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Oral Presentations

Plenary Presentations

Plenary 1
PATHOMECHANISMS AND EXPERIMENTAL THERAPIES OF MITOCHONDRIAL DISEASE

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We have recently demonstrated that activation of the AMPK/PGC1-α axis, the major pathway controlling mitochondriogenesis, improves the clinical and biochemical features of COX-defective recombinant mouse models of mitochondrial myopathy. In particular, we showed that AICAR, an AMPK agonist, is effective in increasing OXPHOS activities in the skeletal muscle of three mouse models of COX deficiency, including a constitutive Surf1 knockout, a muscle-specific COX15 knockout, and a Sco2 knockout/knockin (KO/KI) mouse. Notably, in the $Sco2^{KO/KI}$ mouse model, increased mitochondrial biogenesis was accompanied by normalization of motor endurance. We have now expanded this strategy by treating our $Sco2^{KO/KI}$ mice with a set of potentially mitochondriogenic drugs including (i) metformin, another AMPK agonist that is widely used as an antidiabetic drug; (ii) nicotinamide riboside, a precursor of NAD+, which in turn activates the PGC1-α agonist Sirtuin1, and (iii) resveratrol, a natural polyphenol compound, which activates PGC1-α via inhibition of phosphodiesterase 4. We analyzed motor performance and COX activity in the muscle of treated vs. untreated mice. All three treatments significantly increased the motor performance of our COX-defective $Sco2^{KO/KI}$ mice over four weeks, and nicotinamide riboside significantly increased also COX activity in skeletal muscle. Transcriptomic analysis is underway to further elucidate the molecular mechanisms underpinning the remarkable recovery of motor performance and biochemical proficiency of these treatments in our mitochondrial disease models. Importantly, these results can serve as a proof of principle evidence for the development of rational therapies on patients with mitochondrial (encephalo)myopathy in the near future.

Plenary 2
FROM MITOCHONDRIA TO MOVEMENT: THE GENETICS OF ATHLETIC PERFORMANCE

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The process of exercise-induced adaptation in skeletal muscle involves a multitude of signalling mechanisms initiating replication of specific DNA genetic sequences, enabling subsequent translation of the genetic message and ultimately generating a series of amino acids that form new proteins. The consequences of these adaptations are determined by contractile volume, intensity and frequency, along with the half-life of functionally relevant proteins. Many features of the training adaptation are specific to the type of stimulus, such as the mode of exercise. Prolonged endurance training elicits a variety of metabolic and morphological changes as a direct result of mitochondrial biogenesis. In contrast, strenuous resistance exercise stimulates synthesis of contractile proteins responsible for muscle hypertrophy and increases in maximal contractile force. However, the notion that a single gene or metabolic pathway could regulate the adaptations in skeletal muscle to training stimuli and/or predict athletic performance is a gross oversimplification. One of the reasons for this is that exercise activates many genes and pathways simultaneously with many of these having overlapping actions. Indeed, it may well be that changes in muscle signalling proteins are the consequence of, rather than cause of, changes in muscle metabolism and the subsequent events that culminate in a training adaptation. The molecular bases for the heterogeneous response to exercise training (i.e., responders vs. non-responders) will be discussed, as will evidence for 'mitochondrial dysfunction' as a basis for metabolic disease states. Finally, it will be shown that the search for "single gene master regulators" of physiological adaptation is futile.

Plenary 3
TBA

Dr Liz Broad
Abstract Not Received at Time of Printing

Plenary 4
PROTEOMIC AND METABOLIC ANALYSIS OF A MITOCHONDRIAL COMPLEX I DEFICIENCY MOUSE MODEL OBTAINED BY RETROVIRAL INSERTION IN THE *Ndufs4* GENE

*This information was correct at the time of printing and is subject to change.

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The mitochondrial oxidative phosphorylation (OXPHOS) system consists of 5 protein complexes (I-V) and is responsible for the synthesis of cellular energy in the form of ATP. Defects in this system are the cause of OXPHOS disorders, which form the largest group of inborn errors of metabolism. Here we present the results of the characterization of a mouse model for mitochondrial complex I deficiency, the most common OXPHOS disorder.

Ndufs4$^{fky/fky}$ mice were found to have a retroviral insertion in the *Ndufs4* gene resulting in undetectable levels of the NDUFS4 complex I subunit. The mice have a progressive loss of motor skills and reduced lifespan of approximately 40 days. Biochemically these mice have a severe defect in complex I activity in all tissues. Consequently, the capacity to synthesize ATP by mitochondria isolated from *Ndufs4*$^{fky/fky}$ tissues is decreased. On BN-PAGE Complex I was found to be present in a "crippled" state, similar to that found with fibroblasts of NDUFS4 patients. This crippled state lacks the N-module of Complex I that binds the cofactor NADH, as determined by protein mass spectrometry. Interestingly, our metabolic analyses suggest that this decreased capacity to oxidize NADH has an effect on the NAD^+ dependent step of fatty acid metabolism, as hydroxyacylcarnitines are significantly increased in blood of *Ndufs4*$^{fky/fky}$ mice.

Our results provide new insights in the complex pathogenicity of OXPHOS disorders. Subsequent treatment trials with our model may provide new clues for therapeutic intervention for OXPHOS disorders which currently lacks.

Plenary 5
NONINVASIVE PRENATAL TESTING: HOW FAR DO WE GO AND WHAT DO OUR PATIENTS REALLY WANT?

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This session will review recent trends in prenatal diagnosis including significant advances in earlier, more specific and sensitive screening for aneuploidy utilizing detection of cell-free fetal DNA (cffDNA) in maternal serum. The speaker will provide an overview of the scientific background and current technology with regards to noninvasive prenatal testing. The utility and limitations of this screening will also be reviewed. Information from recent studies on maternal attitudes towards this new testing will be presented.

Plenary 6
PREIMPLANTATION GENETIC DIAGNOSIS OF ANEUPLOIDY AND CHROMOSOMAL TRANSLOCATIONS USING ARRAY COMPARATIVE GENOMIC HYBRIDISATION

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More than 50% of human preimplantation embryos are affected with chromosomal aneuploidies and so have little developmental potential. Such aneuploidies make a significant contribution to pregnancy failure after IVF treatment. Embryo biopsy and preimplantation genetic diagnosis (PGD) can be used to identify embryonic aneuploidy in embryos from patients who may be particularly at risk. PGD using multiple rounds of fluorescent in situ hybridisation (FISH) to enumerate 8-10 chromosomes in the single biopsied cell has met with limited success, primarily because the small number of chromosomes analysed meant that embryos that were aneuploid for non-tested chromosomes were being diagnosed as "normal" and transferred to patients.

Recent advances in microarray technology mean that it is now possible to rapidly enumerate every chromosome in a single cell. We have used the 24sure technology (BlueGnome, UK) to achieve pregnancies after diagnosis of euploidy in single cells from 3-day old embryos. This has confirmed that errors of all chromosomes are common in preimplantation embryos, demonstrating the benefits of analysing all chromosomes in PGD. Many pregnancies have been achieved in poor prognosis IVF patients.

Microarrays can also be used to diagnose unbalanced segregants in the embryos of Robertsonian and reciprocal translocation carriers. This enables the identification of errors of all chromosomes, not just those involved in the translocation as happens when using FISH for translocation PGD.

It is clear that microarray analysis of single cells from embryos is far more effective than FISH. Interpretation is simpler and the method is more reliable. More embryos are being identified as euploid/balanced which provides improved opportunities for patients to achieve pregnancies after PGD.

Plenary 7
ADVENTURES IN PRENATAL TESTING

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The introduction of second trimester maternal serum screening for Down syndrome in 1990 hailed a new era in prenatal screening and diagnosis. Over the following two decades new prenatal screening tests were introduced earlier in pregnancy and combined with advances in cytogenetic and molecular genetic testing gave increased detection for a growing number of genetic disorders.

In 2011 Sydney Ultrasound for Women commenced prenatal testing using targeted microarray CGH. Advances in prenatal testing have provided couples with greater information about the health of their baby however, at the same time created counselling challenges. Our experiences using prenatal microarray CGH will be discussed.

Plenary 8
PUBLIC FUNDING OF PGD – A FAMILY CARE PRIORITY

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Couples who carry a serious genetic disorder can use PGD to conceive an unaffected pregnancy. PGD is strongly supported by the

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medical fraternity, patients and support groups. There is clear governance of the genetic technology and use by the NHMRC and in various state legislations where the use of IVF for the purpose of PGD is supported. PGD provides a viable alternative for patients who want to avoid the cycle of pregnancy/prenatal diagnosis/termination.

Genea has submitted an application to the Medical Services Advisory Committee (MSAC) for MBS funding for PGD. Significant health policy hurdles have been raised including the Health Insurance Act (1973), that an embryo is not considered an eligible person. In contrast, prenatal testing is funded on the MBS. The application has been deferred to the Genetics Working Party, which concludes in December 2012.

The recent Productivity Commission Inquiry report into Disability Care and Support recognised the significant costs and resourcing of disability on the Australian health care system, The National Disability Insurance Scheme will be implemented in 2014. With this in mind, safe and effective alternative to a life with disability should be explored by the government. PGD technology is available to those who can pay in the private sector or the few who may be successful in their application for financial support from the Genea PGD assistance program. This debate is about equity of access for Australians to new technologies that provide significantly improved health care.

Plenary 9
TREATMENT OF CYSTIC FIBROSIS WITH CFTR MODULATORS: SIGNIFICANCE OF NEWBORN SCREENING

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Cystic Fibrosis (CF) is a common genetic disorder that involves several organ systems and leads to death at an early age, primarily through progressive lung disease. After several decades of investigation, much from Australasia, it has been recognized more widely that newborn screening and early diagnosis improve outcome, leading to adoption of screening in many countries. Organ system dysfunction occurs soon after birth indicating the need for very early treatment. One approach to treatment is to modulate the activity of the CFTR, the abnormal protein that causes CF. Although there are hundreds of mutations that lead to CF, only five or so molecular mechanisms of dysfunction have been identified. Agents to treat three of these mechanisms are currently in clinical trials. One, Ivacaftor, was approved in early 2012 in the USA for treatment of patients with G551D, a gating mutation. The effects of Ivacaftor in clinical trials were the first indications that CFTR modulators could be beneficial in CF. In vitro evidence indicates that Ivacaftor may be of benefit in other gating mutations. An agent to treat the processing mutation F508del, the most common mutation in the Caucasian population, is also in clinical trials. Ivacaftor is used with this agent because of ladditive effects. A clinical trial of a pharmacologic approach to treating nonsense mutations has been completed.. A major goal of treatment now is to bring CFTR modulators to infants identified by newborn screening in order to delay or even prevent complications of CF.

Plenary 10
CARRIER SCREENING FOR CYTSIC FIBROSIS IN AUSTRLIA

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Carrier screening for cystic fibrosis (CF) has been available for over 20 years, yet there are few programs in Australia. Carrier screening offers couple planning a pregnancy, or in the early phase of pregnancy, choice with regard to the birth of a child with CF. The aim of this presentation is to give an overview of carrier screening for CF in Australia and review the literature regarding the evidence for establishment of a national carrier screening program. This will include a perspective on the recent developments of CFTR activating therapies to carrier screening.

To determine the Australian context of carrier screening for CF a search was made of the of the Medline and Embase databases to find studies which have been conducted in Australia. Consensus statements from peak bodies such as the HGSA and the Australian and New Zealand College of Obstetricians and Gynaecologists are reviewed.

There are four carrier screening programs for CF currently available in Australia, two population-based (Victoria and Hunter region, NSW) and two through IVF practices (Sydney IVF and Queensland Fertility Group). There are studies of many aspects of carrier screening for CF that have been conducted in Australia, including: screening in general practice, screening in high schools,, uptake of fee-for service screening, declining fee-for service carrier screening, attitudes of obstetricians, CF physicians and clinic co-ordinators, attitudes of adults with CF and health economic considerations.

Convincing national health care providers of the value of carrier screening for CF will be a great challenge.

Plenary 11
TBA

Dr David Jessup

Abstract Not Received at Time of Printing

Plenary 12
POPULATION-BASED CARRIER SCREENING FOR CYSTIC FIBROSIS IN VICTORIA: THE PAST 6 YEARS EXPERIENCE

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Cystic fibrosis (CF) is the most common inherited, life-shortening condition affecting Australian children, with a carrier frequency of one in 25. Carrier screening is possible before a couple has a child with CF. Since 2006, in Victoria, CF carrier screening has been offered to women and couples, planning a pregnancy or early in pregnancy, through obstetricians and general practitioners.

Samples were collected by cheek swab and posted to the laboratory. Twelve CFTR gene mutations were tested. Carriers were offered genetic counselling and partner testing, with prenatal testing available for pregnant carrier couples. The number of people tested, carriers detected and pregnancy outcomes were recorded from January 2006 to December 2011.

8872 individuals were screened and 251 were carriers (2.8%). 218 were carriers of p.F508del. 98% of partners of carriers were tested, with 12 carrier couples identified (3 with non-p.F508del mutations). 8 couples were pregnant at screening and 7 had prenatal diagnosis (2 affected fetuses, 3 carriers, 2 non-carriers). Termination of pregnancy was undertaken for the affected fetuses. Carrier couples utilised prenatal diagnosis and/or PGD for subsequent pregnancies. One child, whose parents screened as low risk, had CF due to paternal uniparental disomy.

