health professionals lack the adequate knowledge, skills, and confidence to adapt to these changes, the specific educational needs of Australian allied health professionals, nurses, and midwives are not well understood. This diverse group of health professionals is primarily involved in the symptomatic treatment and psychosocial care of patients with genetic conditions rather than the diagnostic process. The relevance of genetics and genomics to their clinical practice may therefore differ from medical practitioners and specialists. This paper reports on a study undertaken to identify the perceived genetic knowledge and education needs for this group of health professionals. Allied health professionals, nurses, and midwives were recruited from throughout NSW and invited to participate in semi-structured telephone or face-to-face interviews. A total of 25 geographically and professionally diverse individuals (15 Allied Health, 6 nurses, and 4 midwives) were interviewed. Interview recordings were transcribed and using NVivo software, data were analyzed to identify emergent themes. The results show that this is a group hungry for

https://doi.org/10.1017/thg.2017.46 Published online by Cambridge University Press

information about genetics and genetic services and unsure of reliable sources. The need for a generic update from a trustworthy source was identified and suggested topics to be covered included genetic fundamentals and psychosocial/ethical aspects of genetics testing including informed consent. Findings from this study will inform the development of a targeted, interactive resource for allied health professionals, nurses, and midwives hosted on the NSW Health e-learning system.

Concurrent Session 2 — Australasian Society of Diagnostic Genomics

ASDG Oral 1
A REVIEW OF FIRST-LINE PRENATAL MICROARRAY CLINICAL SERVICE FOR PREGNANCIES AT HIGH RISK FOR CHROMOSOMAL ABNORMALITIES

Ngaire Jose, Samantha Robinson, Melanie Jane Clarke, Sharanbeer Kaur, Con Ngo, and Dale Wright
Sydney Genome Diagnostics, Childrens Hospital Westmead, Sydney, NSW, Australia

Background: Chromosome microarray has recently emerged in prenatal diagnosis. Our laboratory implemented CGH array for first-line prenatal testing in August 2014. *Aim:* To review our prenatal chromosome microarray clinical service and reportable copy number variants (CNV). *Method:* This prospective cohort comprised 1,174 high-risk pregnancies from the Greater Western Sydney region analyzed by CGH microarray between August 2014 and December 2016. The mean maternal age was 32yrs (range 15–47 years) and included chorionic villus ($n = 205$) and amniotic fluid ($n = 969$) samples with mean gestations of 12w3d and 16w3d, respectively. An 8×60K ISCA targeted genome-wide array (Agilent Technologies) was used and CNVs reported when a deletion was ≥0.2 Mb or duplication ≥0.4 Mb in size. CNVs were classified as benign, pathogenic, variant of uncertain significance (VoUS), and VoUS inherited-likely benign. Benign CNVs were not reported. *Results:* Altogether, the overall abnormality rate was 247/1,174 (21.0%). Excluding aneuploidies, the total CNV rate was 101/1174 (8.6%), which included 47/1,174 (4.0%) pathogenic, 18/1,174 (1.5%) VoUS, and 36/1,174 (3.1%) that were reclassified as VoUS inherited-likely benign. Of the pathogenic CNVs, 39/47 (83%) were <10 Mb in size. *Conclusion:* Our obstetric cohort is skewed toward second trimester or later pregnancies, but the total 8.6% CNV rate is consistent with published reports, including 4.0% pathogenic and 1.5% VoUS rates. Importantly, 83% of pathogenic CNVs were <10 Mb, which would be missed by G-band karyotyping and emphasizes the clinical utility of prenatal microarrays.

ASDG Oral 2
RAPID GENOMIC TESTING: CAN THE CHALLENGES BE MET IN ROUTINE CLINICAL PRACTICE?

Zornitza Stark[1,2], Sebastian Lunke[1], Natalie B. Tan[1], Rachel Stapleton[1], Smitha Kumble[1], Dean Phelan[1], Belinda Chong[1], Miriam Fanjul Fernandez[1], Justine Marum[1], Amber Boys[1], Chris Leng,[1] Michael Tamayo[1], Audrey Chong[1], Jessica Riseley[1], Martin Delatycki[1,3], Ravi Savarirayan[1,3], Alison Yeung[1], Matthew Hunter[4,5], Matthew Regan[4], Gemma Brett[1,2], Anna Jarmolowicz[1,2], Yael Prawer[2,4], Justine Elliott, Melissa Martyn[2], Tiong Tan[1,2,3], Clara Gaff[2,3], and Susan M. White[1,3]
[1] *Victorian Clinical Genetics Services, Murdoch Childrens Research Institute, Melbourne, VIC, Australia*
[2] *Melbourne Genomics Health Alliance, Melbourne, VIC, Australia*
[3] *Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia*
[4] *Monash Medical Centre, Melbourne, VIC, Australia*
[5] *Department of Paediatrics, Monash University, Melbourne, VIC, Australia*

Background: Accurate and timely diagnosis is critical in providing prognostic information and guiding treatment in acutely unwell patients with suspected monogenic disorders. *Aim:* We describe the development and implementation of a rapid genomic diagnosis program in a routine clinical setting. *Methods:* Rapid singleton whole-exome sequencing was performed in acutely unwell patients with suspected monogenic disorders from two pediatric tertiary centers. Technical, organizational, and clinician barriers to implementation were addressed through a cycle of continuous audit and improvement. Service performance parameters and the diagnostic and clinical utility of providing rapid WES were assessed. *Results:* During the study period, time to result reduced from 109 days to 13 days (median 18 days), and this was accompanied by changes in referral and test initiation patterns. Of 26 enrolled patients, 14 (54%) received a molecular genetic diagnosis. Clinical management changed in nine diagnosed patients (64%), including the provision of life-saving treatment, avoidance of invasive biopsies, and palliative care guidance. A result was provided prior to death or discharge from hospital in 16 of 26 cases (62%). The rapid diagnosis of a riboflavin transporter defect in one patient is estimated to have saved 113 days in intensive care (AUD$508,500) compared to providing the result with a standard turnaround time. *Discussion:* The provision of rapid genomic results in acutely unwell patients with suspected monogenic disorders is feasible in the routine clinical setting and has high diagnostic and clinical utility. It challenges traditional clinical and laboratory genetics service models, and requires a whole-of-system approach for successful implementation.

ASDG Oral 3
AUSTRALIAN GENOMICS HEALTH ALLIANCE (AGHA) SURVEY OF CURRENT GENETIC TESTING PRACTICES IN AUSTRALIA

Emma Tudini[1], Katia Nones[1], Marcel E. Dinger[2], John Christodoulou[3], Amanda B. Spurdle[1], on behalf of AGHA Program 2 members
[1] *QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia*
[2] *Garvan Institute of Medical Research, Sydney, NSW, Australia*
[3] *Murdoch Childrens Research Institute, Melbourne, VIC, Australia*

The Australian Genomics Health Alliance (AGHA) proposes to integrate genomic medicine into Australian healthcare. Program 2 — A National Approach to Data Federation and Analysis — aims to coordinate curation, storage, and secure sharing of genomic data nationally. To inform project implementation, we surveyed Australian NATA-accredited, self-nominated genetic testing laboratories to assess current practices around germline and somatic variant testing. These laboratories were invited to participate by email, and 22/30 (73%) eligible labs completed the survey online or by telephone interview. General findings were (1) germline testing ranged from single variant to whole genome, with single-gene and in-house/commercial gene panels most commonly performed; (2) 13/16 (81%) responding laboratories use American College of Medical Genetics and Genomics (ACMG) criteria alone, or in combination, for variant classification; (3) 12/14 (86%) respondents report variants of uncertain significance in genes relevant to the condition; (4) 9/13 (69%) respondents report incidental/secondary findings; (5) reasons stated for selecting 'actionable' genes varied greatly, and included use of a standard lab gene list (4/14, 29%); genes requested by a clinician (3/14, 21%); ACMG or other clinical guidelines (3/14, 21%); literature (2/14, 14%); a combination (3/14, 21%). 11/13 (85%) respondents re-evaluate variant classifications, but only 3/11 (27%) re-evaluate periodically, and only 5/9 (55%) re-issue reports; (6) somatic testing appeared to vary considerably with regard to testing services and processes for variant classification and reporting. This survey identified several areas for further investigation that, in consultation with HGSA, RCPA, NPAAC, and NATA, are required to reach national consensus in genetic variant evaluation and reporting in Australia.

https://doi.org/10.1017/thg.2017.46 Published online by Cambridge University Press

ASDG Oral 4
CLASSIFICATION OF TRUNCATING VARIANTS IN TITIN

Dean Phelan[1], Sarah-Jane Pantaleo[1], Justine E Marum[1], Miriam Fanjul-Fernandez[1], Desirée du Sart[1], Ivan Macciocca[1], Sebastian Lunke[1], Paul James[2,3], and Belinda Chong[1]

[1] *Victorian Clinical Genetics Service, Melbourne, VIC, Australia*
[2] *Royal Melbourne Hospital, Melbourne, VIC, Australia*
[3] *Peter MacCallum Cancer Centre, Melbourne, VIC, Australia*

Dilated cardiomyopathy (DCM) is a disease characterized by dilation of the left ventricle of the heart. DCM has a prevalence of ~1:250 individuals and is the most common indication for heart transplant. The titin (TTN) gene encodes a protein localized to the sarcomere in cardiac muscle, which plays a crucial role in heart muscle contraction. Truncating variants in TTN (TTNtv) have been reported to cause DCM in ~27% of cases. However, ~3% of the general population have a TTNtv in the absence of DCM. The presence of TTNtv in apparently asymptomatic individuals complicates the classification of these variants. Recent publications investigating TTNtv, analyzed asymptomatic control cohorts and DCM patient cohorts, and revealed TTNtv located in constitutively expressed exons were more likely to be pathogenic. Utilizing this information in association with the American College of Medical Genetics and Genomics variant interpretation guidelines, we created a curation/classification scheme specific for TTNtv. The aim was to enable a highly reproducible and concordant curation process. To validate this curation scheme, a selection of previously reported pathogenic, likely pathogenic, uncertain, and benign TTNtv were curated and classified by multiple curators. This analysis revealed high reproducibility with no major discordance. The addition of the exon expression data helped to differentiate variants that are more likely to be pathogenic. In conclusion, a curation/classification scheme for TTNtv has been developed that is robust, concordant, and reproducible. The scheme assisted in decreasing the uncertainty of curation and classification of TTNtv, improving clinical outcomes for affected individuals and families.

ASDG Oral 5
IDENTIFICATION OF A DE NOVO HDAC8 PATHOGENIC VARIANT IN A PATIENT WITH SUSPECTED ANGELMAN SYNDROME

Mark Williams[1,2,3], Jason Pinner[4], James Harraway[1], and Helen Heussler[3,5]

[1] *Molecular Diagnostics, Mater Pathology, Brisbane, QLD, Australia*
[2] *Mater Research, Brisbane, QLD, Australia*
[3] *Faculty of Medicine, University of Queensland, Brisbane, QLD, Australia*
[4] *Medical Genomics, Royal Prince Alfred Hospital, Sydney, NSW, Australia*
[5] *Child Development, Lady Cilento Children's Hospital, Brisbane, QLD, Australia*

A 2-year-old female presented with prenatal onset microcephaly, global development delay, short stature, mild intermittent convergent strabismus, ataxia, hyperkinesis, and dysmorphic facial features without an underlying clinical diagnosis. Normal prior investigations included a cerebral MRI scan, EEG, transferrin isoforms, microarray, and urine metabolic screen. Although an atypical presentation, Angelman syndrome (AS) was considered. AS is neurodevelopmental disorder characterized by moderate/severe developmental delay, absent speech, gait ataxia, microcephaly, and seizures. Aberrations of the maternally inherited UBE3A gene result in AS. In this patient, copy number and methylation studies of 15q11-q13 and UBE3A sequencing were normal. These results did not support a diagnosis of AS. Subsequent whole exome sequencing (WES) identified a de novo variant in the HDAC8 gene. Pathogenic HDAC8 variants are rare and were initially reported in patients with a clinical diagnosis of Cornelia de Lange syndrome (CdLS). HDAC8 is a component of the cohesion complex responsible for sister chromatid cohesion during cell division. Mutations in various components of the cohesion complex cause CdLS and related cohesinopathies. HDAC8 is located on the X chromosome, and phenotypes associated with pathogenic variants in this gene are highly variable. Males are severely affected, while females have more variable phenotypes that are thought to be partially due to X-inactivation. The phenotypic overlap and convergent pathways in CdLS, AS, and other related neurodevelopmental disorders are discussed. This case advocates the use of WES (or whole genome sequencing) as the primary method for investigating neurodevelopmental disorders with unclear clinical phenotypes following routine microarray testing.

ASDG Oral 6
MOLECULAR GENOTYPING OF SUSPECTED MOLAR PREGNANCY SPECIMENS IN THE CYTOGENETICS LABORATORY FROM VALIDATION TO APPLICATION

Shanna Suwalksi[1], Ryan Storer[1], Kathryn Friend[1], Jill Lipsett[2], Lynette Moore[2], Nick Manton[2], Yee Khong[2], and Sui Yu[1]

[1] *Cytogenetics and Molecular Genetics, SA Pathology, Women's & Children's Hospital, Adelaide, SA, Australia*
[2] *Surgical Pathology, SA Pathology, Women's & Children's Hospital, Adelaide, SA, Australia*

Hydatidiform mole (HM) is a placental pathology of androgenetic origin, characterized by excessive proliferation of the trophoblast. This disorder occurs in approximately 1 in 1,000–2,000 pregnancies and carries the risk of persistent gestational trophoblastic disease, which is significantly higher for the complete hydatidiform (CHM) mole. The suspicion of HM can be raised at ultrasound and at pathology examination of curetted products of conception by their macroscopic or microscopic features. p57 immunohistochemistry can be performed to detect expression of the paternally imprinted cyclin-dependant kinase inhibitor 1C (CDKN1C) gene. A lack of expression indicates a CHM. However, p57 positive expression may be seen in both a partial mole (PHM) and a non-molar pregnancy, which require different clinical management. To ensure clinical usefulness, our laboratory has developed a protocol which combines molecular testing along with routine karyotyping applied only to p57 positive cases, and p57 negative cases that lack the typical histopathology findings. We perform molecular genotyping using microsatellite analysis on DNA extracted from fresh placental and maternal tissue, as well as culturing the placental sample for routine karyotyping. This process has been successful in confirming the diagnosis of HM in p57 negative cases that lack typical histology, and most importantly distinguishing PHM from digynic triploidy and non-molar pregnancies. Molar pregnancies require close clinical follow-up with repeated serum beta HCG levels while using contraception, so a finding of non-molar pregnancy deems this management unnecessary and is of considerable benefit to patients. We present our laboratory's experience in testing suspected molar pregnancies.

https://doi.org/10.1017/thg.2017.46 Published online by Cambridge University Press

Concurrent Session 3 — Australasian Association of Clinical Geneticists

AACG Oral 1
HETEROZYGOUS BMP2 HAPLOINSUFFICIENCY MUTATIONS CAUSE SHORT STATURE, PALATAL ANOMALIES, CONGENITAL HEART DISEASE, AND SKELETAL MALFORMATIONS

Tiong Yang Tan[1,2,7], Elizabeth Bhoj[3], Kevin Strauss[4], Karlla Brigatti[4], Claudia Gonzaga-Jauregui[5], Erik Puffenberger[4], Dong Li[3], Mai Raabus[7], Mirana Ramialison[6], Jan Kaslin[6], Lee Miles[6], Naomi Baker[7], and Peter Farlie[7]

[1] *Victorian Clinical Genetics Services, Melbourne, VIC, Australia*
[2] *Department of Paediatrics University of Melbourne, Melbourne, VIC, Australia*
[3] *Center for Applied Genomics, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, USA*
[4] *Clinic for Special Children, Philadelphia, PA, USA*
[5] *Regeneron Genetics Center, Tarrytown, NY, USA*
[6] *Australian Regenerative Medicine Institute, Monash University, Melbourne, VIC, Australia*
[7] *Murdoch Childrens Research Institute, Melbourne, VIC, Australia*

Bone morphogenetic protein 2 (BMP2) on chromosome 20p12 belongs to a gene superfamily encoding TGF-beta signaling peptides involved in bone and cartilage biology. Heterozygous chromosome 20p12 deletions are variably associated with cleft palate, short stature, and developmental delay. We report individuals with short stature, a recognizable gestalt, skeletal anomalies, and congenital heart disease but normal intellect with heterozygous mutations in BMP2. Craniofacial features include cleft palate, flat midface, short upturned nose, long philtrum, and low-set ears. Skeletal features include 11 pairs of ribs, clinodactyly, and pectus deformity. Congenital heart disease includes transposition of great arteries and Ebstein anomaly. In affected sisters with a BMP2 splice-site mutation, we demonstrate abnormal exon 2 splicing and paternal mosaicism; in an unrelated individual, we identified a de novo frameshift mutation. A heterozygous chromosome 20p12 deletion involving BMP2 was identified in another individual and his father with a similar phenotype. The craniofacial and skeletal phenotype of individuals with intragenic BMP2 mutations is similar to the deletion phenotype, suggesting that haploinsufficiency of BMP2 is the primary phenotypic determinant. Bmp2-null mice die from defects including heart malformation in early gestation, while mice with heterozygous loss of Bmp2 appear normal. We present analyses of secreted BMP2 peptide in affected and control cell lines as well as the effects of bmp2 knockdown on zebrafish craniofacial/skeletal cartilages and cardiac development. Our data suggest an elevated sensitivity to reduced BMP2 levels in human development and demonstrate involvement of BMP2 mutations in a recognizable human syndrome comprising craniofacial, skeletal, and cardiac malformations.

AACG Oral 2
RETURN OF SECONDARY FINDINGS TO THE HEALTHY ELDERLY

Paul Lacaze and Jane Tiller

Monash University, Melbourne, VIC, Australia

Genetic research into aging, longevity, and late-onset disease is becoming increasingly common. Yet, there is a paucity of knowledge related to clinical actionability and the return of pathogenic variants to otherwise healthy elderly individuals. Whether return of secondary findings should be managed differently from standard practices for younger populations is contentious (Lacaze et al., JMedEthics, 2017). Here we provide an overview of ethical and practical challenges encountered in preparing for a genetic study of ~15,000 healthy Australians aged 70 years or older enrolled in the ASPirin in Reducing Events in the Elderly (ASPREE) study. Participants were free of life-threatening illness, cardiovascular disease, or cognitive impairment at time of enrolment, hence ASPREE can be considered a healthy aging cohort. ASPREE participants provided consent with the understanding results of medical significance may be returned to them, if deemed clinically actionable. Sequencing has now commenced, and based on ACMG criteria, secondary findings are already being discovered and may eventually be found in up to 225–525 individuals (based on 1.5–3.5% estimated rate in Caucasians), raising significant concerns about the scalability, counseling requirements and clinical management of secondary findings at this scale under the Australian system, especially for this elderly age group. An ethically defensible plan for the return of genetic findings has been developed and approved by HREC. However, various challenges still exist, particularly around future genetic counseling demands, which will be discussed.

AACG Oral 3
GENOMIC DIAGNOSES IN FAMILIES WITH ANTERIOR SEGMENT ABNORMALITIES AND COMPLEX MICROPHTHALMIA

Alan Ma[1,4], John Grigg[1,3], Anson Cheng[1,3], Bruce Bennetts[2,4], and Robyn Jamieson[1,3,4]

[1] *Eye Genetics Research Unit, Sydney Children's Hospital Network, Children's Medical Research Institute, University of Sydney, Sydney, NSW, Australia*
[2] *Sydney Genome Diagnostics, Sydney Children's Hospital Network, Westmead, Sydney, NSW, Australia*
[3] *Save Sight Institute, University of Sydney, Sydney, NSW, Australia*
[4] *Discipline of Genetic Medicine, CHW Clinical School, Sydney Medical School, University of Sydney, Sydney, NSW, Australia*

Introduction: Disorders of the ocular anterior segment and microphthalmia/anophthalmia, occur due to abnormalities in several developmental pathways in eye embryogenesis, contributing to their clinical and genetic heterogeneity. We seek to determine the utility of genomic approaches in these conditions. *Methods:* We performed NGS in 63 probands with ocular anterior segment abnormalities (41 cases) or complex microphthalmia/anophthalmia (22 cases). Deletions on CGH microarray had already been excluded. A combination of targeted panel testing of developmental eye genes (Illumina TruSight One, HiSeq 2500), whole exome sequencing (Agilent SureSelect, Illumina Hiseq 4000), and whole genome sequencing (Illumina HiSeq X ten) was performed. We examined known anterior segment abnormality and microphthalmia genes, syndromic and non-syndromic. A customized alignment and variant calling pipeline was utilized, and variants of interest were confirmed with Sanger sequencing and segregation studies. *Results:* In our cohort of 63, likely causative mutations were found in 1/3 of patients. These were found in 37% (15/41) of patients with anterior segment abnormalities, and 27% (6/22) of microphthalmia/ anophthalmia patients. Mutations were found in the known anterior segment abnormality genes FOXC1/PITX2 in 6/41 patients, and also in the more rarely reported genes ADAMTS17, COL4A1, and PXDN. A novel 3.2kb deletion was found in the MIP gene. In the complex microphthalmia cases, mutations were found in SOX2 and OTX2, and also in the rarely reported genes FOXE3 and ALDH1A3. *Discussion:* This study demonstrates a significant yield of mutations in a cohort of patients with complex ocular phenotypes, providing new diagnostic and management information in all cases.

https://doi.org/10.1017/thg.2017.46 Published online by Cambridge University Press

AACG Oral 4
PREVALENCE AND NATURAL HISTORY OF RESPIRATORY CHAIN DISORDERS IN A 10-YEAR BIRTH COHORT

Rocio Rius Rius[1,2], A. G. Compton[1,2], H. S. Mountford[1,2,3], N. J. Lake[1,2], S. Thirukeswaran[1,2], S. E. Calvo[4,5,6], V. K. Mootha[4,5,6], John Christodoulou[1,2,7], and D. R. Thorburn[1,2,7]

[1] *Murdoch Childrens Research Institute, Melbourne, VIC, Australia*
[2] *Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia*
[3] *Department of Biological and Medical Sciences, Oxford Brookes University, Oxford, UK*
[4] *Howard Hughes Medical Institute and Department of Molecular Biology, Massachusetts General Hospital, Boston, MA, USA*
[5] *Department of Systems Biology, Harvard Medical School, Boston, MA, USA*
[6] *Broad Institute, Cambridge, MA, USA*
[7] *Victorian Clinical Genetics Services, Royal Children's Hospital, Melbourne, Australia*

Background: Mitochondrial respiratory chain disorders (RCD) comprise over 200 monogenic disorders; however, well-defined pediatric population-based studies are scarce. *Aim:* To describe the natural history of childhood-onset RC disorders. *Methods:* One-hundred-twelve patients with a definite diagnosis by Bernier criteria (91 with molecular diagnoses), born in South East Australia between 1987 and 1996 with onset by age 16 years, were included. Analyses were conducted using Excel 2017, SPSS v19, and Prism 7. *Results:* Age of onset ranged from 0 to 165.5 months. Male:female ratio was 1.3 ($p = .078$). The minimum birth prevalence per 100,000 (MBP) was estimated overall to be 6.56 (95% CI [5.45, 7.90]), 1.7(95% CI [1.18, 2.44]) for mitochondrial (mt) DNA mutations and 3.63 (95% CI [2.83, 4.66]) for nuclear mutations. The most common clinical syndrome was Leigh (-like) ($n = 38$, MBP 2.23, 95% CI [1.62, 3.06]) followed by Alpers and childhood myocerebrohepatopathy disorders ($n = 14$, MBP 0.82, 95% CI [0.49, 1.38]). Median survival was longer for mtDNA than nuclear mutations (322 vs. 27 months and 25 months for unknown genetic defect; $p = .0007$). Median survival within the mtDNA group was longer for tRNA genes than protein encoding genes (322 vs. 38 months). *Discussion:* The MBP is comparable with our previously published estimate of 6.2 (from 43 patients born between 1991 and 1994). This larger cohort provides estimates for the prevalence of nuclear and mtDNA mutations and important natural history information. *Conclusion:* This study highlights the wide clinical heterogeneity of RCD and provides natural history data, which illustrate how stratification by molecular and clinical phenotype can contribute to genetic counseling, surveillance, and resource allocation.

AACG Oral 5
SEVERE CONGENITAL CUTIS LAXA: IDENTIFICATION OF A NOVEL MOLECULAR CAUSE AND IMPLICATIONS FOR GENETIC COUNSELING

Fiona McKenzie[1,2], Kym Mina[3,9], Bert Callewaert[4], Jan Dickinson[5], Gareth Jevon[6], Gareth Baynam[1,2,7,8], and Aude Beyens[4]

[1] *Genetic Services of WA, Perth, WA, Australia*
[2] *School of Paediatrics and Child Health, The University of Western Australia, Perth, WA, Australia*
[3] *Department of Diagnostic Genomics, PathWest, Perth, WA, Australia*
[4] *Centre for Medical Genetics, Ghent University Hospital, Ghent, Belgium*
[5] *School of Women's and Infants Health, The University of Western Australia, Perth, WA, Australia*
[6] *Perinatal Pathology, PathWest and King Edward Memorial Hospital, Perth, WA, Australia*
[7] *Telethon Kids Institute, The University of Western Australia, Perth, WA, Australia*
[8] *Western Australian Register of Developmental Anomalies, Perth, WA, Australia*
[9] *Molecular Genetics, Douglass Hanly Moir Pathology, Sydney, NSW, Australia*

Two male babies born to a consanguineous Indian couple were diagnosed with a severe lethal form of congenital cutis laxa that presented with early-onset respiratory distress leading to respiratory failure and death within hours of birth, despite full resuscitation. Both babies had redundant and doughy-textured skin and facial dysmorphism. Echocardiography showed thickened and poorly contractile hearts with arterial dilatation and tortuosity. Post mortems in both babies identified mild corneal clouding, cutis laxa, widespread medium- and large-sized arterial ectasia, and tortuosity with abnormal elastin and muscular architecture, myocardial hypertrophy, and rib and skull fractures with abnormal bone matrix. Chromosome microarray identified multiple regions of absence of heterozygosity, consistent with the known consanguinity. Molecular analysis of known cutis laxa genes was inconclusive. Whole exome sequencing from both affected babies and parents identified a homozygous variant in a novel gene. Based on the gene being a member of the 5-lysyl oxidase gene family involved in initiation of cross-linking of elastin and collagen it was considered a likely candidate. A mouse model of a different mutation in this gene has been shown to result in a very similar phenotype to that seen in our family. Subsequent prenatal diagnosis was offered in the couple's third pregnancy and predicted the fetus to be unaffected. A healthy baby was subsequently delivered. The likely pathogenicity of the identified genetic variant will be discussed along with counseling issues associated with offering prenatal diagnosis based on a variant in a gene not previously linked with human disease.