Carrier screening for CF by cheek swab sample can be successfully undertaken prior to pregnancy or in the early stages of pregnancy with genetic counselling for carriers provided by phone. The 12 mutation panel offers an advantage over screening with p.F508del alone in Victoria. Carrier couples' uptake of PGD emphasises the need to promote carrier screening before pregnancy.

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Sutherland Lecture
"What do we need? I think we need very much improved DNA diagnostics. We are doing a disservice to patients who don't carry a molecular diagnosis" (Louis Kunkel, 2004 Allan Award Address, ASHG)

M. F. Buckley[1]

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The Sutherland Lecture honors Professor Grant Sutherland among whose research interests included the identification of the genetic basis of many inherited disorders, with the objective of providing individuals and families with accurate information for genetic diagnosis and counseling.

In 1998 I was struck by the comment made by Lou Kunkel at the inauguration of the Institute for Neuromuscular Research in Sydney and later in his Allan Award address, where he advocated strongly for better mutation detection. In this lecture I will describe the reasons why I believe that limitations on the availability of molecular diagnoses does indeed do patients and their families a disservice, and how my laboratory has progressively implemented new technologies to enable improved genetic diagnostics.

Plenary 13
IDENTIFICATION AND CHARACTERIZATION OF NEW MITOCHONDRIAL DISEASE GENES

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Mitochondria are the major source of ATP that is synthesized by the respiratory chain through the process of oxidative phosphorylation (OXPHOS), a complex biochemical process carried out through the dual control of physically separated, but functionally interrelated, genomes, nuclear and mitochondrial DNAs. The genetic and biochemical intricacy of mitochondrial bioenergetics explains the extreme heterogeneity of mitochondrial disorders, a group of highly invalidating human conditions, for which no effective treatment is nowadays available. In addition to bioenergetic failure, other mechanisms are probably predominant in the pathogenesis of specific syndromes, such as alterations of cellular redox status, the production of reactive oxygen species, compromised Ca^{2+} homeostasis, mitochondrial protein and organelle quality control, and mitochondrial pathways of apoptosis. As a result, only 40% of adult-onset disorders are currently diagnosed at the molecular level, and much lesser so in infantile syndromes. However, new technological and biocomputational tools offer the possibility of rapid and affordable analysis of the exome, i.e. the coding regions of all genes in single individuals or small families. Mitochondrial disease proteins can then be selected by exploiting predictive softwares, dedicated databases, and ex vivo experiments. We have identified several new disease genes, each responsible of distinct defects of the respiratory chain, mtDNA metabolism, or both. Structural analysis and the creation of ad hoc recombinant lines in yeast, flies, and mice have allowed us to dissect out the molecular consequences of the ablation or defects of these proteins, and their physical status in normal and disease conditions.

Plenary 14
EXOME/WHOLE GENOME SEQUENCING IN THE CLINICAL SETTING

M. F. Buckley[1]

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The new generation of DNA sequencing technologies can be used to search for the causes of monogenic disorders in a relatively unbiased fashion by sequencing the entire protein encoding region of the genome. In this plenary I will present different strategies for the identification of Mendelian disorders in the clinical setting. I will argue that as a result of the complexity of result interpretation, the roles of clinical geneticists, laboratory geneticists and genetic counsellors need to be further integrated to improve patient diagnosis, management and outcomes.

Plenary 15
FUNDING GENETIC TESTS IN THE FUTURE

Fifine Cahill
Department of Health and Ageing

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HGSA Oration 2012
TEACHING AND LEARNING IN GENETIC MEDICINE

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The founding parents of the HGSA had considerable foresight in 1977, framing objectives in the constitution as well as envisioning policies in which the continuing education of its membership as well as the broader society might be enlightened by its membership. This presentation will combine elements of the author's personal journey through Human and Clinical Genetics, reflections on the role and achievements of the HGSA and the challenge of teaching and training in a post-genomic era.

My distinguished mentor David Danks firmly believed that teaching genetics at every level, whether it be clients, secondary students, university students or health professionals, was the responsibility of all genetic health professionals. However I will focus in this presentation on genetic health professionals and the challenges which face us. The themes I will address include, how we respond to constant change in knowledge, how can we improve our skills in communication, integrating the "personal interaction in genetic counselling" into the wider educational strategy and how we must grow our cultural competency if we are to be effective in a multicultural world. I will draw from a 40 year study and follow up of people and families with Osteogenesis Imperfecta and what we have learned from individuals, families and friends about living with a genetic disability.

Finally we need not only a New Clinical Genetics but a new vision among teachers, the population and our political leaders about the centrality of concepts of human genetics in our daily lives.

Australasian Society of Cytogeneticists Oral Presentations
ASoC Oral 1
NUMERICAL AND STRUCTURAL ABNORMALITIES OF THE Y CHROMOSOME IN INFERTILITY INVESTIGATIONS

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The human Y chromosome has unique properties; one half of the chromosome consists of tandem repeats of satellite DNA and the rest consists of a few genes, most of which are not involved in meiotic recombination.

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MSY (male specific region of the Y chromosome) consists of 3 classes of euchromatic sequences – X-transposed, X-degenerate and ampliconic sequences. Geographic variation has been demonstrated for Y chromosome haplogroups. The Yq heterochromatin also shows geographic variation – it occupies between 29 and 54% of the metaphase chromosome and is regarded as a polymorphic variant.

AZF, which maps to the long arm of the Y chromosome, consists of AZF a,b and c. Deletions of these regions affect spermatogenesis. AZF deletions can be associated with azoospermia through to oligospermia, with the occasional normal sperm count.

A review of males investigated for infertility in 2011 showed 17.5% of abnormal karyotypes involved the Y chromosome; with 36% numerical and 64% structural abnormalities. Structural abnormalities included translocations, inversions, duplications and deletions. AZF deletions were tested for in 55% of these cases. Interpretation of Yq heterochromatin size can be difficult as there is no homologue for comparison and ethnic origin of the patients needs to be considered. Yq deletions can look similar to iso-chromosomes for the p arm and duplications may be difficult to distinguish from extra heterochromatin. Half of the patients tested for AZF showed deletions in association with a structurally abnormal Y chromosome.

ASoC Oral 2
PROTECTIVE EFFECT OF ASPIRIN ON γ RADIATION INDUCED SPERM MALFORMATION IN SWISS ALBINO MALE MICE

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Objectives: Acetyl Salicylic Acid (ASA) is a Non Steroidal Anti Inflammatory Drug (NSAID),antipyretic and analgesic. The study evaluated in vivo, the genotoxicity of ASA using the mouse sperm morphology test.

Methods: Mice were injected intraperitoneally with 0.5, 5 and 50 mg/kg of ASA for 3 days before γ irradiation. Then mice were exposed to 2 and 4 Gy γ radiation. The sperm suspension was obtained from epididymes and vas difference,then stained with 1% eosin and air-dried smears were prepared on glass slides for the sperm abnormality test. The slides were examined for percentage abnormalities in every 1000 spermatozoa. Then they were compared with the control sperms that were exposed to the same γ radiation doses .

Results: Statistical analysis of the results show that ASA is not significantly. Moreover The total number of sperm that were treated with different concentration of ASA and gamma radiation has been a significant decreased as compared with sperms were treated with γ radiation ($p < 0.05$).

Conclusions: From the results obtained it can be concluded that ASA could effectively reduced the effects of radiation with a dose 2 - 4 Gy in sperms. However, further studies are needed in order to elucidate the mechanisms of antioxidant effect of ASA.

ASoC Oral 3
SNP- ARRAYS FOR THE STUDY OF PLASMA CELL MYELOMA

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Myeloma is a B-cell neoplasm characterised by the accumulation of malignant plasma cells in the bone marrow. Acquired genetic markers have proven to be powerful prognostic indicators in myeloma, but the low mitotic index of malignant plasma cells outside the marrow microenvironment is a limiting factor for conventional metaphase cytogenetics. Techniques that can identify genetic changes in non-dividing plasma cells are therefore an essential adjunct to conventional karyotyping. Fluorescence *in situ* hybridisation (FISH) is a well established technique for detecting known prognostically significant genetic abnormalities in the interphase cells of myeloma patients, but we have demonstrated that the use of cIg-FISH greatly enhances its' performance. The demanding nature of this procedure has proved prohibitive in our laboratory and so we have investigated SNP-array analysis to provide this critical prognostic information.

We compared karyotyping, FISH and Affymetrix Cytoscan HD SNP-arrays in myeloma genetic analysis to determine their relative versatility, sensitivity, and accuracy. Preliminary results from SNP-arrays have revealed a far higher percentage of abnormalities than has previously been detected by conventional metaphase cytogenetic analysis and FISH.

In this report we present data for validation of the SNP-arrays and discuss our new algorithm for the genetic analysis of myeloma within the constraints of a busy diagnostic cytogenetics unit.

ASoC Oral 4
SNP ARRAY TECHNOLOGY IDENTIFIES NOVEL CANDIDATE LOCI FOR HNPCC/LYNCH SYNDROME

B. A. Talseth-Palmer[1,2], E. Holliday[1,3], T. Evans[1,2], D. M. Grice[1,2,4], A. L. Martin[1,2], M. McEvoy[3], J. Attia[3], R. J. Scott[1,2,5]

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Hereditary non-polyposis colorectal cancer (HNPCC)/Lynch syndrome (LS) is a cancer syndrome characterised by early-onset epithelial cancers. The aim of the current study was to use SNP-array technology to identify genomic aberrations which can contribute to the increased risk of cancer in HNPCC/LS patients.

Individuals diagnosed with HNPCC/LS (100) and healthy controls (384) were genotyped using the Illumina Human610-Quad SNP-arrays. SNP-data were processed in GenomeStudio (Illumina Inc.), analysed using Nexus (BioDiscovery) and validated with QuantiSNP (WTCHG). TaqMan Copy-Number assay (Applied Biosystems) was used to confirm the identified CNVs.

We detected CN gains that are significantly different between cases and controls on chromosome 7q11.21 (28% cases and 0% controls, p = 3.60E-20) and 16p11.2 (46% in cases, while a CN loss was observed in 23% of controls, p = 4.93E-21). The CN gain on chromosome 7 was partly confirmed in cases using TaqMan CN assay, while the CN gain on chromosome 16 was not observed with confirmation assay. CNV burden was significantly greater in cases compared to controls.

In conclusion, we have identified one loci located in an intergenic region on chromosome 7q11.21 possibly associated with disease risk in HNPCC/LS and a greater burden of CNVs in cases supporting the notion of higher genomic instability in these patients due to an inadequate DNA repair process. The results from this study raise a lot of question of the validity of CNV analysis in general due to differences observed in the results, especially in the CNV output between the two analysis methods.

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ASoC Oral 5
6p24.2 MICRODELETION INVOLVING TFAP2A WITHOUT CLASSIC FEATURES OF BRANCHIO-OCULO FACIAL SYNDROME

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Branchio-oculo-facial syndrome (BOF, MIM 113620) results from haploinsufficiency of TFAP2A on 6p24.2. The cardinal features of BOF are pseudo-cleft of the upper lip, brachial sinus/post auricular linear skin lesion, auricular/lip pits, lacrimal duct obstruction, short stature and intellectual disability. Other features described include coloboma of the iris/retina and preaxial polydactyly. Here we describe a mother and daughter with a deletion at 6p24.2 involving TFAP2A but with a clinical presentation that would not have led to a diagnosis of BOF.

The proband was seen at 3-months of age. She was growth restricted at birth (1985gm at 37 weeks gestation). Examination revealed a non-dysmorphic infant with no evidence of a branchial sinus, linear skin lesion or pseudo-cleft of the lip. A blocked left lacrimal duct was diagnosed in the first few weeks of life. Numerous investigations were performed because of growth restriction and poor feeding. Hearing was normal and renal ultrasound revealed mild pelvicalyceal dilatation. Array CGH revealed a 593 kb deletion at chromosome 6p24.2-p24.3 involving TFAP2A.

The infant's 26-year-old mother was also found to carry the deletion. She has a mild intellectual disability and good general health. She had lacrimal duct obstruction until 11 years of age, requiring surgical intervention. She had normal hearing and normal kidneys and was of normal stature. Close examination of her branchial region and lips/philtrum was normal.

This case adds to the growing list of atypical presentations of "classical" single gene disorders which have only come to light in the array CGH era.

ASoC Oral 6
BAYLOR EXPERIENCE WITH CHROMOSOMAL MICROARRAY ANALYSIS IN NEURODEVELOPMENTAL AND NEUROBEHAVIORAL DISORDERS. MOLECULAR MECHANISMS AND CLINICAL CONSEQUENCES OF CNVS

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Copy-number variations (CNVs) encompass more total nucleotides and arise more frequently than single nucleotide polymorphisms (SNPs). Both recombination and replication-based mechanisms for CNV formation have been described. CNVs are responsible for human evolution, genetic diversity between individuals, and a rapidly increasing number of traits or susceptibility to traits to a larger extent than SNPs; such conditions have been referred to as genomic disorders. In addition to well-known sporadic chromosomal microdeletion syndromes and Mendelian diseases, many common complex traits, including autism, ADHD, schizophrenia, and obesity can result from CNVs. Both array CGH and SNP genotyping have proven to be powerful technologies in clinical diagnostics. However, intragenic deletions or duplications - those including genomic intervals of a size smaller than a gene - have remained beyond the detection limit of most clinical aCGH analyses. In an effort to provide a comprehensive clinical testing service for both small CNVs and copy neutral absence of heterozygosity (AOH), clinically relevant to identify uniparental disomy, consanguinity, and potential recessive loci, we have designed and implemented a custom oligonucleotide array enabling detection of single exon CNVs for clinically relevant >1800 genes and enhanced it with 120,000 SNP probes. Even though our array has a lower density of SNP probes than other commercially available SNP arrays, it is able to reliably detect AOH events >5-10 Mb as well as intragenic copy number changes beyond the detection limitations of SNP genotyping. I will present the utility of this CMA Comprehensive in patients with various neurodevelopmental and neurobehavioral phenotypes.

ASoC Oral 7
EPILEPSY WITH COGNITIVE DEFICIT AND AUTISM SPECTRUM DISORDERS: PROSPECTIVE DIAGNOSIS BY ARRAY CGH

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Retrospective analyses of large patient cohorts with epilepsy have indicated that many have causative copy number variations (CNVs). These may be rare or novel pathogenic mutations involving small chromosome segments or recurrent susceptibility variants arising from non-allelic homologous recombination mediated by regional DNA sequence architectures. Over an 18 month period more than 2,000 samples were received for array CGH testing in our laboratory. A cohort of 247 of these unrelated cases had epilepsy and one or more of its common co-morbidities of developmental delay, intellectual disability, autism spectrum disorders and congenital abnormalities . Prospective analysis using a standardised oligo-array CGH platform detected seventy three cases (29.6%) with CNVs. Of the 73 positive cases, most would not have been detected by conventional cytogenetics. The CNVs were considered to be causative in 27 (37.0%) of these cases. These 27 cases comprised 10.9% of the total cohort of 247 cases and consisted of 3 cases with microdeletion/microduplication syndromes, 13 cases with pathogenic CNVs and 11 cases with pathogenic disease susceptibility CNVs. The range of pathogenic CNVs associated with seizures validates the presence of many genetic determinants for epilepsy.

ASoC Oral 8
FISH REVEALS HIDDEN COMPLEXITY OF COPY NUMBER VARIANTS

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Array CGH testing for referrals of developmental delay, multiple congenital abnormalities and autism has led to a significant increase in detection of copy number variants. As laboratories become more familiar with array techniques, validating the copy number changes using a second method is sometimes considered un-necessary due to the reliability of the array data. A review of our data shows that ~5% of duplication variants are due to a structural rearrangement which may significantly alter the clinical significance of the array finding. Furthermore, FISH confirmation of CNVs is also useful in unaffected family members where incidental array findings are unwelcome.

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Molecular Genetics Society of Australasia Oral Presentations

MGSA Oral 1
DETECTION OF GENE MUTATIONS CAUSING NOONAN SYNDROME: TWO CASE STUDIES

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Noonan syndrome (NS) is a relatively common developmental disorder characterised by short stature, cardiovascular defects (including hypertrophic obstructive cardiomyopathy and pulmonary valve stenosis), facial dysmorphism, broad or webbed neck, chest wall deformities and, in some cases, mild intellectual handicap. It is an autosomal dominant condition that occurs in 1:1000 to 1:2500 live births. NS is caused by mutations in the *PTPN11* (50%), *SOS1* (10-13%), *RAF1* (3%-17%), *KRAS (<5%)*, *BRAF* (<2%), *MAPK1* (<2%) and *NRAS* (<1%) genes. A sequential tiered testing strategy in NS is recommended. Selected exons of the *PTPN11* gene are preferentially sequenced in the first level of testing. If no mutation is found, the remaining *PTPN11* exons are screened. If no mutation is identified in *PTPN11*, selected exons of *RAF1* and *SOS1* are screened

Here we report two cases. The first is a dysmorphic growth restricted female born at 23 weeks, after antenatal identification of a large cystic hygroma and bilateral hydrothoraces. A p.Thr73Ile mutation was identified in the *PTPN11* gene. The second is a full term male, who died at 34 days. A post mortem revealed hypertrophic cardiomyopathy and genetic testing revealed a p.Gly503Arg mutation in the *PTPN11* gene. Testing of archival tissue from his deceased sibling with Langer-Giedion syndrome and right ventricular hypertrophy failed to demonstrate the same *PTPN11* mutation.

MGSA Oral 2
FMR1 GENE SMALL TRIPLET REPEAT ALLELES ASSOCIATED WITH POF/POI AND EARLY MENOPAUSE

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The expanded CGG repeats in the FMR1 gene, along with abnormal gene methylation, cause Fragile X syndrome with more than 200 CGG repeats and is the most common cause of mental retardation in males. It has been established that pre-mutation alleles (61-199repeats) can cause Fragile X in the next generation due to inheritance of maternal alleles that are unstable and expand (anticipation), however about 20% of women with pre-mutations also have primary ovarian insufficiency (POI) defined as the cessation of menses prior to age 40 years old.

It has been reported (Gleicher et al 2010) that there is an association with Premature Ovarian Failure (POF)/Premature Ovarian Insufficiency (POI) and premature menopause with smaller triplet repeat alleles in the FMR1 gene. The reported association with POF/POI and premature menopause in female patients is with small triplet repeat alleles, classified as less than 26 repeats.

Female patients who were presenting with infertility of unknown cause who were suspected to have POF/POI went on to have Anti-Mullerian Hormone (AMH) and Fragile X screening to assess this association in infertility patients. The level of AMH is age dependant and is thought to be a good indicator of ovarian reserve (described as the number of eggs remaining in the ovaries) as AMH is produced by the pre-antral and antral follicles; as these follicles decrease, the serum level of AMH also decreases. We present here clinical cases and examples of small triplet alleles in women with low AMH, POF/POI and premature menopause in the age range from 23 to 42 years old.

Gleicher N, Weghofer A, Lee IH, Barad DH (2010) *FMR1* Genotype with Autoimmunity-Associated Polycystic Ovary-Like Phenotype and Decreased Pregnancy Chance. PLoS ONE 5(12): e15303

MGSA Oral 3
DETECTING DIFFERENTIAL ALLELIC EXPRESSION USING AMPLIFICATION REFRACTORY MUTATION SYSTEM (ARMS) PCR

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Differential allelic expression occurs when two alleles of a gene are expressed at different levels. It is associated with phenotypic variability and may contribute to complex genetic diseases. This study used an ARMS PCR approach to determine whether *Vegfa* was subject to allelic expression differences in cardiac tissue from heterozygous mice. Two homozygous mouse strains with a single nucleotide difference in *Vegfa* between the strains (Strain 1 = AA; Strain 2 = GG) were crossed. Hearts were collected from six-week old male parents and their heterozygous offspring. Quantitative PCR was used to measure the expression of each allele in both the parental strains and in the heterozygous offspring. ARMS PCR was performed, involving a forward primer that differed at the 3'-terminal, to be specific for either G or A, in combination with a reverse primer. Allele-specific primers were run as separate reactions, and standard curves using varying A:G ratios of parental cDNA were generated to quantify expression for each allele. In the parental strains, ARMS primers detected expression of only one allele, either A or G as predicted. In the heterozygous offspring, both alleles were detected, and a significant difference in the expression of the A and G allele was observed (68% allele A and 32% allele G, $p = 0.007$). This study demonstrates ARMS PCR as a simple and cost effective method to detect differential allelic expression in heterozygous mice. Unequal expression of alleles may play a role in phenotypic variation and should be taken into consideration when investigating differences in gene expression.

MGSA Oral 4
HAEMOPHILIA A: MOLECULAR DIAGNOSIS IS NOT ALWAYS STRAIGHT FORWARD

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Background:Haemophilia A (HA) is an X-linked recessive coagulation disorder caused by mutations in the F8 gene. The incidence is between 1:10,000 to 1:5,000 live male births and is rare in females. About 50% of cases of severe HA are caused by an inversion, d*e novo* mutations are common (25-30%), 10% sporadic cases and in 2% of cases no mutation is identified. Some of the unusual HA cases are presented.

Methods. 203 patients with HA were analysed in the last five years. Patients with severe HA are subjected to inversion analysis using long PCR. Sanger sequencing was performed on all 26 exons and exon/intron margins in the forward and reverse directions. Dosage analysis is performed using MLPA.

Results: One male with severe HA had a *de novo* frameshift mutation (Tyr155Cysfs*14). Two females had mild HA, one appeared to be homozygous for a *de novo* missense mutation (Arg1708His).This patient was found to be 45XO on karyotype analysis, with her phenotype the result of inheritance of a single X-chromosome carrying a *de novo* mutation. The second female carried three F8 mutations; a paternal *de novo* missense mutation (Ser2048Ala) and two maternal

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mutations inherited in *cis* (Ser428_Leu431del and Asp1260Glu). One male with mild HA was found to have a *de novo* truncated LINE 1 element positioned 40 nucleotides prior to the start of exon18 and flanked by a 7 nucleotide duplication.

Conclusion: Molecular analysis of the F8 gene in our laboratory has highlighted the importance of understanding the molecular mechanisms underlying the HA phenotype.

MGSA Oral 5
NIEMANN-PICK DISEASE TYPE C CAUSED BY MATERNAL UNIPARENTAL ISODISOMY OF CHROMOSOME 18

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Niemann-Pick disease type C (NP-C) is an autosomal recessive lysosomal storage disorder with an estimated Australian incidence of 1:140,000. It has a broad clinical spectrum, ranging from neonatal lethal presentation through to adult-onset neurodegenerative disease. NP-C is caused by mutations in either the *NPC1* (18q11.2, ~95% of cases) or *NPC2* (14q24.3) genes. Mutations in these genes lead to abnormal intracellular cholesterol trafficking, detectable by analysis of cholesterol accumulation and esterification in cultured cells.

Patient ES was a term baby born to non-consanguineous parents, presenting at 2-months of age with conjugated hyperbilirubinaemia and hepatosplenomegaly. Cultured fibroblast studies revealed that he was affected by NP-C. He was commenced on oral miglustat therapy at 5-months of age on a compassionate basis. When last reviewed at 15-months of age he had motor and growth delay, but cognitive development was progressing well.

Sequence analysis of *NPC1* revealed homozygosity for a previously unreported single nucleotide deletion in exon 15 (c.2336delT). However, analysis of parental DNA revealed that the mutation was carried by his mother but not his father. Subsequent microsatellite analysis of chromosome 18 demonstrated maternal uniparental isodisomy (UPD) over the length of chromosome 18, revealing the cause of the homozygous mutation in ES. Further, these results strongly suggest a post-zygotic error as the cause of the UPD.

We believe this is the first report of NP-C being caused by UPD for chromosome 18, and this case highlights the importance of parental carrier testing for confirmation of the genetic basis of Mendelian disorders.

MGSA Oral 6
THE DIFFERENCES BETWEEN DISCOVERY AND DIAGNOSTIC DNA METHYLATION MEASUREMENTS MAY IMPEDE CLINICAL APPLICATION.

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Measurement of DNA methylation at promoter regions of specific genes has been recognised as a cancer biomarker for over 20 years, yet to date there is only a single commercially available clinical test that uses this type of marker. The requirements for a clinical blood test are very different from tests used for biomarker discovery; clinical diagnostic tests are likely to be developed to measure the concentration of methylated target DNA in blood while discovery has tended to compare the methylation ratio of a target regions of genomic DNA from malignant and normal tissues. The accuracy of both types of measurements must be known for validating their correlation with disease. Measurement of methylation ratios has a negative bias and our work shows that it may be sequence dependent and strongly influenced by sample work up. Diagnostic measurements of methylated DNA concentration in blood will require reference materials for stringent calibration of measuring systems used for routine measurements. NMIA has developed the technology required for manufacturing and characterising methylated DNA by combining primary DNA quantity measurements from digital PCR with mass spectrometric confirmation of methylation. We have produced control materials that enable calibration of the entire measurement process for both ratio and copy number concentration measurements. We show that when these materials were externally analysed using a mass spectrometry based system both precision and bias of methylation ratios were highly variable between methylation sites. Selection of the most reliable site may lead to a more robust measurement for clinical application.

MGSA Oral 7
GENETIC TESTING FOR MATURITY ONSET DIABETES OF THE YOUNG IN AUSTRALIA

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Maturity Onset Diabetes of the Young (MODY) accounts for about 2% of diabetes mellitus. The term MODY describes a heterogeneous group of disorders caused by mutations in genes involved in pancreatic islet beta cell development, function and regulation, glucose sensing, and in the insulin gene itself. To date, mutations in at least 11 different genes have been identified in patients with MODY.

In 2005, molecular genetic testing for MODY was introduced into Australia by Mater Pathology, Brisbane. Four genes which account for the majority of reported MODY phenotypes, *HNF1A* (MODY3), *GCK* (MODY2), *HNF4A* (MODY1) and *HNF1B* (MODY5) were tested for gene sequence variations and copy number changes.