AACG Oral 6
PLOD3 MUTATIONS RESULT IN A STICKLER SYNDROME-LIKE CONNECTIVE TISSUE DYSPLASIA

Lisa J. Ewans[1,2], Alison Colley[3], Carles Gaston-Massuet[4], Angelica Gualtieri[4], Mark J Cowley[1,2], Mark McCabe[1,2], Deepti Anand[5], Salil A Lachke[5,6], Ying Zhu[5], Kevin Ying[2], Corrina Walsh[6], Eric Lee[6], Edwin P. Kirk[6,7], Michael Field[5], David Miller[2], Michael Buckley[6], Marcel E Dinger[1,2], David Sillence[9], and Tony Roscioli[7]

[1] *St Vincent's Clinical School, University of New South Wales, Sydney, NSW, Australia*
[2] *Kinghorn Centre for Clinical Genomics, Garvan Institute of Medical Research, Sydney, NSW, Australia*
[3] *Clinical Genetics Department, Liverpool Hospital, Sydney, NSW, Australia*
[4] *Centre for Endocrinology, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, John Vane Science Centre, Charterhouse Square, London, UK*
[5] *Department of Biological Sciences, University of Delaware, Newark, DE, United States*
[6] *Center for Bionformatics and Computational Biology, University of Delaware, Newark, DE, United States,* [7] *Newcastle GOLD Service, Hunter Genetics, Newcastle, NSW, Australia*
[8] *SEALS laboratory, Prince of Wales Hospital, Sydney, NSW, Australia*
[9] *School of Women's and Children's Health, University of New South Wales, Sydney, NSW, Australia*
[10] *Centre for Clinical Genetics, Sydney Children's Hospital, Sydney, NSW, Australia*
[11] *Genetic Medicine, University of Sydney, Sydney, NSW, Australia*

Mutations in PLOD3 encoding the enzyme lysyl hydroxylase 3 (LH3) involved in collagen glycosylation were originally described in 2008 in two siblings with an autosomal recessive connective tissue dysplasia (CTD) with skeletal and ocular abnormalities, sensorineural hearing loss, and dysmorphic features. Since that time, there has been no published clinical information or classification of this disorder. We report an additional family with three individuals who share similar CTD features and a homozygous pathogenic variant in PLOD3 that localized within a functional glycosyltransferase domain. Clinical features were collated and compared to known CTDs to assist classification. hPLOD3 mRNA expression studies during human fetal development revealed tissue-specific expression localizing in the developing cochlea, eyes, skin, forelimbs, and cartilage consistent with tissues involved in patient phenotypes. From this work, we propose that the PLOD3-related disorder is an important subtype of Stickler syndrome. Early identification of PLOD3 mutations would enable clinicians to monitor for associated comorbidities and potentially avoid serious adverse ocular and vascular outcomes.

https://doi.org/10.1017/thg.2017.46 Published online by Cambridge University Press

Concurrent Session 4 — Genetics Education

PRENATAL DIAGNOSIS — GREAT ADVANCES SINCE THE 1960s

Nicole Martin

Chief Scientist in Genetics for Virtus Diagnostics, The Pathology Arm of Virtus Health, Australia

Our ability to offer an extensive range of prenatal diagnoses had advanced greatly since the 1960s when the first amniocenteses were performed. Available today are combination of screening and invasive diagnostic testing, utilizing ultrasound, placenta (CVS), amniotic fluid, and cell-free fetal DNA (cffDNA). Prenatal diagnosis can be broadly subdivided into screening and invasive diagnosis for chromosome aneuploidy and specific diagnosis for chromosome translocation carriers and couples who carry autosomal recessive, autosomal dominant, or X-linked genes. Morphological assessment of the fetus by ultrasound can detect soft markers for aneuploidy and other structural abnormalities; for example, neural tube defects. Screening for both chromosome aneuploidy and neural tube defects has been around for several decades. Screening advanced in the 1990s with the use of biochemical analyses and the measurement of fetal nuchal translucency (NT), and this gave an increased detection rate such that 90% of trisomy 21 fetuses could be detected. Screening for common aneuploidies now has moved into the era of non-invasive screening (NIPT) utilizing cffDNA present in the maternal circulation. This screening has greater than 99% sensitivity and specificity with >99.9% negative predictive value. Microarray technology has been applied to prenatal samples with a detection rate 6% greater than for a banded karyotype. This is of value in fetuses with ultrasound abnormalities. Chromosome mosaicism exists and can cause problems with result interpretation for both karyotype, array, and NIPT. The increasing obesity problem has ramifications for both the ability to image fetuses with ultrasound and it also dilutes the amount of cffDNA used in non-invasive screening. With advances in technology, it is now possible to sequence the whole fetal genome and this has even been applied at the level of a small number of cells as part of pre-implantation genetic diagnosis (PGD). Society as a whole needs to consider the value of such testing and subsequent clinical actions given our as yet imperfect knowledge about the pathogenicity or otherwise of many of the changes in DNA that are currently being detected.

Concurrent Session 5 — Australasian Society of Genetic Counsellors

ASGC Oral 7
CLUSTER RANDOMIZED CONTROLLED TRIAL OF A PSYCHOEDUCATIONAL INTERVENTION FOR PEOPLE WITH FAMILY HISTORY OF DEPRESSION

Bettina Meiser[1], Llewellyn Mills[1], Raghib Ahmad[1], Peter Schofield[8,9], Michelle Peate[1,9], Charlene Levitan[1], Lyndal Trevena[3,5], Kristine Barlow-Stewart[4], Timothy Dobbins[3], Helen Christensen[5], Kerry Sherman[6], Kate Dunlop[7], and Philip Mitchell[2]

[1] *Psychosocial Research Group, UNSW Sydney, Sydney, NSW, Australia*
[2] *School of Psychiatry, UNSW Sydney, Sydney, NSW, Australia*
[3] *National Drug and Alcohol Research Centre, UNSW Sydney, Sydney, NSW, Australia*
[4] *Sydney Medical School — Northern, University of Sydney, Sydney, NSW, Australia*
[5] *Black Dog Institute, Sydney, Australia*
[6] *Centre for Emotional Health, Department of Psychology, Macquarie University, Sydney, NSW, Australia*
[7] *Centre for Genetics Education, NSW Health, Royal North Shore Hospital, Sydney, NSW, Australia*
[8] *Neuroscience Research Australia, Sydney, Australia*
[9] *School of Medical Sciences, UNSW Sydney, Sydney, NSW, Australia*
[10] *Department of Obstetrics and Oncology, Royal Women's Hospital, University of Melbourne, Melbourne, VIC, Australia*

Objective: To evaluate the effectiveness of an interactive psychoeducational website (intervention) compared to a general leaflet about depression (control) in facilitating decisions about preventative behaviors in people at increased familial risk for depression. *Design:* Cluster randomized controlled trial. *Population:* GP attendees with at least one first-degree relative with major depressive disorder (MDD) or bipolar disorder (BD). *Methods:* Twenty general practices were randomized to provide eligible patients access to either the intervention ($n = 10$) or control condition ($n = 10$). Participants completed outcome measures at baseline and 2-week follow-up. *Outcome Measures:* The primary outcome was intention to undergo or actually undergoing psychological therapy as a risk reduction strategy for development of depression. Secondary outcomes were knowledge of risk factors and risk reduction strategies, perceived risk of developing MDD or BD, depression symptoms, and perceived stigma. *Results:* Two-hundred-eleven patients completed both questionnaires and were included in the analyses. Compared to the control group, the intervention group participants were more likely to intend to use or use therapy ($OR = 3.45$, 95% CI [1.28, 11.20], $p = .016$), had a significantly greater increase in knowledge (mean difference 0.47, 95% CI, [0.09, 0.88], $p = .022$) and were more likely to accurately estimate their lifetime risk of developing BD (mean difference 11.2, 95% CI [-16.19, -5.48], $p < .001$). There were no significant differences in the other outcomes measured. *Conclusion:* This psychoeducational website can play an important role in improving the outcomes of individuals at familial risk for depression. Testing of the intervention in other health practitioner settings (e.g., psychologists, psychiatrists, genetic counselors) appears warranted.

ASGC Oral 8
VIEWS OF AUSTRALIAN EDUCATION PROVIDERS AND HEALTH PROFESSIONALS ABOUT GENOMIC EDUCATION AND TRAINING NEEDS

Belinda McClaren[1,2,3], Zoe Prichard[1,4], Amy Nisselle[1,2,3], Kate Dunlop[1,4], Debra Graves[1,5], Bronwyn Terrill[1,6], Ainsley Newson[1,7], Clara Gaff[1,3,8], and Sylvia Metcalfe[1,2,3]

[1] *Australian Genomics Health Alliance, Melbourne, VIC, Australia*
[2] *Murdoch Childrens Research Institute, Melbourne, VIC, Australia*
[3] *University of Melbourne, Melbourne, VIC, Australia*
[4] *Centre for Genetics Education, NSW Health, Sydney, NSW, Australia*
[5] *The Royal College of Pathologists of Australasia, Sydney, NSW, Australia*
[6] *Kinghorn Centre for Clinical Genomics, Garvan Institute of Medical Research, Sydney, NSW, Australia*
[7] *Centre for Values, Ethics and the Law in Medicine, University of Sydney, Sydney, NSW, Australia*
[8] *Walter & Eliza Hall Institute for Medical Research, Melbourne, VIC, Australia*

Background: Successful implementation of genomics in health care requires well-informed and engaged health professionals who will request, or identify and refer, patients for genomic testing. *Aim:* To identify future genomic education and training needs of health professionals. *Methods:* Data were collected in semi-structured interviews. Australia-wide, participants were identified through their involvement in delivering recent education activities, or they responded to email invitations sent through professional networks and Colleges. Interviews were audio recorded, transcribed, and analyzed using deductive content analysis to document current education activities; and inductive coding to compare and contrast participant perspectives. Interviews and coding were conducted by BM, ZP, and AEN to ensure analytic rigor. *Results:* To date, 26 education providers and 32 health professionals (representing 15 specialities) have been interviewed. Overwhelmingly, education providers and health professionals stated the scarcity of genomic education/training opportunities needs to be addressed. Future education/training and preferences included (1) undergraduate/formal (medical) university training: curriculum-wide, emphasis on capability, and limitations of genomic technology; (2) registrar/trainee programs: didactic, optional 3–6 months genomics rotation following cases from intake through laboratory processes,

https://doi.org/10.1017/thg.2017.46 Published online by Cambridge University Press

bioinformatics analysis, and variant curation; (3) continuing medical education: intensive, hands-on workshops (e.g., variant curation) with supporting online learning to cover basics of genomics. *Discussion/Conclusions:* Further genomic education/training for health professionals, at a number of levels with targeted approaches, is essential to facilitate best practice in genomic medicine to ensure successful implementation of genomics in health care. This research provides evidence to inform preference and directions for future genomic education/training activities for health professionals.

ASGC Oral 9
AN AUDIT OF UNEXPLAINED CARDIAC DEATHS REFERRED TO GENETIC SERVICES OF WA FOR MOLECULAR AUTOPSY

Helen Mountain[1], Nicholas Pachter[1], Arieh Keren[2], Nik Stoyanov[3], and Jodi White[4]

[1] *Genetic Services of Western Australia, Perth, WA, Australia*
[2] *Sir Charles Gairdner Hospital, Perth, WA, Australia*
[3] *Fiona Stanley Hospital, Perth, WA, Australia*
[4] *PathWest, Perth, WA, Australia*

Background: Collaboration between Genetic Services of Western Australia (GSWA), the Coroner and forensic pathologists saw the development of an integrated approach to referrals to our multidisciplinary cardiac genetics clinic, of families of young people who died suddenly where a cardiac arrhythmia was suspected. *Aim:* This audit aims to assess the utility, and outcomes, of this approach to ascertainment of the cause of sudden cardiac death in young people. *Methods:* Between June 2014 and July 2017, 25 families of persons who died suddenly and without an identifiable cause at autopsy were referred to GSWA. Relatives had pre-clinic and clinic consultation(s) to obtain relevant medical and family history information. Consent to test their deceased relative's stored DNA sample via an Illumina Trusight panel of 34 genes associated with cardiac arrhythmias (with the option to interrogate structural and other genes if suspected) was obtained. A review of all referrals made during the study period was conducted and clinical data, genetic test results, and outcomes recorded. *Results:* Demographic and clinical data, genetic test results, and illustrative case studies will be presented. *Discussion:* An Australasian study identified a clinically relevant cardiac gene mutation in 27% of cases of unexplained sudden death (Bagnall et al., 2016), suggesting this approach to ascertainment is warranted. Potential benefits of molecular autopsy include identifying the cause of unexplained deaths, identification of at-risk relatives and facilitating clinical surveillance in these individuals. Limitations include raising expectations, introducing uncertainty (possibility of finding variants of unknown significance), and burden on bereaved relatives.

ASGC Oral 10
THE IMPACT OF NIPT ON PRENATAL DIAGNOSTIC TESTING IN A TERTIARY REFERRAL CENTER

Cheryl Tse[1], Abhijit Kulkarni[2], Fabricio Costa[1,3,5], and Melody Menezes[1,4]

[1] *Monash Ultrasound for Women, Melbourne, VIC, Australia*
[2] *Monash Pathology, Monash Health, Melbourne, VIC, Australia*
[3] *Monash University, Melbourne, VIC, Australia*
[4] *Genetics Education and Health Research, Murdoch Children's Research Institute, Melbourne, VIC, Australia*
[5] *Monash Medical Centre, Melbourne, VIC, Australia*

Due to its high sensitivity and no associated miscarriage risk, NIPT is increasingly becoming a first-line aneuploidy screening option for many pregnant women in Australia. It also serves as a secondary screening option in situations where invasive prenatal diagnostic testing (PND) is not suitable. The purpose of this study was to examine the impact NIPT has had on PND. A retrospective cohort study was conducted on all patients ($n = 1{,}656$) referred to a tertiary obstetric ultrasound service for PND from 2010 to 2016. The main objective was to determine the differences in the number of PND referrals between the pre-NIPT (prior to April 2013) and post-NIPT period. The secondary objective was to examine the shift in clinical indications and outcomes of PND. An independent *t* test was employed to compare the differences in clinical indications (five categories) and diagnostic testing outcomes (three categories) between the two groups. There was a statistically significant reduction in the number of diagnostic procedures in the post-NIPT period (1,056 pre-NIPT vs. 600 post-NIPT $p < .0001$; 36.2% decrease). In the post-NIPT group, there were a higher number of abnormal PND results. The clinical indications for testing between the groups also differed, and this will be discussed in further depth. There was a reduction in the number of diagnostic procedures in the post-NIPT period, and a notable shift was observed in the clinical indications for diagnostic testing. The significant changes in the landscape of diagnostic testing within a short timespan have demonstrated the growing influence of NIPT on prenatal management.

ASGC Oral 11
GENETIC INFORMATION AND INSURANCE — WHAT SHOULD AUSTRALIA DO?

Jane Tiller[1,2]

[1] *Public Health Genomics, Monash University, Melbourne, VIC, Australia*
[2] *University of Melbourne, Melbourne, VIC, Australia*

The use of genetic information by life insurance companies is of international concern, with countries taking a variety of different regulatory approaches. A number of recommendations made in 2003 regarding this critical issue in Australia have not been implemented, and the resulting lack of regulation and uncertainty for consumers is untenable. With the life insurance industry under close scrutiny in 2017, the policy situation is ripe for change. How should Australia be regulating insurers' use of genetic information? Should there be a moratorium? It is clear that Australia should be addressing this issue, but the best way forward is less clear. The uncertainty surrounding how genetic information will be used by insurance companies in Australia is particularly relevant to the return of genetic findings to elderly participants in the ASPirin in Reducing Events in the Elderly (ASPREE) study, which has collected and commenced sequencing ~15,000 biobank samples of healthy Australians aged 70 years or older. This presentation will explore the complexity of this issue and the difficulty in reaching a consensus on future policy direction. It will discuss the submission of the Australian Genetic Non-Discrimination Working Group (which includes medical, legal, ethical, research, and insurance experts) to the current Parliamentary Inquiry into the Life Insurance Industry and the Groups's recommendations. A national survey is currently being implemented in conjunction with Paul Lacaze, PhD and Louise Keogh, PhD to explore the attitudes and practices of genetics professionals regarding genetic testing and insurance and an update on that study will be presented.

ASGC Oral 12
PARENT OPINIONS ON THE USE OF STORED PEDIATRIC TUMOR SAMPLES FOR GENETIC RESEARCH

Kathryn Visser[1,2], Adrienne Sexton[1,3], Alexandra Sexton-Oates[2], and Richard Saffery[2]

[1] *Department of Paediatrics, The University of Melbourne, Melbourne, VIC, Australia*
[2] *Murdoch Childrens Research Institute, Melbourne, VIC, Australia*
[3] *Genetic Medicine & Familial Cancer Centre, The Royal Melbourne Hospital, Melbourne, VIC, Australia*

Pediatric central nervous system (CNS) tumors are rare but contribute significantly to childhood mortality and morbidity. More research is needed to increase quality of life and prevent death from childhood brain cancer, necessitating access to CNS tumor samples. With a lack of studies exploring parents' views on use of their child's

https://doi.org/10.1017/thg.2017.46 Published online by Cambridge University Press

archived tumor sample, this study aimed to elucidate their opinions and preferences relating to sample storage and use in genetic research. Nine semi-structured interviews were conducted with parents of children who had died from cancer, employing a phenomenological framework, and thematic analysis in order to identify emergent themes from the data. This study demonstrates that despite their ongoing grief, parents are willing to consent to the use of their child's sample for genetic research, driven by altruistic motivations. Retrospective notification of sample storage was met with acceptance and understanding, and parents dispelled the need for their permission to be acquired for use of these archived samples. Support from healthcare professionals created a positive experience among their chaos and grief, and parents favored the chance to receive individual results if relevant to their family. This study's findings inform researchers, genetic counselors, ethics boards, and healthcare professionals about these parents' opinions and experiences, and some of the factors shaping their attitudes, thus enabling them to modify protocols and practice.

Concurrent 6 — Australasian Society of Diagnostic Genomics

ASDG Oral 7
CNV ANALYSIS FROM HISEQ X WHOLE GENOME SEQUENCING DATA: FIT FOR CLINICAL USE

Ben Lundie[1], Andre E. Minoche[2], Velimir Gayevskiy[2], Greg Peters[3], Dale Wright[3], Benjamin Nash[3], Marcel Dinger[1,2,5], Andreas Zankl[2,3,4], Michael Buckley[1,5,6], Tony Roscioli[5,6], Leslie Burnett[1,4,5], and Mark J. Cowley[2,5]

[1]*Genome.One, Sydney, NSW, Australia*
[2]*Garvan Institute of Medical Research, Sydney, NSW, Australia*
[3]*Sydney Genome Diagnostics, Children's Hospital Westmead, Sydney, NSW, Australia*
[4]*Sydney Medical School, University of Sydney, Sydney, NSW, Australia*
[5]*St Vincent's Clinical School, UNSW, Sydney, NSW, Australia*
[6]*SEALS Genetics, NSW Health Pathology Service, Sydney, NSW, Australia*

Microarrays have been in routine clinical use for more than a decade. The rapidly decreasing cost of whole genome sequencing (WGS) presents a unique opportunity to improve detection of CNVs. We have developed a pipeline that identifies regions of CNV utilizing evidence from split reads, discordant pairs, and depth of coverage. Multiple quality attributes and annotations enable us to obtain a comprehensive high-confidence CNV call-set. By adding human population allele frequencies for CNVs, we are able to find rare disease-causing variants. Further, we developed a streamlined visualization procedure that allows the inspection of CNV and the underlying evidence in genome browsers. We have performed extensive validation against clinical microarrays (50 samples) and NA12878 gold standards. Analytical sensitivity as assessed against NA12878 for deletions >500 bp is 99.1% with reproducibility for CNVs between replicates of 98.9%. CNV detection <500 bp is more challenging (~86.6%) and primarily due to mapping of sequences within repetitive regions. Comparison against microarray shows 100% concordance for reportable variants. Overall CNV concordance between WGS and microarray for high and medium confidence calls was 83% and 44%, respectively. We attribute the lower concordances to false calls made by microarray software, although we note that some diagnostic array labs routinely filter these out, by reference to their own in-house databases. We conclude that WGS data provides wider, more uniform, and higher resolution coverage than current best-practice use of microarray, being superior in terms of analytic sensitivity and specificity.

ASDG Oral 8
SOMATIC MOSACISM IS READILY DETECTED VIA SNP MICROARRAY, A CONSIDERATION FOR WES/WGS ANALYSIS PIPELINES

Amber Boys, Ralph Oertel, Sebastian Lunke, Louise Hills, Paula Lall, Lorna Williams, Prabhakara Krishnamurthy, Fiona Norris, and David Francis

Victorian Clinical Genetics Services, Royal Children's Hospital, Melbourne, VIC, Australia

The prevalence of somatic mosaicism based on SNP microarray has not been published. At VCGS, we have performed approximately 70,000 SNP microarray analyses on a mixture of prenatal and postnatal samples. The sensitivity of SNP microarray and our analysis protocols allows for the detection of low-level somatic mosaicism for copy number variants, uniparental isodisomy, and chimerism. We report clinically relevant somatic mosaicism in approximately 0.82% of patient's presenting for SNP microarray in our pediatric cohort and in approximately 0.68% of unaffected parents of clinically affected children. The detection of mosaicism allows for more accurate determination of recurrence risks and appropriate reproductive options for affected families. For those laboratories performing routine diagnostic whole exome or genome sequencing (WES/WGS), does the existence of parental somatic mosaicism have an impact on the accuracy of trio analysis pipelines? Are WES/WGS technologies sensitive enough to detect somatic mosaicism, and are these technologies able to exclude parental somatic mosaicism to a respectable level? WES/WGS studies on patients with intellectual disability using trio analysis have revealed that the majority of causative mutations are autosomal dominant and apparently de novo in origin. Parental germline mosaicism is implied only after the reoccurrence of a second affected child. Is the risk of parental germline mosaicism high enough that PGD/PND should be offered to all parents whose child has a known pathogenic mutation, as is standard procedure for Duchenne muscular dystrophy (DMD) where the empirical risk of germline mosaicism is as high as 15–20%?

ASDG Oral 9
GENOME SEQUENCING OF 15,000 HEALTHY ELDERLY AUSTRALIANS

Paul Lacaze

Monash University, Melbourne, VIC, Australia

The ASPREE Healthy Ageing Biobank contains ~15,000 consented samples from individuals aged 70 years or older participating in the ASPirin in Reducing Events in the Elderly (ASPREE) study — Australia's largest clinical trial and longitudinal study of healthy aging. ASPREE represents a randomly ascertained biobank population depleted of typical genetic disease, meaning it can act as an ideal reference population for clinical genetics, providing population data on penetrance of predictive risk variants in elderly unaffected individuals. All ASPREE biobank samples are being sequenced using a targeted 'super-panel' of 750 genes used commonly in clinical testing, covering clinical actionable familial cancer genes, cardiovascular, and neurological disease genes on the ACMG list. Over 4,000 samples have been sequenced (April 2017), identifying actionable pathogenic variants in individuals lacking any apparent signs and symptoms of disease well beyond the age of onset 75 years and older (i.e., the non-penetrant). Results will be presented on these findings, providing much needed insight into clinical actionability for genes used in predictive testing. Participation in the Resilience Project will also be described, which is a global initiative to identify rare individuals with highly penetrant pathogenic mutations who do not appear to develop typical signs and symptoms of disease. Studying these rare individuals may inform future therapeutic strategies based on inherent disease protection mechanisms.

https://doi.org/10.1017/thg.2017.46 Published online by Cambridge University Press

ASDG Oral 10
HEPARIN SULFATE PROTEOGLYCANS (HSPGS) AND RUNX2 MEDIATE HUMAN BREAST CANCER EPITHELIAL CELL PROLIFERATION

Larisa Haupt
IHBI-QUT, Brisbane, QLD, Australia

Previous studies have observed roles for HSPG core proteins including syndecans (SDC1-4) and glypicans (GPC1-6) in breast cancer and hepatocellular carcinoma. In this study, we examined the expression profile of HSPGs core proteins along with their key initiation and modification enzymes in human breast cancer epithelial cells. Gene expression in relation to cell proliferation was examined in two human breast cancer cell lines (MCF-7 and MDA-MB-231 cells) following treatment with the HS agonist heparin. The addition of heparin increased gene expression of chain initiation and modification enzymes including EXT1 (MCF-7; $p = .0002$, D1 inc; MDA $p = 1.77\times1e\text{-}8$, D3 inc) and NDST1 (MCF-7 $p = .016$, D1 inc; MDA $p = 3.31\times1e\text{-}5$, D3 inc). In addition, significant changes in core protein gene expression were observed, including SDC1 (MCF-7 $p = .02$, D1 inc; MDA $p = .011$, D3 dec) and GPC6 (MCF-7 $p = 1.6\times1e\text{-}7$, D3 inc; MDA $p = 2.94\times1e\text{-}9$, D3 inc). When we investigated the HS/Run×2 axis in MDA-MB-231 cells, we observed reduced cell migration following Runx2 siRNA down regulation. Finally, we investigated the cultures for associated expression changes in the Wnt pathway. We observed increased proliferation of the more invasive MDA-MB-231 cells associated with activation of members of the Wnt signaling pathway. Specifically, there was substantial up-regulation of the AXIN1, 9-fold inc, $p = 1.4\times1e\text{-}5$, WNT4A, 15-fold inc, $p = .006$ and MYC, 6-fold inc, $p = .0003$ genes at D5 in MDA-MB-231 cells. In contrast, MCF-7 cells showed a small increase in Wnt genes at D1 (AXIN1, 1.5-fold inc, $p = .01$; MYC, 1.3-fold inc, $p = .005$; FZD5, 1.9-fold inc, $p = .007$).

ASDG Oral 11
A NOVEL APPROACH TO THE VISUALIZATION OF LARGE-SCALE GENOMIC INTERACTIONS USING 'ABSTRACT RENDERING' COMPUTATIONAL TECHNIQUES

Po Liu[1,2], and Leslie Burnett[1,2,3,4]
[1] *Garvan Institute of Medical Research, Sydney, NSW, Australia*
[2] *Sydney Medical School, University of Sydney, Sydney, NSW, Australia*
[3] *Genome.One, Sydney, NSW, Australia*
[4] *St. Vincent's Clinical School UNSW, Sydney, NSW, Australia*

The advent of high-throughput sequencing methods in both clinical and research settings has produced a large volume of genomic data for bioinformatic analysis. Investigations in genomic interactions can be rate limited by the speed and power of visualization tools. We present a novel method of genomic interaction data visualization using a strategy known as Abstract Rendering (AR). AR was originally developed for use in the software industry and has been applied to rapidly generate interactive high-resolution visualizations of a publicly accessible geospatial Uber dataset of over 10 million New York City taxi trips. The computational technique consists of a series of steps: selection of data properties to visualize, aggregation in fixed bin size, and transfer via a mapping function into a visual property. We implemented our bio-informatic pipeline to use AR in order to analyze over 25 million genomic interactions in various test data sets of eukaryotic genes. The AR visualization solution was validated by accurately identifying the same regions of interest described in previous studies using conventional visualization tools. The advantages of our AR solution included a speedup of two orders of magnitude and the ability for on-the-fly lossless real-time interaction compared to previous methods using standard plotting and visualization tools. The cross-pollination of AR for use in genomic interaction data analysis showcases the benefits of the rapid and meaningful interpretation of large-scale sequencing data.