Of 159 families screened for MODY, the laboratory identified 53 mutations. This consisted of 27 GCK mutations (6 novel), 13 *HNF1A* mutations, 7 *HNF4A* mutations (2 novel) and 6 *HNF1B* mutations. In patients with a high index of suspicion (negative pancreatic auto-antibodies and autosomal dominant pedigree), mutations were identified in 70% of cases.

Our rate of detection of mutations and proportions of each MODY subtype was similar to other international studies of MODY. There are important implications of confirming the clinical diagnosis of MODY and identifying the specific MODY subtype. For this reason, genetic testing should be more widely utilised in patients with an autosomal dominant pedigree who are negative for pancreatic autoantibodies. A high index of suspicion coupled with availability of genetic testing should decrease the interval between clinical diagnosis of diabetes mellitus and confirmation of MODY subtype.

MGSA Oral 8
DEVELOPMENT OF BEST PRACTICE GUIDELINES FOR GENETIC TESTING FOR HEREDITARY RECURRENT FEVERS

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Hereditary recurrent fevers (HRFs) are a group of monogenic autoinflammatory diseases characterized by recurrent bouts of fever

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and serosal inflammation. They are caused by variants in genes regulating innate immunity and particularly the IL1b pathway. The main disorders and their relevant genes are: familial Mediterranean fever (FMF – gene *MEFV*); mevalonate kinase deficiency (MKD, gene *MVK*), TNF receptor-associated periodic syndrome (TRAPS, gene *TNFRSF1A*,) and cryopyrin-associated periodic syndrome (CAPS, gene *NLRP3*). FMF and MKD are primarily autosomal recessive disorders; and TRAPS and CAPS are autosomal dominant disorders.

Under the auspices of the European Molecular Quality Network, 32 scientists and clinicians from Europe, the Middle East, USA, Japan and Australia met in Bruges, Belgium to develop best practice guidelines for genetic testing for HRFs based on the experience of the HRF External Assurance Program and the literature. There was a wide range of practices in terms of testing, regulatory requirements and reporting employed across the different countries represented at the meeting. However, by the process of emails over several months a version was adopted. This manuscript has been accepted by the Annals of the Rheumatic Diseases and will be published shortly. As the Australian representative to the meeting I will be highlighting the findings of the meeting, particularly for the laboratories involved in the genetic testing of HRF.

MGSA Oral 9
2011 MOLECULAR GENETICS QUALITY ASSURANCE PROGRAM REVIEW

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The outcome and findings of the 2011 series of Quality Assurance Programs (QAPs) from the Cystic Fibrosis Quality Assurance Program, European Molecular Genetic Quality Network and the RCPA Molecular Genetics QAP (including Mitochondrial Myopathy, DNA sequencing and EGFR/KRAS/BRAF mutation screening) modules will be presented.

In this presentation, the overall performance of participants in the Cystic Fibrosis QAP plus an assessment of Bayesian risk calculations will be discussed. Some identified areas for improvement include:

- Reporting variants using current HGVS nomenclature,
- Eliminating clerical errors in reports,
- Providing a correct interpretation of the results based on the clinical scenario,
- Using up to date population specific carrier frequencies in risk calculations,
- Specifying a recommendation for genetic counselling.

Notable observations and actions required will be presented.

An open forum with participants will be co-ordinated to discuss issues plus collect feedback on further improvements to the quality assurance process administered by the RCPA Molecular Genetics QAP.

MGSA Oral 10
THE ATM-MEDIATED DNA DAMAGE RESPONSE: MOVING BETWEEN THE FOREST AND THE TREES

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Genome stability is essential for prevention of undue cellular death and neoplasia. A central axis in maintaining genome stability is the DNA damage response (DDR) – a complex signaling network that is vigorously activated by DNA double strand breaks (DSBs). The primary transducer of the DSB response is the serine-threonine kinase ATM, which is missing in patients with the genomic instability syndrome ataxia-telangiectasia (A-T). The *ATM* gene, which encodes the ATM protein and is mutated in A-T patients, was identified in our lab in 1995 using positional cloning. Since then we have been studying the ATM-mediated DNA damage response network. An important characteristic of this system is that it is based on a core of proteins dedicated to the damage response, and a cadre of proteins borrowed temporarily from other cellular processes to help meet the challenge. Interestingly, protein machineries recruited to damage sites may act differently in stressed and in unstressed cells, or may serve the same role in both situations. We are exploring this complex network at the transcriptional and post-transcriptional levels using systems biology tools and proteomic and genetic high-throughput screens. Subsequently, in-depth analysis of novel pathways is carried out. Special attention is paid to the growing interface between the ubiquitin and the DDR arenas. An important meeting point combines players from the two arenas, as well as chromatin organization and DNA repair. The delicate interplay between these proteins, which finally leads to timely damage repair, is orchestrated mainly by protein phosphorylation and ubiquitylation. Examples will be presented.

MGSA Oral 11
OFFERING CFTR-PGD WITHOUT A DELAY FOR WORK UP; REALITY OR FICTION?

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Pre-implantation genetic diagnosis (PGD) enables the biopsy of an embryo created in the laboratory and the offers the possibility to screen each embryo for the inherited mutations that can cause genetic diseases, such as Cystic Fibrosis (CF). Screening of Australian infertility patients has shown an increased carrier rate of 1 in 21 patients*, or potentially a carrier couple every 441 couples coming into the IVF clinic. This data supports the screening of all couples (one partner per couple in the first instance) but also allows for a more direct treatment pathway to PGD if that is what the couple decides. Prenatal diagnosis, donor embryos and donor gametes are also options for treatment pathways.

With this increased carrier rate in the infertile population over the normal background rate, CFTR-PGD is the most commonly requested PGD test in our clinic. We are able to offer these carrier couples the option to proceed with CFTR-PGD within a couple of weeks of their carrier status being confirmed. Using a standard panel (Abbott Molecular v3 31 mutation panel) and standard reactions, we can now proceed with PGD on their first IVF cycle, immediately after confirmation of their carrier status, providing Genetic Counselling has already been completed.

By using the standard panel, 31 alleles/mutations act as linked markers and enable all carrier couples a cheaper pathway to identifying embryos with two CFTR causing mutations. However, CFTR-PGD does not always produce the expected result, ensuring adequate Genetic Counselling and general counselling support is available is a priority before initiating a PGD cycle.

* FIELD, P. D. and MARTIN, N. J. (2011), CFTR mutation screening in an assisted reproductive clinic ANZJOG, 51: 536–539.

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MGSA Oral 12
INTEGRATED MICRORNA AND MRNA PROFILING OF THE MOUSE VENTRICLES DURING DEVELOPMENT OF SEVERE HYPERTROPHIC CARDIOMYOPATHY AND HEART FAILURE

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Hypertrophic cardiomyopathy (HCM) is a primary disorder of the myocardium characterised by left ventricular hypertrophy, myocyte disarray and interstitial myocardial fibrosis. HCM is caused by autosomal dominant mutations primarily affecting genes encoding proteins of the sarcomere, however, it is less clear how these mutations alter intracellular signalling, leading to cardiac remodelling and hypertrophy. MicroRNAs (miRNAs) are short non-coding RNAs that regulate post-transcriptional gene expression during development and disease. We have used TaqMan Low Density Arrays to measure the expression of 335 murine miRNAs and determine the miRNA signatures of early- and end-stage HCM in a severe, transgenic mouse model of the disease. Seven miRNAs were dysregulated at an early stage of HCM development. Time-course analysis revealed that decreased expression of miR-1 commences at a pre-disease stage, with a consequent upregulation of target genes causal of cardiac hypertrophy and fibrosis, and thus represents an early disease change. At end-stage HCM, 21 miRNAs are dysregulated to form a stress signature resembling that of other forms of cardiac hypertrophy, suggesting common responses. Analysis of the mRNA transcriptome using Affymetrix GeneChip Arrays revealed that miRNAs potentially target 19.7% upregulated and 6.7% downregulated mRNAs at end-stage HCM, and regulate mRNAs associated with cardiac hypertrophy, calcium signalling, fibrosis and the TGF-b signalling pathway. Collectively, these results highlight the regulatory roles of miRNAs in the development and progression of HCM, and shed light on critical miRNA regulated gene networks involved in disease pathogenesis. Furthermore, strategies to maintain miR-1 levels may represent a therapeutic opportunity in HCM.

MGSA Oral 13
MOLECULAR GENETICS OF MIGRAINE; IMPLICATIONS FOR THERAPEUTIC DEVELOPMENT

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Migraine is a severe neurological disorder that affects a significant proportion of the population. Prevalence estimates for the disorder vary between 12 and 25% depending on the population studied. The disorder has a significant genetic component showing high levels of familial aggregation. Although a number of genes involved in a rare and severe sub-type of migraine, termed familial hemiplegic migraine have been identified, the number and identity of all the genes involved in the more common types of migraine have yet to be defined. Genetic linkage and GWAS studies have implicated a number of genomic regions including on chromosomes 1, 4, 11, 19 and the X chromosome and several susceptibility variants have been implicated in the disorder. Neurotransmitter pathways have been the main focus of studies investigating the molecular mechanisms of the disorder. However vascular and hormonal triggers disturbances also occur in migraineurs, as highlighted by alterations in cerebral blood flow and hormonal triggers of migraine, particularly in women and hence factors affecting these functions may also be involved. This presentation will focus on migraine gene studies in our laboratory, including recent GWAS results, as well as studies implicating hormone receptor genes and MTHFR gene variants. In addition an overview of results from two recently completed clinical trials that involved genetic profiling in conjunction with a nutriceutical therapeutic treatment will be presented. These clinical trial results are very promising and highlight the potential importance of pharmacogenetic interventions in this disorder.

MGSA Oral 14
WHOLE EXOME SEQUENCING IDENTIFIES A NOVEL MISSENSE MUTATION IN TWO AFFECTED CHILDREN WITH A SUSPECTED RARE MENDELIAN DISORDER

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There are around 7,000 known or suspected Mendelian disorders. In the past, genes causing Mendelian disorders have been identified through several strategies, including meiotic mapping, positional cloning, physical mapping and candidate-gene sequencing. Over the past few years, new high-throughput genotyping technologies have been developed and introduced, including autozygosity mapping and next generation sequencing (NGS), using either targeted, whole exome or whole genome analysis for the discovery of disease genes in apparently novel Mendelian disorders.

We describe here a consanguineous Lebanese family whereby 2 of the 4 children have an as yet, unknown genetic disorder, presenting with hypertonia, dysmorphism, contractures and hyperexcitability. Routine metabolic and genetic investigations have been inconclusive. We have performed whole exome sequencing (WES) in four individuals of this family (parents and both probands). Exome capture was carried out using Agilent SureSelect and the captured DNA was sequenced using an Illumina HiSeq 2000 Sequencer. The resulting mapping and sequencing data identified a homozygous missense variation in the *DYT1* gene at c.806T>C (p.Phe269Ser) in both probands. Sanger sequencing confirmed this missense mutation to be homozygous in the two probands, wild type on one unaffected sibling and heterozygous in the other unaffected sibling as well as in both parents. Further investigations are being undertaken to elucidate the pathogenicity of the mutation as well as providing us with a better understanding of the biology of the disorder associated with the gene. Thus, using WES, we have identified an autosomal recessive mutation that could potentially be pathogenic in a rare Mendelian disorder.

Australasian Society for Inborn Errors of Metabolism Oral Presentations
ASIEM Oral 1
SKELETAL MUSCLE: THE LOCUS OF CONTROL FOR METABOLIC HEALTH

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Skeletal muscle displays remarkable plasticity enabling major adaptive modifications in its metabolic potential and functional characteristics in response to external stimuli such as contraction and nutrient availability. Recent evidence demonstrates that nutrient availability serves as a potent modulator of many of the acute (i.e. minutes to hours) responses and chronic (weeks to months) adaptations to both endurance- and resistance-based exercise. This is because changes in macronutrient intake rapidly alter the concentration of blood-borne substrates and hormones, causing marked perturbations in the storage profile of skeletal muscle and other insulin-sensitive tissues. In turn, muscle energy status exerts profound effects on resting fuel metabolism and patterns of fuel utilization during exercise as well as acute regulatory processes underlying gene expression, cell signaling and ultimately phenotypic modifications. In obesity, insulin resistance and type 2 diabetes (so-called 'metabolic syndrome'), the composition and biochemistry of skeletal muscle are altered compared to healthy individuals. In health, skeletal muscle oxidizes both carbohydrate- and lipid-based fuels and transitions between them in response to hormonal and substrate signals (i.e., metabolic flexibility). In patients with metabolic syndrome there is a loss of muscle plasticity and, instead, there is metabolic inflexibility. Other clinical conditions associated with aberrant skeletal muscle substrate handling are ageing and inactivity in which there is a loss of muscle protein (i.e., sarcopenia) leading to deterioration in muscle quantity and quality. This talk will show that skeletal muscle is the locus of control for metabolic health in humans and highlight the importance of mechanical loading and nutrient availability in the prevention and treatment of many chronic diseases.

ASIEM Oral 2
THE EVIDENCE FOR ENERGETIC SUPPLEMENT USE IN ELITE SPORT

Dr Liz Broad

Abstract Not Provided at Time of Printing

ASIEM Oral 3
DIETARY PROTEIN IN INBORN ERRORS OF METABOLISM: HOW MUCH? WHICH? HOW? WHICH? HOW?

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The prescribed daily protein intake of patients with inborn errors of metabolism (IEM) varies considerably. The immediate goal in restricting protein intake in disorders of protein metabolism is to prevent metabolic decompensation, whilst enabling normal long-term growth. In certain disorders high protein diet is prescribed as an accessible energy source or to promote muscle regeneration. In general, "Metabolic Diets" are based on 'recommended daily intake' guidelines for protein, energy etc. These guidelines are based on large population studies of healthy individuals. More specifically, "Metabolic Diet" recommendations are based on theoretical disease-specific considerations, practice and experience, rather than on clear evidence. Their adequacy has never been properly studied. Moreover, the biological value of protein substitutes, which are prescribed in certain disorders, has not been established beyond the 'normalisation' of plasma amino acid concentrations.

What is a safe range of protein intake for patients with IEM and to what should it be related? Is the Protein:Energy ratio pivotal to the adequacy of a "Metabolic Diet"? Have we neglected the possibility of high-protein diets for patients with certain disorders? Can we explore the possibility of prescribing natural protein rich or poor in certain amino acids that may influence metabolic control? What is the best route to provide protein and promote anabolism in acute states? These questions, and others, open a wide scope for research into a more evidence-based approach to the dietary management of patients with IEM.

ASIEM Oral 4
MANAGEMENT OF PKU IN AUSTRALIA - A SURVEY OF CLINIC PRACTICES

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A survey of phenylketonuria (PKU) management practices was undertaken as background to the National Institutes of Health Phenylketonuria Scientific Review Conference, Washington DC, February 2012. Questionnaires were sent via email to the Metabolic Clinicians Google Group and ASIEM Dietitians Group. Responses were received from all PKU Clinics in Australia, except one adult clinic.

Treatment of infants with hyperphenylalaninaemia/ PKU in Australian clinics commences at blood phenylalanine (phe) levels between 350 - 400μmol/l. Only 2 clinics initially admit infants to hospital and only 2 undertake tetrahydrobiopterin (BH4) loading in addition to standard testing of urine pterins, neurotransmitters and dihydropteridine reductase activity. Only Victoria manages BH4 responsive infants with sapropterin therapy. All clinics support breastfeeding the infant with PKU as per the ASIEM handbook protocol. Routine blood tests and frequency of testing and clinic visits varies between clinics, but all modify with need and social factors. Whilst acceptable upper blood phe levels in the 0-5 year age group range from 350 -400μmol/l, there is greater variation amongst clinics in older age groups with 3 clinics having $<$700 μmol/l as the target level for over 12 year olds. The upper acceptable treatment phe level for pregnancy varies from 150 to 300μmol/l.

The aim of the Scientific Review Conference was to examine recent research findings, current treatments, future research needs and to inform clinical practice guideline development. There are still unanswered questions about when treatment is required and what is optimal. Consensus management guidelines in Australasia would ease confusion amongst patients and guide practice.

ASIEM Oral 5
TWO EXTREMES OF ORNITHINE TRANSCARBAMYLASE DEFICIENCY IN MALES

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Background: Ornithine transcarbamylase deficiency (OTCD) is an X-linked urea cycle disorder. Males classically present with neonatal encephalopathy, hyperammonaemia, elevated glutamine, decreased citrulline and arginine and elevated urinary orotic acid and uracil.

Case 1: A 2-day-old male presented with lethargy and poor feeding. Ammonia measured day 3 was elevated. High dose dextrose, nitrogen scavenging medications and haemofiltration commenced. Plasma amino acids, urine organic acids and later *OTC* gene sequencing confirmed OTCD. Natural protein was recommenced within 24 hours and established on 0.9g/kg natural protein and 0.9g/kg protein-equivalent from Essential Amino Acid Mix®. At 10 weeks of age he had a relatively normal neurological examination. He was listed for urgent LT which occurred at 13 weeks. At 8 months he has some neurological deficits and feeds an unrestricted diet.

Case 2: A 20-year-old Commerce student presented with confusion, lethargy and vomiting. Towards the end of recovery a normal

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ammonia, mildly elevated glutamine and just detectable orotic acid and uracil were revealed. Prior to admission he had commenced a high protein diet, L-carnitine and creatine supplements pre-gym work-outs. OTCD was confirmed on *OTC* gene sequencing. A normal protein diet, gym work-out plan and emergency regimen were commenced. Following a further admission with delayed presentation, profoundly elevated ammonia and glutamine, sodium benzoate was introduced. Six months later he has had no further admissions.

Conclusion: There is a broad spectrum of severity in Male OTCD. Case 1 was more clinically complex however Case 2 exemplifies some of the subtle features of adult-onset disease.

ASIEM Oral 6
TOWARDS THE DEVELOPMENT OF A GENETICALLY MODIFIED PROBIOTIC AS A NOVEL THERAPY FOR PHENYLKETONURIA (PKU).

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Phenylketonuria (PKU), an inborn error of metabolism, is due to a defect of phenylalanine hydroxylase, causing severe mental retardation if untreated. Current treatment is a phenylalanine (phe)-restricted diet. Dietary compliance is a major issue due to palatability of the diet. There is a critical need to develop novel approaches to therapy.

We have developed a genetically modified (GM) probiotic that produces functional phenylalanine ammonia-lyase (PAL). Five Pah^{ENU2} PKU mice were treated with GM *Lactococcus Lactis* (10^9 cells) via orogastric gavage (OG). No drop in blood phe was seen, possibly due to failure of the probiotic to lyse and present PAL to the small intestinal brush border, and/or due to the catabolic state of the mice due to OG.

Using a Caco2 cell culture system we are examining viability of the GM probiotic in the gastric and small intestinal milieu, and determining the optimum approach for the delivery of active PAL to its phe substrate.

We are also developing an *in vivo* stable isotope approach to more accurately quantitate the acute effect of the GM probiotic on blood phe and tyrosine (tyr) levels on protein loading.

In addition, we are evaluating a strategy to further enhance GM probiotic survival through induction of BilE expression, and to improve PAL activity by the introduction of a protective chaperone protein.

With further optimisation of the GM probiotic system we will be in a better position to re-evaluate the possible efficacy of this novel approach to PKU therapy in the PKU mouse model.

ASIEM Oral 7
PROPIONIC ACIDAEMIA, NEPHROTIC SYNDROME AND ISCHAEMIC GUT: A NUTRITIONAL CHALLENGE

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Propionic Acidaemia (PA) is a disorder of protein metabolism requiring treatment with a protein restricted diet. A 3y old boy with PA diagnosed through newborn screening and treated since the first days of life presented at age 2y10m with nephrotic syndrome, which was resistant to conservative treatment. Renal failure developed within several weeks and he required continuous haemofiltration to control body fluids. He suffered an episode of gut ischaemia necessitating large bowel resection, and later percutaneous enteroscopic jejunostomy due to gut stasis.

Management challenges included: 1) providing adequate protein and energy to prevent metabolic decompensation and protein deficiency in the context of renal failure and continuous haemofiltration; 2) unreliable body weight measurements due to fluid overload; Clinical signs such as hair loss suggested protein deficiency; 3) periods of intolerance of enteral nutrition due to gut malfunction; 4) strict daily fluid restriction requiring hyper-concentrated enteral and parenteral formulae/fluids.

Assumptions regarding protein requirements had to be made in view of amino acids loss and multiorgan disease. Nutritional care involved the use of manipulated enteral nutrition including combinations of several specialised precursor free amino acid formula, and manipulating standard total parental nutrition solutions in the context of acute daily changes. This required daily negotiations with multiple medical teams.

The management of this patient presents a most extreme challenge to the metabolic dietitian. Ongoing considerations include maximising energy intake, providing adequate protein during periods of dialysis, adjusting feeds due to electrolyte disturbances and fluid restrictions and the potential reintroduction of oral diet.

ASIEM Oral 8
MARKEDLY EFFECTIVE GENE THERAPY IN AN ETHYLMALONIC ENCEPHALOPATHY MOUSE MODEL

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Ethylmalonic Encephalopathy (EE) is an invariably fatal disease, characterized by the accumulation of hydrogen sulfide (H_2S), a highly toxic compound. The *ETHE1* gene, encoding sulfur dioxygenase (SDO), which takes part in the mitochondrial pathway that converts sulfide into harmless sulfate, is mutated in this disease. In mammals, the main source of H_2S is the anaerobic bacterial flora of the large intestine, although this compound is also produced in trace amount by tissues, where it acts as a physiological "gasotransmitter". Effective therapy for EE must aim at either reducing the production of H_2S, or increasing its clearance and detoxification, or both. This rationale underpinned a partially successful, however palliative, treatment, applied to both EE patients and $Ethe1^{-/-}$ mice, based on administration of N-acetylcysteine (NAC), a precursor of H_2S-buffering glutathione, or metronidazole, a bactericidal agent specific against anaerobic bacteria, or both. AAV2/8-mediated, *ETHE1*-gene transfer to the liver of a genetically, metabolically, and clinically faithful mouse model of EE resulted in full restoration of *in vitro* SDO activity, associated with correction of plasma thiosulfate, a biomarker reflecting the accumulation of H_2S, and spectacular clinical improvement. Most of treated animals are alive and well >5-7 months after birth, whereas untreated individuals live 26 ± 7 days. Our results provide proof-of-concept on the efficacy and safety of AAV2/8-mediated liver gene therapy for Ethylmalonic Encephalopathy, and alike conditions caused by the accumulation of harmful compounds in body fluids and tissues, which can directly be transferred to the clinic.

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ASIEM Oral 9
NOVEL DISORDERS OF THE MITOCHONDRIAL RESPIRATORY CHAIN IDENTIFIED BY MITOEXOME NEXT-GENERATION SEQUENCING

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Advances in next-generation sequencing (NGS) promise to facilitate diagnosis of inherited disorders but using NGS efficiently for diagnosis of single individuals without a family history remains a challenge. Mitochondrial respiratory chain disorders comprise over 120 distinct genetic disorders and provide an excellent test case for NGS. We performed targeted NGS in 42 unrelated infants with clinical and biochemical evidence of mitochondrial respiratory chain disease (Calvo, Compton, et al., 2012, *Sci Transl Med* **4**, 118ra10). "MitoExome" sequencing targeted mitochondrial DNA (mtDNA) and exons of ~1000 nuclear genes encoding mitochondrial proteins. We prioritized rare mutations predicted to disrupt function. Because patients and healthy control individuals harbored a comparable number of such heterozygous alleles, we could not prioritize dominant-acting genes. However, patients showed a fivefold enrichment of genes with two such mutations that could underlie recessive disease. In total, 23 of 42 (55%) patients harboured such recessive genes or pathogenic mtDNA variants. Firm diagnoses were enabled in 10 patients (24%), 9 of whom had mutations in nuclear genes previously linked to disease, while one had a 7.2kb mtDNA deletion identified by *de novo* assembly of mtDNA. Thirteen patients (31%) had mutations in nuclear genes not previously linked to disease. The pathogenicity of two such genes, *NDUFB3* and *AGK*, was supported by complementation studies and evidence from multiple patients, respectively. Preliminary data suggest that at least another 5 of the candidate genes are likely to be *bona fide* disease genes. The results underscore the potential and challenges of deploying NGS in clinical settings.

ASIEM Oral 10
ENZYME DIAGNOSIS OF FUMARASE DEFICIENCY IN NON-IDENTICAL TWINS

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Fumarase deficiency is a rare autosomal recessive defect of the Krebs Tricarboxylic Acid (TCA) Cycle caused by mutations in the Fumarate Hydratase (FH) gene. The FH gene encodes two isoenzymes, one in the cytosol and the other in the mitochondrial matrix. Patients with Fumarase deficiency can present with poor feeding, microcephaly, fumaric aciduria and limb dystonia. Neurological symptoms can include severe developmental delay, infantile spasms, seizures and regression. All patients described so far appear to have had a defect of both cytosolic and mitochondrial fumarase. Carriers of FH mutations are predisposed to dominantly inherited uterine fibroids, skin leiomyomata and papillary renal cell cancer.

Over the last 20 years, we have diagnosed Fumarase deficiency in 5 Australasian patients enzymologically and most of these have subsequently had mutations confirmed in the FH gene. The residual enzyme activity of these patients has typically been <20% of mean control values, with the exception of one patient with relatively mild disease who had approximately 40% residual activity.

We assayed Fumarase activity in non-identical twins who presented with a variety of clinical features indicative of a metabolic condition including microcephaly, dystonia, developmental delay and feeding problems. A urine metabolic screen had revealed several metabolites that were above the upper limit of reference, including fumarate, succinyladenosine and 2-ketoglutarate. Both patients had undetectable Fumarase activity and both died within the first year of life.