ASDG Oral 12
CHALLENGES OF CURATION IN DIAGNOSTIC PRACTICE: A LEARNING EXPERIENCE

Sebastian Lunke[1], Paul James[2], Natalie Thorne[3], Zornitza Stark[1], Tiong Yang Tan[1,4], Susan M. White[1,4], Miriam Fanjul Fernandez[1], Dean Phelan[1], Justine Marum[1], Belinda Chong[1], and Melbourne Genomics Health Alliance[3]
[1] *Victorian Clinical Genetics Service, Melbourne, VIC, Australia*
[2] *Royal Melbourne Hospital, Melbourne, VIC, Australia*
[3] *Melbourne Genomics Health Alliance, Melbourne, VIC, Australia*
[4] *Department of Paediatrics University of Melbourne, Melbourne, VIC, Australia*

New sequencing technologies have enabled mainstreaming of genomics into diagnostics. With exome and genome sequencing increasingly accessible, laboratories face the challenge of having to curate thousands of variants without a standardized framework. In 2015, the American College of Medical Genetics and Genomics (ACMG) attempted to address this challenge by issuing recommendations for the interpretation of sequence variants. While these guidelines are now forming the basis of many variant classification schemes, they are open to interpretation in many aspects, leading to discordance in variant classification between laboratories performing genomic testing. To mitigate the risk of discordant variant classifications and to increase the traceability of the curation process, we have adapted the ACMG guidelines into our own variant curation scheme, which employs automated calculation of a suggested variant classification as well as detailed evidence tracking, resulting in an accurate reflection of the curators' decision-making process. Testing our approach using independent curators across two laboratories to analyze the same variants (27 variants, 3 curators per variant), we achieved 95% curation concordance, attesting the process to be highly robust and reproducible even with little prior training. In addition to a well-defined curation scheme, our approach utilizes clinically driven variant prioritization, and an interactive team of scientists. As a result, we have an average analysis workload of approximately 8 hours per exome, with an approximate curation time of 2 hours per case (avg. 55 min per variant (St. Dev. 22 min), avg. two variants per case), while maintaining a diagnostic yield of approximately 35%.

Concurrent Session 7 — Australasian Association of Clinical Geneticists

AACG Oral 7
WHOLE EXOME SEQUENCING IN INFANTS WITH CONGENITAL DEAFNESS

David Amor[1,2,3,4], Lilian Downie[1,2,3], Jane Halliday[2,3], and Rachel Burt[2,3]
[1] *Victorian Clinical Genetics Service, Melbourne, VIC, Australia*
[2] *Murdoch Children's Research Institute, Melbourne, VIC, Australia*
[3] *University of Melbourne, Melbourne, VIC, Australia*
[4] *Royal Children's Hospital, Melbourne, VIC, Australia*

Background: The Melbourne Genomics Health Alliance is working to establish a system for rolling out genomic medicine in Victoria. The Congenital Deafness project is offering genomic testing to families who have a child with moderate or worse bilateral hearing loss born in 2016 or 2017. *Aim:* To define the genetic etiology of congenital hearing loss, streamline the care of affected children, explore parents' interest in genomic testing, and gain further information on whole exome sequencing. *Methods:* Whole exome sequencing allows for the sequencing, simultaneously, of all genes known to play a role in hearing loss. Exome sequencing generates data for all known disease-causing genes, not just those for hearing loss. We are also offering families the opportunity to receive results about genes

https://doi.org/10.1017/thg.2017.46 Published online by Cambridge University Press

that cause diseases other than hearing loss that present in childhood. Families who have an eligible child are identified by the Victorian Infant Hearing Screening Program. They are informed about (1) the pediatrician-run clinics for children with hearing loss, (2) the VicCHILD databank, and (3) genomic testing. *Results:* We are currently in the recruitment phase and have identified 56 patients; 18 have consented for genetic testing, 2 have received results, 15 patients are awaiting booked clinic appointments, 5 patients have declined participation, and the remainder are yet to be contacted. *Discussion/Conclusion:* This research will provide important evidence on the genetic causes of hearing loss and parents preferences when being offered additional findings using next generation sequencing technology.

AACG Oral 8
GENOMIC SEQUENCING REANALYSIS AT 12 MONTHS BOOSTS MENDELIAN DIAGNOSIS AND IS COST-EFFECTIVE IN INTELLECTUAL DISABILITY

Lisa J. Ewans[1,2], Deborah Schofield[2,3,4], Rupendra Shrestha[3], Ying Zhu[5], Velimir Gayevskiy[2], Kevin Ying[2], Corrina Walsh[6], Eric Lee[6], Edwin P Kirk[6,7,8], Alison Colley[9], Carolyn Ellaway[7,10], Anne Turner[7,8], David Mowat[7,8], Lisa Worgan[9], Mary-Louise Freckmann[7,8], Michelle Lipke[7,11], Rani Sachdev[7,8], David Miller[2], Michael Field[5], Marcel E Dinger[1,2], Michael Buckley[6], Mark J. Cowley[1,2], and Tony Roscioli[7]

[1] *St Vincent's Clinical School, UNSW, Sydney, NSW, Australia*
[2] *Kinghorn Centre for Clinical Genomics, Garvan Institute of Medical Research, Sydney, NSW, Australia*
[3] *Faculty of Pharmacy, Charles Perkins Centre, University of Sydney, Sydney, NSW, Australia*
[4] *Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, VIC, Australia*
[5] *The Genetics of Learning Disability Service, Newcastle, NSW, Australia*
[6] *SEALS laboratory, Prince of Wales Hospital, Sydney, NSW, Australia*
[7] *Centre for Clinical Genetics, Sydney Children's Hospital, Sydney, NSW, Australia*
[8] *School of Women's and Children's Health, University of New South Wales, Sydney, NSW, Australia*
[9] *Clinical Genetics Department, Liverpool Hospital, Liverpool, Australia*
[10] *Disciplines of Child and Adolescent Health and Genetic Medicine, University of Sydney, Sydney, NSW, Australia*
[11] *Lady Cilento Children's Hospital, Brisbane, QLD, Australia*

Purpose: Whole exome sequencing (WES) has revolutionized Mendelian diagnostics; however, there has not been a consensus on the timing of review of data in undiagnosed individuals and only preliminary data on the cost-effectiveness of this technology. We aimed to assess the utility of WES data reanalysis for diagnosis in Mendelian disorders and to analyze the cost-effectiveness of this technology compared to a traditional diagnostic pathway. *Methods:* WES was applied to a cohort of 54 patients from 37 families with a variety of Mendelian disorders to identify the genetic basis to their disease. Reanalysis was performed after 12 months with an improved WES diagnostic pipeline. A comparison was made between costs of a modeled WES pathway and a traditional diagnostic pathway in a cohort with intellectual disability (ID). Cost-effectiveness of WGS compared to WES was made for a number of hypothetical scenarios with a range of diagnostic rates and costs of WGS. *Results:* Reanalysis of WES data at 12 months following initial assessment improved diagnostic success from 30% to 38% due to interim publication of disease genes, expanded phenotype data from referrer, and an improved bioinformatics pipeline. Cost analysis on the ID cohort showed cost savings when genomic studies were applied early in the patient diagnostic journey. *Conclusion:* Early application of WES in Mendelian disorders is cost-effective and reanalysis of undiagnosed individual at a 12-month time point increases diagnoses by 8%.

AACG Oral 9
USER ACCEPTABILITY OF WHOLE EXOME PRECONCEPTION CARRIER TESTING FOR CONSANGUINEOUS COUPLES IN AUSTRALIA

Sarah Josephi-Taylor[1,2], Kris Barlow-Stewart[3], Arty Selvanathan[1], Tony Roscioli[1,2], Alan Bittles[4], Bettina Meiser[6], Lisa Worgan[5], Sulekha Rajagopalan[5], Alison Colley[5], and Edwin P. Kirk[1,2]

[1] *Centre for Clinical Genetics, Sydney Children's Hospital, Sydney, NSW, Australia*
[2] *School of Women's and Children's Health, UNSW Medicine, University of New South Wales, Sydney, NSW, Australia*
[3] *Sydney Medical School Northern, University of Sydney, Sydney, NSW, Australia*
[4] *Centre for Comparative Genomics, Health Research Centre, Murdoch University, Perth, WA, Australia*
[5] *Pyschosocial Research Group, Prince of Wales Clinical School, Sydney, NSW, Australia*
[6] *Department of Clinical Genetics, Liverpool Hospital, Sydney, NSW, Australia*

Background: Autosomal recessive (AR) disorders are a major cause of morbidity and mortality. Consanguineous couples are at greater risk of having children with AR conditions. Preconception exome sequencing has the potential to identify couples at risk of AR as well as X-linked conditions. *Aim:* To explore with consanguineous couples in Australia their experience and views regarding the acceptability and potential utility of preconception exome sequencing. *Methods:* Semi-structured interviews were conducted with 21 consanguineous couples with diverse ethnic and religious backgrounds, recruited through clinical genetics services prior to an offer of genomic testing. Interviews were audio-recorded, transcribed, de-identified, and coded with concordance assessed by two coders; thematic analysis was informed by an inductive approach. *Results:* Four major themes were identified: the consanguineous couple, childhood illness, genomic screening perceived utility, and communication. The majority of couples reported perception of increased risk of having affected children and were aware of congenital childhood illness within their family or community. Stigma as a result of their consanguinity in Australia was rare. All were supportive of the availability of genomic preconception screening. If found to be carriers of a severe childhood condition, 15/21 couples would test a pregnancy, 11/15 would consider termination, and 7/21 would consider not having further children. The majority would communicate a potential at risk status to their family members. *Discussion:* The majority of couples were open to preconception genomic screening, understood the potential and limitations, and would utilize the results with the goal of preventing childhood illness associated with suffering.

AACG Oral 10
VALIDATION OF NEXT GENERATION SEQUENCING (NGS) FOR PRE-IMPLANTATION GENETIC SCREENING (PGS)

Jun Xia, Ping Liu, Dayang Chen, Yong Qiu, Qianyu Shi, Zhu Zhu, Lin Xie, and Fang Chen

BGI, Shenzhen, China

Chromosome abnormalities are the major factor of abnormal development of embryos with normal morphology, thus cause implantation failure and early reproductive losses in IVF treatments. Preimplantation genetic screening (PGS) allows selecting embryos with normal chromosome to increase the success rate of implantation and decrease early pregnancy losses. Advances in NGS technology have generated a new method for PGS of human embryos from IVF cycles. This study aimed to investigate the effects of PGS based on NGS. This study consisted of two parts: the first part was to validate the effectiveness of NGS-based PGS by detecting national standard samples, which included 73 human cell-line samples with different CNVs (>1M) and aneuploid, 10 normal karyotype human cell line samples (one for data QC), and 6 simulated mosaic samples. The second part aimed to compare PGS based on NGS and aCGH by detecting retrospective clinical samples, including 301 blastocysts

https://doi.org/10.1017/thg.2017.46 Published online by Cambridge University Press

and 157 blastomeres, which have aCGH results. The chromosome abnormalities detection results of NGS were obtained by BGISEQ-500 platform. A total of 801 national standard samples were detected by NGS-based PGS. The sensitivity was 99.26% (670/675), four samples failed to construct libraries, and one failed to detect CNV (<4M). The specificity was 100% (90/90), and 70% and 30% mosaic detection rate was 68.51% and 64.81%, respectively. Paired comparison between NGS and array-CGH from 301 blastocysts and 157 blastomeres showed concordant results (280/294(95.2%), 134/142(94.4%)). Seven blastocysts and 15 blastomeres failed to get aCGH results. NGS-based PGS has high sensitivity and specificity, and provided highly consistent with aCGH in clinical samples.

AACG Oral 11
DISCOVERING THE NON-PENETRANT: IDENTIFICATION OF COGNITIVELY HEALTHY APOE E4 HOMOZYGOTES

Paul Lacaze[1] and Aamira Huq[2]

[1]*Monash University, Melbourne, VIC, Australia*
[2]*Department of Genetic Medicine, Royal Melbourne Hospital, Melbourne, VIC, Australia*

APOE ε4/ε4 homozygosity is the strongest genetic risk factor for late onset Alzheimer's disease (LOAD), increasing lifetime risk from 11% for males and 14% for females to 51% and 68%, respectively. In some cases, however, ε4 homozygotes live well beyond the expected age of onset without developing typical signs and symptoms, suggesting protection or reduced penetrance to increased genetic risk. These protected or 'resilient' individuals are difficult to find and validate, given genetic testing of healthy elderly individuals is rare. Even rarer is the availability of detailed phenotypic and cognitive function data alongside an APOE ε4 genotype to confirm the absence of cognitive decline. Here we present a scalable screening approach to identify cognitively healthy APOE ε4 homozygotes among ∼15,000 elderly participants of the ASPirin in Reducing Events in the Elderly (ASPREE) biobank. We present the baseline characteristics of 22 such individuals aged over 75 years who were identified through our first round of screening of 2,200 ASPREE biobank participants. We present demographic and clinical characteristics of these resilient individuals who had no prior diagnosis of dementia at study enrolment and a score of ≥77 in the Modified Mini-Mental State Examination (3MS). A cohort of unaffected APOE ε4 homozygotes will be formed to enable future studies of penetrance and genetic resilience, an approach that will be expanded to other genes used in predictive testing. This is the first step in studying the genetic and environmental factors in individuals who do not develop disease despite a significant genetic predisposition.