ASIEM Oral 11
CHILDHOOD SPASTIC DIPLEGIA IN A NOVEL FORM OF NON-KETOTIC HYPERGLYCINAEMIA, ASSOCIATED WITH PYRUVATE DEHYDROGENASE COMPLEX DEFICIENCY, CAUSED BY GLRX5 DEFICIENCY OF THE IRON-SULFUR CLUSTER

J Van Hove[2] E Spector, [2]K Bhattacharya[1], Gupta S[1], B Robinson, [3]D Thorburn[4], B Wilcken[1], G Scharer[2], G Creadon-Swindel[2], J Aicher[2], T Shaikh[2], F Frerman[2], M Friederich[2], M Woontner[2], J Cameron[3], P Procopis, [1]D Gill[1]

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Objective: To describe the phenotype in a novel genetic disorder affecting both glycine cleavage and pyruvate dehydrogenase complexes.

Case Presentation: Two girls with normal development from apparently unrelated families originating from the same village in North Lebanon, presented in childhood with progressive spastic diplegia. Plasma and CSF glycine levels were elevated with normal CSF: plasma ratios. Cranial MRI revealed leukodystophy (Case 1- 2.5 years) and small areas of hyper-intense signal in the deep frontal white matter for Case 2 (8 years). Spinal MRI in both cases showed large linear T2 hyper-intense lesions in the posterior cervical cord. Case 1 was confirmed to have hepatic deficiency in the glycine cleavage enzyme system. Both cases had deficiency of pyruvate dehydrogenase complex identified on cultured skin fibrobalsts. A hypothesis of defective lipoylation was proposed as causing both deficiencies.

Case 1, now 11 years old, is able to ambulate with the help of crutches and has mild learning difficulties. Case 2, now 10 years old, ambulates independently with orthotics and has normal intellect.

Methods: Candidate genes for endogenous lipoate synthesis were sequenced and no defects were found. Homozygosity mapping showed 3000 areas of shared homozygosity, Candidate genes were selected by mitochondrial location and correct tissue expression. One candidate gene (GLRX5) for iron-sulfur cluster biosynthesis, the co-factor lipoate synthase, was identified. A common mutation c.151-153delAAGp.K51del was found, carried in the heterozygote state by both sets of parents.

Conclusion A novel disorder of lipoate synthesis affecting both pyruvate dehydrogenase and glycine complex systems has been identified.

ASIEM Oral 12
HARMONISATION OF NEWBORN SCREENING PROGRAMMES WORLDWIDE

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Newborn baby metabolic screening is offered to families in all developed countries as early detection and treatment of certain inborn errors of metabolism is highly effective in reducing morbidity and mortality. Screening programmes typically use large centralized

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laboratories, often just one for a state or country. The dried blood spot technology generally used in newborn screening has little other wide application. There are difficulties in standardization of assays not found in routine clinical chemistry which lead to difficulties in comparison of screening performance between programmes. This presentation (as previously given at the SSIEM/ISNS meeting in Geneva in September 2011) covers both successful (punch card design, quality assurance programmes, ISNS phenylalanine standard, collection paper specifications, Clinical and Laboratory Standards Institute Guidelines) and unsuccessful (ISNS TSH standard, definition of screened disorders) international efforts at harmonization of screening practice.

ASIEM Oral 13
NEWBORN SCREENING FOR CONGENITAL ADRENAL HYPERPLASIA

V Wiley[1,2]

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Each year in Australia approximately 25 babies are born with congenital adrenal hyperplasia (CAH). The symptoms include virilisation and severe salt wasting. Females with ambiguous genitalia may be detected and treated early. However, males (and females with incorrect sex assignment) can develop severe salt wasting adrenal crisis, usually in the second week of life, leading to death or permanent disability. Despite early diagnosis and treatment leading to reduced mortality and morbidity, population screening for CAH is not performed in Australia. Reasons for this include the time to diagnosis, the specificity and the cost.

For ∼90% of cases, CAH is due to 21-hydroxylase deficiency which leads to an elevation of 17-hydroxyprogesterone (17OHP) detectable in blood samples. The most common methods used for measuring 17OHP are immunoassays. Analytical performance of an immunoassay depends on the specificity of the antibody with many commercially available assays having cross-reactive interference from other steroids in blood especially in premature, low birthweight and severely stressed infants.

Further testing on the initial blood spot can improve the predictive value of screening. Various approaches have been used including ether extraction prior to immunoassay, DNA mutational analysis and steroid profiling using mass spectrometry.

In NSW, 99.85% of babies >2kg birthweight and 94% of babies <2kg had CAH excluded on the initial sample using immunoassay. Steroid profiling significantly reduced the false positives. In 2011 99.4% of babies would have had results by day 9.

In conclusion, immunoassay plus mass spectrometry provides optimal sensitivity and specificity with rapid turnaround time.

ASIEM Oral 14
QUANTITATIVE AMINO ACID ANALYSIS: COMPARISON OF UPLC TANDEM MASS SPECTROMETRY WITH ION-EXCHANGE CHROMATOGRAPHY WITH POST COLUMN NINHYDRIN DETECTION

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Introduction: Analysis of amino acids (AA) is an essential service for the diagnosis and management of inborn errors of metabolism. We employ a Biochrom 30 analyser based on ion exchange chromatography with ninhydrin derivatisation. Recently, we developed a rapid method using UPLC tandem mass spectrometry (MS/MS). To validate the method we have analysed stored samples from the ERNDIM assurance program (EAP) and patient samples.

Method: Plasma is ultrafiltered and mixed with stable isotope internal standards (IS). AAs are separated on a Kinetex C18 column using an ion pairing reagent and detected by MS/MS in MRM mode analysing 21 AA using 16 IS. Calibration utilised a 2 point standard curve using a plasma based calibrator. A series of 7 stored EAP samples were analysed in triplicate. Plasma from 40 patients were analysed in parallel using both methods.

Results: MS/MS results of EAP samples showed linear response($y = 0.86$ to 1.12, $R2 = 0.97$ to 0.99) for all AA except histidine. Comparison with the EAP results for all laboratories revealed half of the analytes had some results >2SD from the method mean. Bland-Altman plots confirmed significant proportional and or absolute bias for most amino acids.

Conclusion: MS/MS results are linear and some analytes compatible with the consensus mean of the EAP. However, there is evidence of instrument or calibration bias, hence reference ranges established using the Biochrom are not transferable to the MS/MS method.

ASIEM Oral 15
BIOCHEMICAL SCREENING FOR ANTIQUITIN DEFICIENCY: AUSTRALASIAN EXPERIENCE

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Antiquitin (2-aminoadipic semialdehyde dehydrogenase) deficiency is caused by mutations in the *ALDH7A1* gene and results in seizures, often presenting in the neonatal period, that are responsive to pyridoxine treatment. The disorder results in the accumulation of 2-aminoadipic semialdehyde (AASA) in CSF, plasma and urine. AASA is a reactive molecule and undergoes an internal cyclisation reaction to form an equilibrium product, piperideine-6-carboxylic acid (P6C). Since 2006, biochemical testing for antiquitin deficiency has been performed in Australasian patients by measurement of urine metabolites. Testing was initially done using a GC-MS method for AASA but this was replaced with an LC-MSMS method for P6C in 2010. The current protocol for identification of metabolic disorders involves a preliminary comprehensive urine MSMS screen which includes detection of P6C and its dimer. LC-MSMS testing is then performed on samples with high levels of P6C or when antiquitin deficiency testing is specifically requested. Results are reported qualitatively due to the instability of AASA/P6C. 18 patients were identified with increased levels of AASA/P6C, all having clinical features highly suggestive of antiquitin deficiency or pathogenic *ALDH7A1* mutations. Most patients were treated with pyridoxine at the time of sampling. This experience indicates that urine screening for P6C is effective in diagnosing antiquitin deficiency even when patients are treated with pyridoxine. A further benefit of the comprehensive screening protocol is exemplified by 2 neonates who were initially suspected to have antiquitin deficiency but were found to have hypophosphatasia.

ASIEM Oral 16
INBORN ERRORS OF METABOLISM: SIGNIFICANT IMPACTS ON FAMILIES AND HEALTH SERVICES

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Patients with a rare disease and their families experience significant health and social burdens, yet there are few data describing these impacts in Australia. We developed a generic self-administered

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questionnaire for parents incorporating pre-validated tools where appropriate, to assess the impacts of rare disease on families. The questionnaire was piloted among families from the Genetic Metabolic Clinic at the Children's Hospital at Westmead. Forty-nine families were invited and 30(61%) responded. Most (93%) of these found the length acceptable and the questions relevant (91%). Patients were aged 1-17 years, 47% male, 60% had a lysosomal storage disease and 40% a mitochondrial disorder. Over a half (52%) saw between 3 and 10 doctors before receiving the final diagnosis and 43% felt that the diagnosis was delayed. 30% of families were dissatisfied with the way the diagnosis was given. Only 41% of respondents were offered psychological support but 80% think it should always be offered. Thirteen (43%) were informed of relevant peer-support groups but 26 (87%) would have liked this information. Most families (77%) were receiving financial assistance but over half believed this support was insufficient. Impact on health services over one year was high: the 30 children in our sample accounted for 168 visits to GPs, 268 visits to specialists and 260 visits to allied health professionals. Pilot data echoed results from studies conducted abroad, showing significant impacts on families including delays in diagnosis, lack of information about the disease and lack of psychological support or information about support groups.

ASIEM Oral 17
PREDICTIVE VALUE OF IMMUNOREACTIVE TRYPSIN FOR DETECTION OF CYSTIC FIBROSIS IN NSW

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The screening protocol for CF in NSW includes measurement of immunoreactive trypsin (IRT). Samples with IRT >99%ile are tested for the common CF-causing DNA mutation, p.phe508del. Babies with 2 mutations have CF; those with one mutation are referred for a sweat test and further mutational analysis; while those with no mutation detected are missed by screening unless there is a family history or clinical indicator. Amongst babies missed by this protocol (no common mutation detected) we investigated whether the IRT level predicted those most likely to have CF.

We screened 1.178 million babies from Jan 2000 to Dec 2011. The annual median population IRT ranged from 16 to 21ug/L, with the 99%ile 59-71ug/L. There were 13,462 with elevated IRT; 336 (2.5%) of these had CF, 171 homozygous; 915 were heterozygous with 142 proven to have CF. Twenty-three babies had CF but no copy of p.phe508del, 11 of whom had no mutation detected and a further 5 with one mutation despite a panel of over 30 mutations being sought.

The current incidence of CF is 1:3,500 live births. The overall risk of CF for those with elevated IRT was 1:40. For those with one mutation the risk was 1:6. With no mutation the risk was 1:570.

The IRT level of these missed babies ranged from 38 to 366ug/L, with no level practical to use as a high-risk indicator. Half would have remained undetected despite extensive mutation analysis. We conclude that our current protocol is the most effective for use in 2012.

ASIEM Oral 18
IMPLEMENTING A TWO-STAGE WRITTEN CONSENT PROCESS FOR NEWBORN SCREENING IN VICTORIA

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The primary goal of newborn screening programs is the early detection and treatment of debilitating childhood disorders and widespread support exists for this goal amongst the public and health professionals. Less clear are issues surrounding the consent for testing and the long-term storage of newborn screening dried blood spot cards and their potential use in clinical research. There has been growing evidence of a lack of public awareness of newborn screening and concern about inadequate consent being obtained from parents. Apprehension also exists in relation to long term screening card storage and secondary use. A staged introduction of a two-part written consent process was implemented across Victoria as a means of strengthening program transparency, quality and supporting parental choice. In addition, more comprehensive information covering all aspects of the program was developed for parents. At the time of sample collection, parents provided consent for screening and indicated whether or not the sample could be used for secondary research. Six months of laboratory data show that while refusals for screening have increased, overall participation remains above 99%. The percentage of parents opting out of research use is 7.5%. This quality improvement project has demonstrated that parents can participate more fully in the newborn screening process without jeopardising high uptake. As a secondary benefit, the public health resource of stored cards can be maintained with parental support. Future work needs to examine the quality of consent being given by parents and investigation of the reasons why some choose to decline.

ASIEM Oral 19
5 YEAR FOLLOW UP OF 2 SIBLINGS WITH KRABBE DISEASE TRANSPLANTED AT 4 AND 5 WEEKS OF AGE FOLLOWING POSTMORTEM DIAGNOSIS IN A SIBLING.

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Three children with Krabbe disease were born to non-consanguineous Sudanese parents. The first affected child presented with weight loss, hypotonia and hyporeflexia at four months and subsequently deteriorated and died at 5.5 months of age. The diagnosis was made at autopsy and confirmed by fibroblast β-galactocerebrosidase activity. Two siblings born subsequently had Krabbe disease diagnosed in the neonatal period by leukocyte β-galactocerebrosidase activity prior to transplant at 5 and 4 weeks respectively. They both received a Busulfan/Cyclophosphamide/ATG unrelated cord transplant and had 100% donor engraftment and correction of peripheral blood leukocyte β-galactocerebrosidase activity. They received their transplants prior to becoming symptomatic at a few months of age.

Five years post transplant the elder sibling was neurologically abnormal, being unable to walk and requiring gastrostomy feeds. He has some speech. His EEG, nerve conduction studies (NCS) and visual evoked responses (VER) are abnormal. Cognitive testing had deteriorated from earlier assessments to the mildly impaired or delayed range of cognitive ability.

The youngest sibling had a more complicated post-transplant course with 3 admissions to paediatric intensive care with gram negative sepsis. She had a shunt for hydrocephalus. 5 years post transplant she has spastic quadriparesis, is gastrostomy fed, and remains dependent for all cares. She has some speech. EEG, NCS and VER are abnormal.

Although survival is improved with early transplant, the disease course has been slowed rather than cured. Parents need to be fully informed about the limitations of transplant for Krabbe disease.

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ASIEM Oral 20
AN OBSERVATIONAL STUDY OF NINE ADULT LATE-ONSET POMPE DISEASE PATIENTS TREATED OR UNTREATED WITH ACID ALPHA-GLUCOSIDASE ENZYME REPLACEMENT THERAPY

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OBJECTIVES: To review nine patients referred to one centre with late-onset Pompe disease, seven of whom received enzyme replacement therapy (ERT) with recombinant human acid alpha-glucosidase (rhGAA).

METHODS: Neuromuscular outcome measures include standard test of muscle strength and endurance, and muscle MRI. Respiratory outcome measures included erect/supine forced vital capacity (FVC), maximal inspiratory (MIP) and expiratory (MEP) pressures. Quality of life (QOL) data were collected using the SF-36, Fatigue Severity Scale, and Rotterdam Handicap Scale.

RESULTS: A total of 7 males and 2 females, with a mean current age of 58.9 years (range 35-73), and mean age at diagnosis of 50.9 years (range 24-68) were reviewed. Presenting symptoms were abnormal gait (n = 4), difficulties with stairs (n = 2), or respiratory failure (n = 3). In the treated group, the mean duration of symptoms prior to ERT was 21 years (range 3-44y), and duration of ERT 3 months to 6 years. Detailed muscle MRC scores in 4 patients receiving ERT remained stable during a mean follow-up period of 4.3 years; erect FVC remained stable during a mean follow-up of 3.3 years. QOL in 4 treated patients showed a trend towards stable (n = 1) or worse (n = 3). Six patients had in total 11 muscle MRIs, all of whom had variable degrees of fatty infiltration of lower limb girdle and/or paravertebral muscles. Both of the untreated patients have remained active, not requiring any walking aids at ages 60 & 71 years respectively.

CONCLUSION: ERT was well-tolerated and there was stabilization of neuromuscular and respiratory involvement. There was a suggestion of worsening QOL over time in some patients.

ASIEM Oral 21
DENOSINE KINASE DEFICIENCY, A NOVEL CAUSE OF HYPERMETHIONINEMIA PRESENTING AS A SLOWLY PROGRESSIVE ENCEPHALOPATHY WITH EPILEPSY, MYOPATHY AND LIVER DISEASE

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To date, four inborn errors of metabolism are known to cause hypermethioninemia by directly interfering with the methionine cycle and they include; Methionine adenosyltransferase I/III, Glycine-Nmethyltransferase, S-adenosylhomocysteine hydrolase (SAHH) and Cystathionine beta-synthase. Here we describe the clinical, biochemical and molecular studies of 6 patients with a novel form of persistent hypermethioninemia secondary to Adenosine Kinase (ADK) deficiency. The disorder was first studied in 2 Swedish siblings with a presentation of a severe, slowly progressive encephalopathy, epilepsy, myopathy, dysmorphic features, macrocephaly and liver dysfunction. Biochemical analysis revealed increased plasma levels of methionine, S-adenosylmethionine, and S-adenosylhomocysteine but normal or mildly elevated homocysteine levels. SAHH deficiency, which causes a similar biochemical phenotype had been excluded by using genetic and biochemical techniques. Exome sequencing identified a homozygous c.902C>A (p.Ala301Glu) missense mutation in the ADK gene which was subsequently validated by Sanger sequencing. Functional studies including in vivo demonstration of increased urinary adenosine excretion and in vitro assays of reduced ADK activities in the recombinant proteins confirmed ADK deficiency. Four additional Malaysian patients from two unrelated families with a similar presentation were identified and shown to have a homozygous c.653A>C (p.Asp218Ala) and c.38G>A (p.Gly13Glu) mutation, respectively, in the ADK gene. ADK deficiency is a previously undescribed, severe IEM that disrupts the methionine cycle through a functional link with adenosine metabolism. Awareness of this disorder is imperative and should be considered in the diagnostic evaluation of hypermethioninemia particularly if liver disease is involved, as it may otherwise be disregarded as a non specific association.

ASIEM Oral 22
LIVER TRANSPLANTATION FROM AN ADULT DONOR WITH AN UNRECOGNIZED UREA CYCLE DISORDER TO A PAEDIATRIC AND AN ADULT RECIPIENT

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Australia has one of the lowest organ donation rates in the world and there is intense pressure to optimise every possible organ donor. Shortage of donors for solid organ transplantation has led to procedures to maximise donor utilisation, including split and live donor grafts. Ideally the cause of death should be ascertained before accepting a cadaveric donor organ; this decision can be difficult given the time pressure to accept or reject a donor organ, often out of regular hours, and particularly in the setting of severe waiting list pressures. Recognising and investigating inborn errors of metabolism can be challenging. The rarity of UCD presenting in adulthood means that this diagnosis is often not considered by adult physicians.

We report the outcomes of adult and paediatric split liver transplantation from an adult male donor who died due to an unrecognised Urea Cycle Disorder (UCD), Ornithine Transcarbamylase (OTC) deficiency. This case highlights the importance of considering an inborn error of metabolism in any patient with an unexplained encephalopathy, including adults. It is vital that a definitive diagnosis is established in a donor prior to consideration for organ donation.

Australasian Association of Clinical Geneticists Oral Presentations
AACG Oral 1
PRENATAL DIAGNOSIS OF THE RASOPATHIES

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This presentation will compare and contrast the perinatal features of the various RAS/MAPK syndromes in order to provide the opportunity to make an earlier clinical diagnosis allowing for more effective patient management and counseling.

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	Noonan syndrome	Costello syndrome	CFC syndrome
Increased NT/NF	+++	+	+
Lymphatic	++	+	+
Polyhydramnios	+++	++++	+++
Short long bones	++	++	+
Ventriculomegaly		+	+
Renal	+	+	+
Macrocephaly		++	
Macrosomia		++	+
Cardiac	+	++	

Note: Lymphatic: cystic hygroma, pleural effusions, ascites, skin thickening, hydrops
Renal: pelviectasis, echogenic kidneys
Cardiac: malformations, ventricular hypertrophy, arrhythmias

AACG Oral 2
A GUIDE TO THE PRENATAL EVALUATION OF SKELETAL DYSPLASIAS

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The inherited disorders of bone and cartilage (a.k.a. skeletal dysplasias) are a group of collectively common disorders caused by abnormalities in the development, growth and maintenance of the human skeleton. Numerous genes and pathways have been elucidated as the cause of these pleiotropic conditions.

The increasing use of antenatal imaging modalities had led to the possibility of diagnosis of these conditions *in utero*, leading to further antenatal and postnatal management decisions. Currently, standardized antenatal protocols for evaluating a suspected skeletal dysplasia are lacking and practice varies from centre to centre across Australia, and worldwide.

This talk will give a brief overview of these conditions and will focus on a practical approach to the rational evaluation of these conditions. It will outline the key issues that need to be addressed and answered in this setting, provide examples of common conditions, discuss the differential diagnoses, and propose immediate and longer-term management and follow-up of such pregnancies.

AACG Oral 3
FUNDING FOR GENETIC TESTS

Dr Richard Bartlett, First Assistant Secretary Medical Benefits Division

Abstract Not Received at Time of Printing

AACG Oral 4
TARGETED THERAPY FOR NEURO-DEVELOPMENTAL DISORDERS INVOLVING THE MTOR PATHWAY

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In the1970s an antifungal, called Rapamycin, was discovered in a soil sample from Easter Island (Rapa Nui). In the 1990s the protein, mechanistic or mammalian Target Of Rapamycin (mTOR) was identified in yeast and found to have immunosuppressive effects and the ability to suppress cell proliferation. TOR is highly conserved and found in all eukaryocytes including yeast, algae, slime moulds, plants, worms, flies and mammals. Loss of TOR function is lethal during embryogenesis. The mTOR protein forms part of two intracellular complexes. TORC1 (rapamycin sensitive) drives translation of oncogenes, inhibits autophagy, up regulates HIF1alpha increasing angiogenesis and enhances accumulation of lipids. TORC2 (rapamycin insensitive) is involved in axon guidance, synapse function, activating AKT and promoting cell proliferation and survival. The mTOR pathway is now known to be involved in an increasing number of neurodevelopmental disorders. Rapamycin, an mTOR inhibitor has been used as an immunosuppressive agent following renal transplantation for a number of years.

Much of our knowledge of mTOR and its central role in cellular function has been acquired from cancer research. The mTOR pathway amongst others (PI3 kinase, AKT and p53) is overactive in a large number of different tumours. The understanding and interaction of these signalling pathways is subject to extensive study. The role of mTOR, TORC1/TORC2 and PI3 kinase inhibitors in cancer treatment is being explored. "In vitro" and "in vivo" assays are being developed to identify and assess small molecules, in isolation or in combination, that act on these pathways. These studies are likely to lead to improved treatments for certain tumours as well as identifying new therapeutic agents for mTOR related disorders.

The mTOR pathway is involved in the pathogenesis of a range of neurological diseases including tuberous sclerosis, neurofibromatosis 1, Fragile X syndrome, Alzheimers disease, Huntington disease, brain injury, epilepsy and autism. The potential for treatment of some aspects of these disorders is becoming a realistic possibility and is currently subject to study.

AACG Oral 5
AN EXPLORATORY DYSMORPHOMETRIC ANALYSIS TO DEFINE 3D FACIAL PHENOTYPIC SIGNATURES AS A FOUNDATION FOR NON-INVASIVE MONITORING OF LYSOSOMAL STORAGE DISORDERS

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Background: Some Lysosomal Storage Disorders (LSDs), including Mucopolysaccharidosis type 1 (MPS1), are associated with characteristic facies and their clinical recognition and delineation can be challenging. Fortunately, objective methods, such as three-dimensional (3D) facial scanning and geometric morphometric techniques, have the potential to circumvent subjective assessments and address the inherent overlap in facial phenotypes within these disease spectra. Methods: 3D facial images of 400 reference subjects (aged 5-25 years), and three MPS1-affected individuals were obtained using a 3dMD camera (Atlanta, Georgia). Images were fitted with an anthropometric mask (AM), comprising a set of spatially dense quasi-landmarks. A statistical face-space was constructed from a reference facial image set. Facial scans of MPS1-affected individuals were assessed against this face-space according to a recently developed methodology, known as dysmorphometrics, facilitating identification of harmonic versus discordant facial regions. A relative significant discordance (RSD) score quantified proportional facial discordance for a given individual, whilst a root-mean-squared-error (RMSE) score measured the degree of the facial discordance providing a severity measure. Results: A consistent facial pattern, with notable differential severities, primarily affecting the frontal, nasal, infraorbital and cheek regions, was detected in all three MPS1-affected individuals. As expected, there was greater discordance (RMSE, RSD) with clinically diagnosed severe MPS1 when compared to attenuated MPS 1. Conclusions: Objective detection and localisation of MPS1 facial characteristics was achieved,

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and severity scores were attributed to three individuals. The demonstration of a facial phenotypic signature that alters with disease severity supports potential uses of this dysmorphometric approach including non-invasive treatment monitoring.

AACG Oral 6
OI TYPE III-FKBP10 IN NON-CONSANGUINEOUS AUSTRALIAN FAMILIES

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We report the first known Australian patients with Osteogenesis Imperfecta (OI) due to FKBP10 mutations. All three patients presented with bone fragility, long bone deformities and progressive protrusio acetabulae. All had congenital talipes and two more had extensive contractures. Two patients from non-consanguineous Anglo-Celtic backgrounds were compound heterozygotes with novel mutations. The third patient, from a Samoan background, was homozygous for the Samoan founder mutation.

Mutations in FKBP10 coding for the FKBP 506 protein result in a type of OI. Initially described in a consanguineous Turkish family and a Mexican- American family, cases have since been reported from Saudi Arabia, Southern Africa, Northern India, Samoa, Indonesia and Germany. To date, a majority of reported cases have been found to have homozygous mutations in FKBP10. Fractures may present prenatally, at birth or much later in life. Some affected have talipes or joint contractures. Skeletal features included osteopenia, progressive long bone deformities, protrusio acetabulae and kyphoscoliosis. Intrafamilial variability has been a feature marked in the Samoan population. Of the reported cases, most had normal sclerae and three had dental anomalies. Patients had been classified as having Bruck syndrome, Arthrogryposis Multiplex Congenita, OI Type IV or OI Type III.

OI type III-FKBP10 may be more common than previously thought not only in the OI and Arthrogryposis clinic populations but in other groups of patients presenting for orthopaedic care. The diagnosis should be entertained particularly in patients with progressive protrusio acetabulae with or without bone fragility.