AACG Oral 12
SOLVING THE UNSOLVED: SYSTEMATIC REANALYSIS OF THE NEGATIVE EXOME

Natalie Tan[1], Tiong Y Tan[1,2], Zornitza Stark[1], Alicia Oshlack[3], Susan M. White[1,2], Maie Walsh[1], Monique M. Ryan[4], Katrina M. Bell[3], Clara L. Gaff[5], Peter Georgeson[5], Anthony Marty[5], Gayle Philip[5], Natalie Thorne[5], Belinda Chong[1], Sebastian Lunke[1], Damien Bruno[1], and Alison Yeung[1]

[1]*Victorian Clinical Genetics Services, Murdoch Childrens Research Institute, Melbourne, VIC, Australia*
[2]*Department of Paediatrics, The University of Melbourne, Melbourne, VIC, Australia*
[3]*Murdoch Childrens Research Institute, Melbourne, VIC, Australia*
[4]*Department of Neurology, The Royal Children's Hospital, Melbourne, VIC, Australia,*
[5]*Melbourne Genomics Health Alliance, Melbourne, VIC, Australia*

Background: Many reasons have been postulated for the lack of diagnosis after whole exome sequencing (WES), including imperfect sequencing, variant annotation and filtering, evolution of patient phenotype, and incomplete knowledge of gene- and variant-disease associations and gene function. *Methods:* We reanalyzed the data from unsolved WES cases from two Melbourne Genomics Health Alliance (MGHA) cohorts (Childhood Syndromes and Hereditary Neuropathy flagships, 2014–2015), and cases referred for WES to the Clinical Exome Laboratory at Victorian Clinical Genetics Services between January 2016 and March 2017. Reanalysis involved review of existing WES data, using updated versions of the Mendeliome generated every 6 months from review of current literature. Reanalysis also incorporated bioinformatics pipeline updates to improve variant calling and filtering. *Results:* A diagnosis was achieved in 124 out of 350 patients on initial analysis (35%). The reanalysis of WES data from a total of 124 unsolved patients recruited through the two MGHA flagships yielded a new diagnosis in nine cases (7%) over an 18-month period. Systematic reanalysis was also applied to the first 100 unsolved clinical WES cases performed by VCGS. *Conclusion:* All additional diagnoses in this study resulted from the identification of variants in genes newly reported in the literature as being associated with monogenic disorders. This study illustrates the diagnostic value of storage and reanalysis of existing genomic data, and supports the need for periodic, systematic, and fully auditable re-evaluation of WES data from unsolved cases when there is a high suspicion of a Mendelian disorder.

https://doi.org/10.1017/thg.2017.46 Published online by Cambridge University Press

Concurrent Session 8 — Submitted Orals

Oral 1
PUSHING THE LIMITS OF EXOME SEQUENCING: FINDING DONSON MUTATIONS IN 29 PATIENTS WITH MICROCEPHALIC DWARFISM

Louise Bicknell[1,2], John Reynolds[3], Paula Carroll[2], Martin Higgs[3], Ranad Shaheen[4], Jennie Murray[2], Dimitrios Papadopoulos[5], Andrea Leitch[2], Olga Murina[2], Zygimante Tarnauskaite[2], Sarah Wessel[6], Anatasia Zlatanou[3], Audrey Vernet[3], Alex von Kriegsheim[2], Rachel Mottram[3], Clare Logan[2], Hannah Bye[7], Yun Li[8], Alexander Brean[3], Sateesh Maddirevula[4], Rachel Challis[2], Kassiani Skouloudaki[5], Agaadir Almoisheer[4], Hessa Alsaif[4], Ariella Amar[7], Natalie Prescott[7], Michael Bober[9], Angela Duker[9], Eissa Faqeih[10], Mohammed Zain Seidahmed[11], Saeed Al Tala[12], Abdulrahman Alswaid[13], Saleem Ahmed[14,15], Jumana Yousuf Al-Aama[14,15], Janine Altmuller[16], Mohammed Al Balwi[17], Angela Brady[18], Luciana Chessa[19], Helen Cox[20], Rita Fischetto[21], Raoul Heller[22], Bertram Henderson[23], Emma Hobson[24], Peter Nurnberg[16], E. Ferda Percin[25], Angela Peron[26,27], Luigina Spaccini[26], Alan Quigley[28], Seema Thakur[29], Carol Wise[30], Grace Yoon[31,32], Maha Alnemer[33], Pavel Tomancak[5], Gokhan Yigit[8], Malcolm Taylor[3], Martin Reijns[2], Michael Simpson[7], David Cortez[6], Fowzan Alkuraya[4], Christopher Mathew[7,34], Andrew Jackson[2], and Grant Stewart[3]

[1] *University Of Otago, Dunedin, New Zealand*
[2] *MRC Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK*
[3] *Institute of Cancer and Genomic Sciences, College of Medical and Dental Sciences, University of Birmingham, Birmingham, UK*
[4] *Department of Genetics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia*
[5] *Max-Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany*
[6] *Department of Biochemistry, Vanderbilt University School of Medicine, Nashville, TN, USA*
[7] *Department of Medical and Molecular Genetics, King's College London, London, UK*
[8] *Institute of Human Genetics, University Medical Center Gottingen, Gottingen, Germany*
[9] *Nemours-Alfred I. duPont Hospital for Children, Wilmington, NC, USA*
[10] *Department of Pediatric Subspecialities, Children's Hospital, King Fahad Medical City, Riyadh, Saudi Arabia*
[11] *Department of Pediatrics, Security Forces Hospital, Riyadh, Saudi Arabia*
[12] *Armed Forces Hospital, SR. P.D. Genetics Unit, Khamis Mushayt, Saudi Arabia*
[13] *Department of Pediatrics, King Abdulaziz Medical City, Riyadh, Saudi Arabia*
[14] *Department of Genetic Medicine, King Abdulaziz University Hospital, Jeddah, Saudi Arabia*
[15] *Princess Al-Jawhara Al-Brahim Center of Excellence in Research of Hereditary Disorders, Jeddah, Saudi Arabia*
[16] *Cologne Center for Genomics and Center for Molecular Medicine Cologne, University of Cologne, Cologne, Germany*
[17] *Department of Pathology and Laboratory Medicine, King Abdulaziz Medical City, National Guard Health Affairs, Riyadh, Saudi Arabia*
[18] *North West Thames Regional Genetics Service, London North West Healthcare NHS Trust, Harrow, London, United Kingdom*
[19] *Department of Clinical and Molecular Medicine, University La Sapienza, Roma, Italy*
[20] *West Midlands Regional Clinical Genetics Service, Birmingham Women's Hospital, Birmingham, UK*
[21] *Pediatric Hospital Giovanni XXIII, Bari, Italy*
[22] *Institute of Human Genetics, University Hospital of Cologne, Cologne, Germany*
[23] *Divison of Clinical Genetics, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa*
[24] *Department of Genetics, Yorkshire Regional Genetic Service, Chapel Allerton Hospital, Leeds, UK*
[25] *Department of Medical Genetics, Gazi University Faculty of Medicine, Besevler Ankara, Turkey*
[26] *Clinical Genetics Unit, Divison of Maternal Fetal Medicine, Department of Obstetrics and Gynecology, V. Buzzi Children's Hospital, Universita' degli Studi di Milano, Milan, Italy*
[27] *Child Neuropsychiatry Unit-Epilepsy Center, San Paolo University Hospital, Department of Health Sciences, Universita' degli Studi di Milano, Milan, Italy*
[28] *Department of Radiology, Royal Hospital for Sick Children, Edinburgh, UK*
[29] *Department of Genetic and Fetal Medicine, Fortis Lafemme, New Delhi, Indi*
[30] *Sarah M. and Charles E. Seay Center for Musculoskeletal Research, Texas Scottish Rite Hospital for Children, Dallas, TX, USA*
[31] *Divison of Clinical and Metabolic Genetics, Hospital for Sick Children, University of Toronto, Toronto, Canada*
[32] *Department of Pediatrics, Division of Neurology, Hospital for Sick Children, University of Toronto, Toronto, Canada*
[33] *Department of Obstetrics and Gynecology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia*
[34] *Sydney Brenner Institute for Molecular Bioscience, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*

To ensure efficient genome duplication, cells have evolved numerous factors that promote unperturbed DNA replication and protect, repair and restart damaged forks, with many of these factors associated with microcephaly and associated primordial dwarfism. During our studies of such patients, we identified a clinically similar subgroup in which gene panels for microcephaly and dwarfism genes had been negative. Our hypothesis was therefore that this cohort harbored a novel disease gene. Exome sequencing followed by standard bioinformatic analysis was not initially fruitful; however, by incorporating additional cryptic splicing predictions alongside manual interrogation of sequence reads, we identified an intronic variant weakly predicted to create a cryptic splice-site embedded within a rare Neanderthal-derived haplotype extending 130 kb across DONSON. This haplotype was inherited in trans with truncating variants, and contained three DONSON variants; two benign missense variants in addition to this key intronic change. Studying these variants in a cellular context revealed the least obvious missense mutation was in fact functionally deleterious. Two other concurrent collaborative studies identified further biallelic mutations in DONSON and with 29 affected individuals; DONSON represents a common cause of microcephalic dwarfism. DONSON was a poorly characterized gene, but through extensive cellular workup we demonstrated that DONSON is an essential component for stabilizing replication forks during genome replication. Hypomorphic mutations in DONSON substantially reduce DONSON protein levels and impair fork stability, consistent with defective DNA replication underlying this disease phenotype. This study reiterates the need for repeated and creative interrogation of NGS data in identifying novel causes of disease.

Oral 2
GENES MUTATED TO CAUSE PERIVENTRICULAR NODULAR HETEROTOPIA REGULATE NEUROPROGENITOR STEM CELLS

Stephen Robertson[1], Adam O'Neill[1], Christina Kyrousi[2], Johannes Klaus[2], David Markie[1], and Silvia Cappello[2]

[1] *University of Otago, Dunedin, New Zealand*
[2] *Max Planck Insitute of Psychiatry, Munich, Germany*

Background: Disorders of neuronal mispositioning are phenotypically heterogeneous and characterized clinically by epilepsy and intellectual disability. In periventricular neuronal heterotopia (PH), neurons fail to populate the outer cortex of the brain resulting in their heterotopic positioning along their sites of origin — the lateral ventricles. Currently, only 25% of sporadic instances of the disease have a definable molecular genetic cause. *Methods:* To characterize the contribution of rare genetic variants toward the causation of PH, we performed exome sequencing on 65 probands and their parents and filtered for de novo and rare recessive genotypes. *Results:* Fifty rare, coding, de novo, or rare biallelic variants were identified and although no two patients were mutated at the same locus across the entire cohort, a likelihood analyses, accounting for gene size and mutability, identified an excess of de novo variants in loci intolerant to functional change ($p = 1.28\times10–12$). An estimated 28% of these de novo variants contribute to the causation of the PH phenotype (95% CI: 16–42%). Specifically focusing on a set of genes linked to human neural stem cell transcriptional network demonstrated an excess ($p = .024$) of de novo variants at these loci. Finally, a knockout of a human-specific isoform was identified and further studies of this spliceform in mouse and human brain organoids suggest a regulatory role in human neurogenesis. *Conclusion:* PH exhibits considerable genetic heterogeneity with genes that are mutated to cause the condition being preferentially embedded in neural stem cell networks and primate-novel regions of the coding genome.

https://doi.org/10.1017/thg.2017.46 Published online by Cambridge University Press

Oral 3
USP9X MUTATIONS CAUSE A SPECTRUM OF NEURODEVELOPMENTAL DISORDERS UNDERPINNED BY DISRUPTED DEVELOPMENTAL SIGNALING PATHWAYS

Lachlan Jolly[1], Brett Johnson[1], Raman Kumar[1], Thomas Burne[2], Michael Piper[2], Stephen Wood[3], and Jozef Gecz[1]

[1] *University of Adelaide, Adelaide, SA, Australia*
[2] *University of Queensland, Brisbane, QLD, Australia*
[3] *Griffith University, Brisbane, QLD, Australia*

Mutations in the X-linked gene USP9X have been associated with intellectual disability (ID) in both males and females. Nineteen mutations causing haploinsufficiency of USP9X in females with ID and recognizable brain structural and dysmorphic features have been reported. In males, only three missense mutations had been reported, and as such the involvement of USP9X in male ID remained less certain. We report 26 additional USP9X missense mutations associated with male ID, with 21 mutations considered strong candidates for pathogenicity based on segregation and in-silico metrics. We describe an evolving phenotypic spectrum associated with USP9X missense mutations in males: In addition to ID and developmental delay, we found speech delay and hypotonia, visual impairment, autistic behavior, aggressiveness, and seizures also frequently identified (64–100% of cases). Brain structural imaging found evidence of disrupted white matter, thin corpus callosum, and cortical malformations. Our knockout USP9X mouse model displayed overlapping brain structural features, and we now resolve severe learning in memory defects highlighting its utility to understanding mechanisms of pathology. USP9X is a deubiquitylating enzyme capable of protecting substrates from proteasomal degradation. We show in embryonic brains of USP9X knockout mice, multiple key substrates belonging to signaling pathways are altered, and as such defective mTOR, WNT, NOTCH, and TGFβ signaling pathways are observed. Furthermore, we found evidence of these key substrates disrupted in patient-derived fibroblast cells lines, suggesting defective signaling underlies pathology. Collectively, our data demonstrate the involvement of USP9X in male ID and other neurodevelopmental disorders, and identify plausible mechanisms of pathogenesis.

Oral 4
GENOMIC APPROACHES TO THE RETINAL DYSTROPHIES: NEW DIAGNOSES AND STRATEGIES TOWARD THERAPIES

Benjamin Nash[1,2,3], John Grigg[1], Dale Wright[2,3], Bruce Bennetts[2,3], and Robyn Jamieson[1,3]

[1] *Eye Genetics Research Unit, Children's Medical Research Institute, Children's Hospital at Westmead, Save Sight Institute, University of Sydney, Sydney, NSW, Australia*
[2] *Sydney Genome Diagnostics, The Children's Hospital at Westmead, Sydney, NSW, Australia*
[3] *Discipline of Genetic Medicine, CHW Clinical School, University of Sydney, Sydney, NSW, Australia*

Introduction: The retinal dystrophies (RD) are phenotypically and genetically heterogeneous, affect approximately 1:3500 people, and are now more common as a cause of blindness in the working-age population than diabetes. Results from gene therapy clinical trials hold significant promise for therapeutic approaches for these conditions. This underlines the imperative for genomic approaches to achieve molecular diagnosis for these patients. *Methods:* In a cohort of 71 probands with familial or sporadic RD, we applied genomic approaches including targeted panel testing of retinal dystrophy genes (Illumina TruSight One, HiSeq 2500), and whole genome sequencing (Illumina HiSeq X ten). Variants detected in 217 RD genes of interest were filtered and prioritized on in silico allele frequencies, conservation and pathogenicity prediction scores, and final candidate variants were categorized using ACMG guidelines. *Results:* In this cohort, likely causative mutations were identified in 2/3 of probands. The mutation detection rate was higher in those with retinitis pigmentosa (30/41, 73%) than those with cone, cone-rod, or macular dystrophy (9/19, 47%). We found mutations in 8/11 (73%) patients with Leber congenital amaurosis. Clinical diagnoses were changed as a result of the genomic testing in several cases, including categorization to specific types of retinal dystrophy with future prospects for clinical trial activity. *Discussion:* Genomic approaches in the retinal dystrophies provide new diagnostic and clinical information for patients and families in a high proportion of cases. They also pave the way toward targeted genome editing and new therapeutic strategies for these patients.

Concurrent Session 9 — Submitted Orals

Oral 5
EVALUATION OF WHOLE GENOME SEQUENCING FOR THE GENETIC DIAGNOSIS OF PEDIATRIC MITOCHONDRIAL RESPIRATORY CHAIN DISORDERS

Lisa Riley[1,2], Mark Cowley[3], Velimir Gayevskiy[3], Tony Roscioli[3], David Thorburn[4,5], Melanie Bahlo[6,7], Carolyn Sue[3,8], Shanti Balasubramaniam[9,10], David Coman[11,12], and John Christodoulou[1,2,4,5,9,10]

[1] *Genetic Metabolic Disorders Research Unit, Western Sydney Genetics Program, The Children's Hospital at Westmead, Sydney, NSW, Australia*
[2] *Discipline of Child and Adolescent Health, Sydney Medical School, University of Sydney, Sydney, NSW, Australia*
[3] *Kinghorn Centre for Clinical Genomics, Garvan Institute of Medical Research, Sydney, NSW, Australia*
[4] *Murdoch Childrens Research Institute and Victorian Clinical Genetic Services, Royal Children's Hospital, Melbourne, VIC, Australia*
[5] *Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia*
[6] *Population Health and Immunity Division, The Walter and Eliza Hall Institute of Medical Research, Melbourne, VIC, Australia*
[7] *Department of Medical Biology, University of Melbourne, Melbourne, VIC, Australia*
[8] *Department of Neurogenetics, Kolling Institute of Medical Research, University of Sydney and Royal North Shore Hospital, Sydney, NSW, Australia*
[9] *Western Sydney Genetics Program, The Children's Hospital at Westmead, Sydney, NSW, Australia*
[10] *Discipline of Genetic Medicine, Sydney Medical School, University of Sydney, Sydney, NSW, Australia*
[11] *Department of Metabolic Medicine, Lady Cilento Children's Hospital and Department of Paediatrics, Wesley Hospital and School of Medicine, University of Queensland, Brisbane, QLD, Australia*
[12] *School of Medicine, Griffith University, Gold Coast, QLD, Australia*

The diagnosis of mitochondrial respiratory chain disorders (MRCD) is often long and potentially invasive, usually involving a combination of clinical evidence, biochemical screening, and functional testing of the mitochondrial respiratory chain enzymes. Despite a firm enzymatic diagnosis, the genetic etiology, which may be nuclear or mitochondrial in origin, can remain elusive. We have been investigating the utility of trio whole genome sequencing (WGS) for diagnosis of pediatric MRCD in a cohort of 42 patients with clinical features suggestive of a MRCD, from four state-based pediatric genetic metabolic referral centers. Potential causal variants have been identified in 28 cases (67%) and involved known nuclear MRCD genes (ACAD9, BCS1L, COX10, ECHS1, GFM1, PET100, PNPT1, RARS2, SERAC1), and known mitochondrial DNA-encoded genes (MT-ATP6, MT-CO2 MT-TL1, MT-TS1, MT-CYB). A novel gene was identified and functionally confirmed in one case (MECR), and three other novel candidate genes are currently being evaluated. In the remaining cases, despite evidence of a MRCD, variants were identified in disease genes with no previous association with a mitochondrial disorder (ARX, EPG5, HCFC1, HRAS, SKIV2L, SLC39A8), and in each case, the clinical features were consistent with the known phenotypes associated with these genes. In these cases, the primary diagnosis of MRCD may be incorrect and the functional mitochondrial abnormalities may be secondary. Alternatively, the underlying causative mutations may still remain obscure. We suggest that WGS rapidly and efficiently identifies variants in known mitochondrial disease genes of both nuclear and mitochondrial origin, with a positive detection in at least 50% of cases.

https://doi.org/10.1017/thg.2017.46 Published online by Cambridge University Press

Oral 6
ATAD3 GENE CLUSTER DELETIONS CAUSE CEREBELLAR DYSFUNCTION ASSOCIATED WITH ALTERED MITOCHONDRIAL DNA AND CHOLESTEROL METABOLISM

David Thorburn[1,2,3], Ann Frazier[1,3], Nicole Lake[1,3], Alison Compton[1,3], Hayley Mountford[1,3], Elena Tucker[1,3], David Francis[2], George McGillivray[2,4], Sebastian Lunke[1,2,5], Simone Mandelstam[3,6], David Stroud[7], Mike Ryan[7], Anne Turner[8], Ian Andrews[8], Radha Desai[9], Romina Durigon[10], Aleck Jones[10], Alice Mitchell[10], Harshil Patel[11], Abdul Sesay[11], Deborah Jackson[11], Miriam Di Re[12], Illaria Dalla Rosa[10], Lambert van den Heuvel[13], Jan Smeitink[13], Johannes Spelbrink[13], Derek Burke[14], Fanny Mochel[15], Boris Keren[15], Claude Jardel[15], Simon Heales[10,14], Masakazu Kohda[16], Akira Ohtake[16], Kei Murayama[17], Yasushi Okazaki[16], Anne Lombes[18], Ian Holt[9,10,19], and Antonella Spinazzola[10]

[1] *Murdoch Childrens Research Institute, Melbourne, VIC, Australia*
[2] *Victorian Clinical Genetics Services, Melbourne, VIC, Australia*
[3] *Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia*
[4] *Royal Women's Hospital, Melbourne, VIC, Australia*
[5] *Department of Pathology, University of Melbourne, Melbourne, VIC, Australia*
[6] *Department of Radiology, University of Melbourne, Melbourne, VIC, Australia*
[7] *Monash Biomedicine Discovery Institute, Monash University, Melbourne, VIC, Australia*
[8] *Sydney Children's Hospital, Sydney, NSW, Australia*
[9] *MRC Laboratory, Mill Hill, London, UK*
[10] *Institute of Neurology, University College London, London, UK*
[11] *Francis Crick Institute, London, UK*
[12] *Mitochondrial Biology Unit, University of Cambridge, Cambridge, UK*
[13] *Radboud University Medical Center, Nijmegen, The Netherlands*
[14] *Institute of Child Health, University College London, London, UK*
[15] *Pitie-Salpetriere University Hospital, Paris, France*
[16] *Saitama Medical University, Saitama, Japan*
[17] *Chiba Children's Hospital, Chiba, Japan*
[18] *Inserm U1016, L'Universite Paris-Descartes, Paris, France*
[19] *Biodonostia Health Research Institute, San Sebastian, Spain*

Mitochondrial disorders are clinically heterogeneous with causative mutations identified in ~250 genes. However, the molecular diagnosis is unsolved in up to 50% of cases, partly due to some genomic regions being refractory to analysis. We and others recently identified large deletions, gene conversions, and de novo point mutations in one such region, encoding three highly homologous tandemly arrayed genes (ATAD3C, ATAD3B, and ATAD3A). We used SNP microarray, exome sequencing and long-range PCR analyses to identify six subjects from five unrelated families with impaired cerebellar development and neurological function who carried deletions or gene conversions in the ATAD3 locus. Five subjects had highly similar clinical presentations including congenital pontocerebellar hypoplasia and early death. In these subjects, two similar deletions of ~38 Kbp resulted in an ATAD3B/ATAD3A fusion gene that produced an mRNA encoding a protein 99% identical to ATAD3A, but under the control of the ATAD3B promoter. Immunoblotting and quantitative proteomics identified a striking reduction in the amount of ATAD3 in cells and tissues. The sixth subject had a milder presentation, surviving into adulthood with cerebellar atrophy and ataxia. Her ATAD3 rearrangements included a heterozygous deletion involving ATAD3C/ATAD3B, plus gene conversion events within ATAD3B and ATAD3A. Although high homology within the ATAD3 locus complicates genomic analyses, putative deletions can be identified by targeted re-analysis of existing SNP and exome data. Our results identify mtDNA abnormalities and indicators of abnormal cholesterol metabolism in ATAD3 deficient fibroblasts and emphasize the broad clinical spectrum of mitochondrial disorders resulting from ATAD3 rearrangements.

Oral 7
NAD DEFICIENCY CAUSES MULTIPLE CONGENITAL MALFORMATIONS THAT ARE POTENTIALLY PREVENTABLE BY NIACIN SUPPLEMENTATION

Hongjun Shi[1,2], Annabelle Enriquez[1,2,3,4,5], Melissa Rapadas[1], Ella Martin[1], Roni Wang[1], Julie Moreau[1], Chai K Lim[6], Justin Szot[1,2], Eddie Ip[1,2], James Hughes[7], Kotaro Sugomoto[1], David Humphreys[1,2], Aideen McInerney-Leo[8,9], Paul Leo[8,9], Ghassan Maghzal[2,10], Jake Halliday[1], Janine Smith[4,5], Alison Colley[3], Paul Mark[11], Felicity Collins[4,5], David Sillence[4,5], David Winlaw[12,13], Joshua Ho[1,2], Gilles Guillemin[6], Matthew Brown[8,9], Kazu Kikuchi[1,2], Paul Thomas[7], Roland Stocker[1,2], Eleni Giannoulatou[1,2], Gavin Chapman[1,2], Emma Duncan[8,9,14,15], Duncan Sparrow[1,2], and Sally Dunwoodie[1,2]

[1] *The Victor Chang Cardiac Research Institute, Developmental and Stem Cell Biology, Sydney, NSW, Australia*
[2] *UNSW, Sydney, NSW, Australia*
[3] *Liverpool Hospital, Department of Clinical Genetics, Sydney, NSW, Australia*
[4] *Children's Hospital at Westmead, Department of Clinical Genetics, Sydney, NSW, Australia*
[5] *University of Sydney, Discipline of Genetic Medicine, Sydney, NSW, Australia*
[6] *Macquarie University, Faculty of Medicine and Health Sciences, Sydney, NSW, Australia*
[7] *University of Adelaide, School of Biological Sciences, Adelaide, SA, Australia*
[8] *Queensland University of Technology, Institute of Health and Biomedical Innovation, Brisbane, QLD, Australia*
[9] *Translational Research Institute, Brisbane, Brisbane, QLD, Australia*
[10] *Victor Chang Cardiac Research Institute, Vascular Biology, Sydney, NSW, Australia*
[11] *Spectrum Health Medical Group, Medical Genetics, Grand Rapids, MI, USA*
[12] *University of Sydney, Medical School, Sydney, NSW, Australia*
[13] *Children's Hospital at Westmead, Heart Centre for Children, Sydney, NSW, Australia*
[14] *Royal Brisbane and Women's Hospital, Endocrinology, Brisbane, QLD, Australia*
[15] *University of Queensland School of Medicine, Brisbane, QLD, Australia*

Background: Congenital malformations can manifest in isolation or as combinations that co-occur more often than expected by chance. VACTERL association is one example. We investigated the possible genetic causes in four unrelated patients displaying cardiac, vertebral, and renal defects, among others. *Methods:* We used genomic sequencing to identify potentially pathogenic gene variants in four families. For functional validation, we quantified metabolites in patient plasma and used in vitro enzyme activity assays. We generated mouse models using CRISPR/Cas9 to determine whether these candidate genes affect embryonic development. *Results:* We identified loss-of-function variants in 3-hydroxyanthranilate 3,4-dioxygenase (HAAO), and kynureninase (KYNU), genes encoding kynurenine pathway enzymes. Three patients had homozygous variants (HAAO p.D162*, HAAO p.W186*, or KYNU p.V57Efs*21). Another patient had heterozygous KYNU variants (p.Y156* and p.F349Kfs*4). All mutant enzymes had greatly reduced activity in vitro. Nicotinamide adenine dinucleotide (NAD) is synthesized de novo from tryptophan via the kynurenine pathway. Affected patients had reduced circulating NAD levels. Haao or Kynu null mouse embryos exhibited similar defects to the patients, due to NAD deficiency. In null mice, reversing NAD deficiency during gestation prevented organ malformations. *Conclusions:* Disruption of NAD synthesis leads to NAD deficiency and congenital malformations in humans and mice. We propose that any cause of NAD deficiency during gestation might result in congenital malformation, in combination or in isolation. Collectively these can be termed congenital NAD deficiency disorders. Of greatest clinical relevance, our findings indicate that niacin supplementation can ameliorate or prevent cases of congenital malformations.

https://doi.org/10.1017/thg.2017.46 Published online by Cambridge University Press

Oral 8
EXOME SEQUENCING OF 249 FAMILIES WITH PRIMARY IMMUNODEFICIENCIES: TRANSLATIONAL GENOMICS WITH DIRECT CLINICAL IMPLICATIONS

Peer Arts[1], Annet Simons[1], Mofareh S. AlZharani[2], Elanur Yilmaz[1,3], Eman Alldrissi[2], Koen J. van Aerde[4], Michiel Van der Flier[4], Marcel van Deuren[5], Christian Gilissen[1], Erika H Gerkes[6], Chantal HH Kerkhofs[7], Riika Keski-Filppula[8], Arjen R. Mensenkamp[1], Jukka Moilanen[8], Jaap ten Oever[5], Maaike Vreeburg[7], Gijs TJ van Well[7], Evelien Zonneveld-Huijssoon[6], Wendy A. G. van Zelst-Stams[1], Joris A Veltman[1,7,9], Eissa A. Faqeih[2], Frank L. van de Veerdonk[5], Mihai G. Netea[5], and Alexander Hoischen[1,5]

[1]*Department of Human Genetics, Radboud University Medical Center, Nijmegen, Netherlands*
[2]*Department of Pediatrics, King Fahad Medical City, Riyadh, Saudi Arabia*
[3]*Department of Medical Biology, Faculty of Medicine, Akdeniz University, Antalya, Turkey*
[4]*Department of Pediatric Immunology, Pediatrics, Radboud University Medical Center, Nijmegen, Netherlands*
[5]*Department of Internal Medicine, Radboud university medical center, Nijmegen, Netherlands*
[6]*Department of Genetics, University Medical Center Groningen, Groningen, Netherlands*
[7]*Department of Clinical Genetics, Maastricht University Medical Center, Maastricht, Netherlands*
[8]*University of Oulu and Department of Clinical Genetics, Oulu University Hospital, Oulu, Finland*
[9]*Institute of Genetic Medicine, Centre for Life, Newcastle University, Newcastle-upon-Tyne, UK*

Background: Diagnosis of primary immunodeficiencies is complex and expensive, yet important for the clinical management of the disease. *Objective:* To test the clinical utility and assess the diagnostic yield of whole exome sequencing (WES) for patients with primary immunodeficiencies. *Methods:* We have performed WES in a diagnostic setting for 254 PID patients from 249 families. For the majority of cases, the clinical diagnosis was based on clinical criteria including rare and/or unusually severe bacterial, viral, or fungal infections, sometimes accompanied by autoimmune-manifestations, and was interpreted in the context of aberrant immune cell populations, aberrant antibody levels, or combinations of these factors. *Results:* For 62 patients from 58 families (23%), WES allowed us to provide a molecular diagnosis by focusing on disease-causing mutations in well-established primary immunodeficiency genes. An exome-wide analysis, considering mutations in novel disease genes and tissue-specific defects, resulted in a diagnosis for 10 additional families (4%). Altogether, WES granted a diagnosis in 72 patients from 68 families (27%). *Conclusion:* Exome sequencing can provide a genetic diagnosis in a significant number of patients with PIDs. It is important to perform exome-wide analyses after an analysis of the known PID genes because many new PID genes are only just being discovered. The molecular diagnosis provided novel insight in therapeutic options for a subset of our patients.

Concurrent Session 10 — Submitted Orals

Oral 9
MATERNAL CAUSES OF FALSE POSITIVE AND DISCORDANT CELL-FREE DNA SCREENING RESULTS

Mark Pertile[1,2], Olivia Giouzeppos[1], Grace Shi[1], Clare Love[1], Ralph Oertel[1], Fiona Norris[1], and Damien Bruno[1]

[1]*Victorian Clinical Genetics Services, Melbourne, VIC, Australia*
[2]*Department of Paediatrics, University of Melbourne, Melbourne, VIC, Australia*

Cell-free (cf)DNA screening for fetal aneuploidy, also known as non-invasive prenatal testing (NIPT), is based on massively parallel sequencing of cfDNA from the plasma of pregnant women. Approximately 10% of the cfDNA is fetal in origin and is derived from placental trophoblast. The remaining 90% is maternal. Both components are analyzed during cfDNA screening. There are several known biological causes of false positive and discordant NIPT results, including confined placental mosaicism, co-twin demise, and maternal causes. Over the course of running a high-volume NIPT service during the past 2 years (April 2015–2017), we have accumulated significant evidence for known and novel maternal causes of discordance. This includes cases of mosaicism for large copy number abnormalities, sex chromosome mosaicism, non-mosaic sex chromosome aneuploidy, autosomal trisomy mosaicism, as well as novel Y-chromosome derived copy number variants. Evidence for maternal malignancy has been rare with no confirmed cases in over 25,000 samples tested. Monosomy × mosaicism is a frequent finding and can involve >25–50% monosomy. We have determined conventional karyotyping to be a poor follow-up test for confirming maternal mosaicism in these cases. Other cytogenetic or molecular methods are more sensitive. We summarize our experience in investigating maternal biological causes for discordant NIPT results and provide recommendations on cytogenetic follow-up and management of these cases.

Oral 10
AUSTRALIAN LIFE INSURERS USE OF GENETIC TEST RESULTS IN UNDERWRITING DECISIONS

Mia Liepins[1], Margaret Otlowski[2], Alan Doble[3], and Kristine Barlow-Stewart[1]

[1]*Genetic Medicine University of Sydney, Sydney, NSW, Australia*
[2]*University of Hobart, Hobart, TAS, Australia*
[3]*None, Sydney, NSW, Australia*

Since 1999, the Financial Services Council (FSC) has requested its Australian life insurance member companies provide data on applications where a genetic test is disclosed. The FSC provided data collected 2010–2013 to enable repetition of an independent analysis undertaken of applications 1999–2003 (Otlowski et al., 2007, *Aust J Law and Medicine*). Data included de-identified insurer, age, gender, genetic condition, reason for testing and result, underwriting decision maker, and insurance cover. Data were classified as to test result alone or in addition to other factors relevant to risk, underwriting decision. Where necessary, the FSC facilitated clarification by insurers. A total of 340/547 applications were for adult-onset conditions: hereditary haemochromatosis (HH-200), cancer (51); thrombophilia (31), cardiovascular (17), neurodegenerative (13), neuromuscular (9); and other (19). The genetic test result solely influenced the underwriting decision in 170/340 applications: 24 positive, 139 negative, 2 uninformative, 3 pending, and 2 unknown. Policies were provided at standard rate for all negative test results with evidence of reassessment of previous non-standard decisions and 20/24 positive results with recognition of risk reduction strategies. Non-standard polices were provided for positive BRCA2 (2) and Lynch syndrome results; for the two BRCA1/2 uninformative results, breast cancer exclusion and 50% loading were applied, respectively; and for results pending (cancer-2, Huntington disease-1) applications were denied. Limitations in the data influence interpretation and generalizability of the findings including the context of the testing setting (research/clinical). Recent updates to the standards governing life insurers' practice will be discussed and genetic counseling practice implications of the findings.

https://doi.org/10.1017/thg.2017.46 Published online by Cambridge University Press

Oral 11
'THE MORE I KNOW ABOUT GENETICS …': RESEARCH TO INFORM AUSTRALIAN COMMUNITY CONVERSATIONS ABOUT PERSONAL GENOMICS

Bronwyn Terrill[1], Jacqueline Savard[4,1], Chriselle Hickerton[2,3], Rigan Tytherleigh[2,3], Ainsley Newson[4,1], Clara Gaff[5], Kathleen Gray[2], Anna Middleton[6], Brenda Wilson[7], and Sylvia Metcalfe[2,3]

[1] *Garvan Institute of Medical Research, Sydney, NSW, Australia*
[2] *The University of Melbourne, Melbourne, VIC, Australia*
[3] *Murdoch Children's Research Institute, Melbourne, VIC, Australia*
[4] *The University of Sydney, Sydney, NSW, Australia*
[5] *Melbourne Genomics Health Alliance, Melbourne, VIC, Australia*
[6] *Wellcome Trust Sanger Institute, Hinxton, UK*
[7] *University of Ottawa, Ottawa, ON, Canada*

Background: The 'genetically literate' citizen has a working knowledge of genetics and uses it to inform their decisions. However, what constitutes a working or sufficient knowledge of genetics is unresolved. *Aim:* To explore Australians' genetic literacy using concepts in the educational, technical, and sociological literature and data from Genioz (Genomics: National Insights of Australians), a national multidisciplinary project investigating Australians' awareness, understanding, and expectations of personal genomic testing. *Methods:* Fifty-six members of the public participated in seven focus groups hosted over a 2-month period in 2015. Themes generated from the focus groups, existing literature and a modified Delphi technique involving the research team and other experts were used to develop an online survey of public views and experiences of personal genomics that was appropriate to the Australian context. The survey included 15 questions addressing knowledge of genetics and concepts relevant to personal genomic testing. *Results:* From the focus groups ($n = 56$), participants' descriptions of DNA, genetics and genomics reflected familiarity with concepts of heredity, acknowledged genetic, and non-genetic influences on characteristics, and highlighted genetic uniqueness. From the survey ($n = 1{,}739$), knowledge questions were answered well but more than 30% of respondents were uncertain about: key molecular concepts and patterns of heredity. They also demonstrated lack of familiarity with genomic terminology. *Discussion:* Findings from the research challenge the language and structure of content in existing educational materials about genomic testing. The data suggest that refined approaches are required to tailor terminology around specific technologies, their applications, and contexts.

Oral 12
COST-EFFECTIVENESS OF WHOLE EXOME SEQUENCING FOR SUSPECTED MONOGENIC DISORDERS IN INFANCY: A FOLLOW-UP STUDY

Deborah Schofield[1,2,3,5], Khurshid Alam[1,2,5], Rupendra Shrestha[2], Luke Rynehart[1], Zornitza Stark[1,4], Sue White[1,5], and Clara Gaff[4,5]

[1] *Murdoch Childrens Research Institute, Melbourne, VIC, Australia*
[2] *Faculty of Pharmacy, University of Sydney, Sydney, NSW, Australia*
[3] *Garvan Institute of Medical Research, Sydney, NSW, Australia*
[4] *Melbourne Genomics Health Alliance, Melbourne, VIC, Australia*
[5] *University of Melbourne, Melbourne, VIC, Australia*

Aim: To assess the cost-effectiveness of using whole exome sequencing (WES) for the diagnosis of suspected monogenic disorders, taking into account longer term impacts on patients and families *Methods:* A study within the Melbourne Genomics Health Alliance collected follow-up data on 80 infants who underwent WES for diagnosis of suspected monogenic disorders. Data on costs of management and changes in health and reproductive outcomes for patients and families who received a molecular diagnosis by WES were collated and analyzed to assess the cost-effectiveness of WES. *Results:* Re-analysis of existing WES data in undiagnosed patients at 18 months was more cost-effective than ongoing standard diagnostic investigation, with a cost saving of $1,059 per additional diagnosis. Within the follow-up period, the patients for whom a molecular diagnosis was achieved through WES were found to provide a cost saving to the health system at a ratio of $1,272 per quality-adjusted life-year (QALY) gained. Additional cost-effectiveness analysis is performed upon the directly observed reproductive outcomes of the families within the study including the costs of reproductive services used and the health status of children born during the follow-up period. These reproductive outcomes are then included in the assessment of cost-effectiveness as an incremental cost per additional QALY gained. *Discussion:* Cost-effectiveness analysis is critical to inform decisions about the allocation of scarce, publicly funded health resources. This study extends the short-term assessment of cost-per-diagnosis and captures the longer term flow-on cost impacts of introducing genomic testing into clinical care.

Special Interest Group Meetings, August 5, 2017

Australasian Association of Clinical Geneticists
'WHAT DO WE DO WITH ALL THESE HYPERMOBILE KIDS?'

Mark Scheper[3], Leslie Nicolson[2], Roger Adams[4], Louise Tofts[1], and Verity Pacey[5]

[1] *Narrabeen Sports Medicine Centre /the Childrens Hospital at Westmead, Sydney, NSW, Australia*
[2] *Discipline of Biomedical Sciences, University of Sydney, Sydney, Australia, Sydney, NSW, Australia*
[3] *ACHIEVE, Center for Applied Research, Faculty of Health, University of Applied Sciences Amsterdam, Amsterdam, the Netherlands*
[4] *Discipline of Physiotherapy, University of Sydney, Sydney, Australia, Sydney, NSW, Australia*
[5] *Department of Health Professions, Macquarie University, Sydney, NSW, Australia*

Background: A better understanding of the natural history of JHS/EDS-HT is crucial for the identification of children at risk of adverse outcomes and for development of interventions. *Methods:* One-hundred-one children with JHS/EDS-HT were observed for 3 years and assessed at three time points for primary outcomes (functional impairments) and secondary outcomes (connective tissue laxity, muscle function, motor control, musculoskeletal, and multisystemic complaints). Cluster analysis was performed to identify severity subgroups. Clinical profiles were determined for these subgroups and differences were assessed by MANCOVA. The contribution of baseline patient characteristics identified by exploratory factor analysis toward disability at follow-up was assessed by mixed linear models. *Results:* Three clusters of children were identified in terms of severity at follow-up (able, functional impairments, mild disability) based on results of their 6-minute walk test, self-reported physical activity participation, and quality of life. Disability at baseline was predictive of worsening functional impairment over the next 3 years. Multiple interactions between the secondary outcomes were observed but four underlying constructs were identified. All four constructs (multisystemic effects, pain, fatigue, and loss of motor control) contributed significantly to disability ($p = <.046$). *Conclusion:* Children diagnosed with JHS/EDS-HT who have a high incidence of multisystemic complaints (particularly orthostatic intolerance, urinary incontinence, and diarrhoea) and poor motor control, in addition to high levels of pain and fatigue at baseline, are most likely to have further functional loss resulting in disability over the next 3 years.

https://doi.org/10.1017/thg.2017.46 Published online by Cambridge University Press