AACG Oral 7
INTERNATIONAL SARCOMA KINDRED STUDY (ISKS) – KNOWLEDGE OF GENETICS AMONGST PATIENTS, FAMILIES AND HEALTH PROFESSIONALS

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ISKS is a population based study recruiting individuals with sarcoma, their partners and genetic relatives. Biospecimens, clinical and epidemiological data have been collected. Within the study questionnaire is a section asking about their

1. Beliefs about the genetic component of aspects of health and well-being
2. Feelings towards new genetic discoveries
3. Attitudes towards genetic testing for inherited conditions
4. Attitudes towards predictive testing for sarcoma
5. The possibility of "incidental findings" as a result of genetic investigations

Results were available on 493 probands, 480 genetically related family members and 147 spouses. For further comparison, the question related to point 1 above was also given to 80 health professionals/ researchers in the field of sarcoma.

Genetic knowledge appears similar between the three groups but was markedly different from health professionals. Partners were more optimistic about new genetic discoveries than probands and their family members. Between 70-90% of all three groups had positive responses towards genetic testing for inherited conditions in general and over 90% thought a predictive test for sarcoma should be done by anyone who requests it, if it was available, while 63-70% believed everyone should be tested for it. Even when there was no prevention measure available, 67% of probands and family members and 75% of partners thought people should be informed about incidental findings.

Predictive genetic testing for sarcoma is not yet available and there may be consequences of receiving results of unknown clinical significance, but this study group demonstrate substantial interest in having genetic information.

AACG Oral 8
14q13 MICRODELETION: A RECOGNIZABLE CONTIGUOUS GENE SYNDROME ENCOMPASSING BRAIN/THYROID/LUNG AND DENTAL PHENOTYPE

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We report 3 patients with a microdeletion at chromosome 14q13 identified by microarray-based comparative genomic hybridization that variably spans 0.7- 6Mb; one case presented with the triad of chorea, neonatal respiratory distress and mild thyroid anomalies (brain/thyroid/lung-BTL) and the other 2 presented with the afore mentioned triad with the additional feature of oligodontia. The deletion contains the *NKX2-1* and *PAX 9* genes and it is the absence of these genes that results in the BTL presentation and oligodontia respectively. The *NKX2 -1* gene has an important role in transcriptional embryogenesis of the forebrain, thyroid and lung while PAX9 is responsible for posterior permanent dentition. We propose that this phenotype is characteristic of this deletion and note that all patients had extensive, invasive, expensive neurogenetic/metabolic investigations that could potentially been avoided if this distinctive but subtle clinical presentation was recognized. In addition all patients had normal or near normal mentition, and thus microarray studies were not part of first line investigation. This report will emphasize the constellation of features associated with this genotype to highlight the characteristics of this recognizable microdeletion syndrome.

AACG Oral 9
PAX6 MUTATION SPECTRUM IN AN AUSTRALIAN AND NEW ZEALAND ANIRIDIA COHORT

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PAX6 is a critical gene in eye development and haploinsufficiency leads to aniridia, often with associated anomalies of the cornea, lens and retina. There is a high risk of ongoing vision loss due to glaucoma. There are three events leading to haploinsufficiency; *PAX6* deletion, intragenic loss-of-function mutations, and disruption of the 3' regulatory region. Contiguous gene deletion at 11p13 of *PAX6* in conjunction with a nearby gene *WT1* leads to WAGR (Wilms tumour, Aniridia, Genitourinary abnormalities and mental Retardation) Syndrome. This study involves analysis of genotypes and phenotypes in an Australian and New Zealand cohort of 28 probands and family members with aniridia. It comprises the largest study of an Australian and New Zealand aniridia population group. Nineteen patients were the first identified in their family, while nine were familial cases. All patients underwent 11p13 FISH, CGH microarray, and *PAX6* sequencing. In total, twenty-one independent mutations were identified in this cohort, with an overall mutation detection rate of approximately 80%, consistent with previous series. Sequence alterations were found in the majority of patients with isolated aniridia, while *PAX6* region deletions were present in approximately 15% of both the sporadic and familial cases. While we have used exome sequencing in *PAX6* mutation identification in one patient subsequent to this series, our overall results highlight that in addition to sequence analysis, there is a need for deletion testing in aniridia for full mutation identification as well as detection of newly diagnosed young children that may be at risk of Wilms tumour.

AACG Oral 10
MUTATIONS IN EXONS 41 AND 42 OF FIBRILLIN 1 CAUSE SHORT STATURE OF THE ACROMELIC TYPE.

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Heterozygous mutations in the TGF beta binding-protein-like-domain 5 of FBN1 (exons 41 and 42) have recently been shown to cause Geleophysic (GD) and Acromicric dysplasia (AD). These are classified as Acromelic dysplasias. Gelophysic dysplasia was previously thought to be an autosomal recessive condition and Acromicric dysplasia an autosomal dominant disorder.

We report the clinical features and molecular genetics in three patients with heterozygous mutations in FBN1 from NSW; two with Geleophysic dysplasia phenotype and one with Acromicric dysplasia phenotype. All three patients presented with short stature, short hands and feet, variable joint contractures and characteristic facial features. Additionally the two patients with Geleophysic dysplasia had progressive cardiac involvement. Skeletal features include delayed bone age, short long tubular bones, ovoid vertebral bodies and J-shaped sella. Notching of the second and fifth metacarpals and internal notching of the femoral head were additional skeletal features seen in our patient with Acromicric dysplasia.

The mutations in exon 41 and 42 encoding the TB5 domain of Fibrillin 1 found in our patients alter binding of Fibrillin to TGF beta resulting in marked enhancement of TGF beta signalling.

Geleophysic and Acromicric dysplasia should be considered in patients referred with "normal" birth length, short stature, short hands and feet and delayed bone age. The finding of relative macrocephaly and a J-shaped sella further suggest this diagnosis. Cardiac echocardiography is needed in all patients in this spectrum of disorder to help to clinically differentiate between the two allelic conditions.

Australasian Society of Genetic Counsellors Oral Presentations

ASGC Oral 1
POSTNATAL MOTHERS ATTITUDES TO NEWBORN SCREENING FOR FRAGILE X SYNDROME

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Fragile X syndrome (FXS) is the commonest cause of inherited intellectual disability with a mean age of diagnosis at 5.5 years. Newborn screening for FXS provides an early diagnosis, preventing the 'diagnostic odyssey' for parents, allowing access to early interventions, and reproductive information for families. Parents of affected children support newborn screening, but few clinical studies have evaluated community attitudes. A pilot study was undertaken in 2009-2010 to explore maternal attitudes. FXS testing was offered to male and female newborns with their routine newborn screening. Mothers were provided with information about FXS, inheritance pattern, carrier status and associated adult-onset disorders. 2000 newborns were tested with 1971 / 2094 (94%) mothers participating, of which, 86% completed the attitudinal questionnaire. The questionnaire data was evaluated by multiple logistical regression analysis and the written comments by thematic analysis. Almost all mothers (99%) wanted to know both premutation and full mutation status in their newborn and had little concerns about identification of carrier status or associated adult-onset disorders. Most mothers (96%) were comfortable being approached in the postnatal period and supported testing because no extra blood test was required. Mothers considered an early diagnosis beneficial to help prepare for a child with additional needs (93%) and for reproductive planning (64%). Some were anxious about the potential test results (10%) and others felt their feelings towards their newborn may change if diagnosed with FXS (16%). High participation rates and maternal attitudes indicate a high level of maternal acceptance and support for newborn screening for FXS.

ASGC Oral 2
CASE PRESENTATION - "GETTING OVER THE SHOCK OF IT" THE IMPACT OF IMPLANTABLE DEFIBRILLATORS"

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Hypertrophic cardiomyopathy (HCM) is an autosomal dominant heart disease affecting 1 in 500 in the general population, characterized by thickening of the left ventricular wall. The most severe complication of HCM is sudden cardiac death (SCD). The only proven treatment against SCD is the implantable cardioverter defibrillator (ICD). EJ is a 39-year-old female with HCM, diagnosed after developing shortness of breath. Her family history reveals her father, sister and brother are affected by HCM. Her sister suffered a resuscitated cardiac arrest whilst pregnant, and went onto develop heart failure requiring transplant. Her brother died suddenly age 35, whilst running on a beach. EJ has an ICD implanted. Since implant she has had 5 life saving appropriate shocks.

Here I discuss a young woman coming to terms with an ICD. I reflect on her anxiety surrounding appropriate shocks and facing the fear of having an ICD shock in public. I discuss her coping with

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the lived experience of both ends of the spectrum of disease, i.e. her brother dying suddenly and her fathers heart failure and subsequent death. I explore the literature on the impact of ICD implants and the implications for genetic counseling. The genetic counsellor plays a key role in the ongoing management and support of families affected by inherited heart disease.

ASGC Oral 3
PSYCHOLOGICAL IMPAIRMENT PARTICULARLY IN MOTHERS FOLLOWING SUDDEN CARDIAC DEATH IN THE YOUNG

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Purpose: Sudden cardiac death (SCD) in the young is a devastating event for the family and often due to an underlying genetic heart disease. Managing these families is complicated by uncertainty regarding clinical management, genetic testing options and profound grief. This study sought to evaluate psychological wellbeing of at-risk relatives following SCD in the young.

Methods: Family members who attended the Genetic Heart Disease Clinic, RPAH Sydney following the SCD of a young relative ($\leq$ 40 years; within 10 years of death) were invited to complete the Hospital and Anxiety Depression Scale (HADS). Clinical and genetic data was collected. Primary outcome measures were the HADS anxiety (HADS-A) and depression (HADS-D) subscales.

Results: Fifty family members from 29 families returned surveys (males = 42%, mean time since death 4 ± 2 years, mean age of decedent 23 ± 9 years). There was significant impairment in overall mean HADS-A (8.74 ± 4.33, $p<0.0001$) and HADS-D (5.83 ± 3.56, $p<0.0001$) scores compared to general population. Female gender predicted worse HADS-A ($p = 0.001$) and HADS-D ($p = 0.049$) scores. Subgroup analysis identified "relationship to the deceased" as an important predictor of poor HADS scores, with mothers showing significant anxiety (mean HADS-A 10.95 ± 4.0, $p = 0.001$) and depression (mean HADS-D 7.32 ± 3.32, $p = 0.001$). 53% of mothers had a HADS-A score above 11, suggesting probable generalised anxiety disorder.

Conclusion: The SCD of a young relative has significant emotional implications for the family, particularly the mothers. Our results highlight the need for additional psychological support for mothers of a young SCD case.

ASGC Oral 4
THE AUSTRALIAN NATIONAL GENETIC HEART DISEASE REGISTRY

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There are now over 40 cardiovascular diseases known to have a genetic cause. Current studies are limited by lack of information and cohort size, leaving many key clinical and genetic questions unresolved. The Registry aims to recruit every Australian family with a genetic heart disease, and is already proving to be a valuable resource to better understand these conditions.

Patients are recruited from specialised cardiac genetic clinics and through self-referral. Written informed consent is required and clinical data are collected and entered into a central Registry database. Diseases included are the inherited cardiomyopathies (e.g. hypertrophic cardiomyopathy [HCM]), primary arrhythmogenic disorders (e.g. long QT syndrome [LQTS]) and familial valve diseases.

To date 1087 individuals from 643 families have enrolled, with the largest subgroup being HCM families (57%). Importantly, 40% of families have never had any genetic testing carried out suggesting a clear issue regarding access to these services. Important data has already emerged from the Registry database and contributed to key studies, such as an important health economic analysis of HCM genetic testing and a large quality of life study to examine psychosocial aspects of genetic heart diseases. A particular research focus is to assess psychosocial implications of many aspects of a diagnosis of a genetic heart disease (such as genetic testing and sudden death), allowing the development of more tailored genetic counselling-based strategies to improve such outcomes.

The National Genetic Heart Disease Registry is a unique initiative and has already emerged as an important resource for future research in genetic heart diseases.

ASGC Oral 5
CARDIAC CHAOS: A HYPOTHETICAL ABOUT CARDIAC GENETIC SERVICES, ISSUES AND CHALLENGES.

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Follow the journey of the main character, Olivia, who, in this interactive hypothetical discovers that she has an inherited cardiovascular condition (ICC) in her family. Hear from an expert panel, how genetic counsellors, geneticists and cardiologists manage her problems and discover why researchers and ethicists have become involved. As genetic testing for ICCs such as long QT syndrome and hypertrophic cardiomyopathy becomes more common, genetics professionals need to be familiar not only with the medical and genetic aspects of these conditions, but also the unique challenges faced by families with ICCs. Sudden death, a small but real risk in these conditions, can occur at any time in individuals who are unaware of their risk status. Thus, the stakes are high for members of these families, which raises many dilemmas: are the usual strategies used by genetic professionals to facilitate communication about genetic risk sufficient in these cases? Could a more proactive approach be taken that honours patient confidentiality and respects individual autonomy? How should cardiac genetic services be delivered to meet these needs?

It is hoped that this hypothetical will stimulate discussion about different models of service delivery as well as the ethical issues and practical demands of ICCs on families and health practitioners. Audience participation will be encouraged to enable participants to compare and contrast approaches to the provision of cardiac genetic services around Australasia and reflect on counselling strategies that optimize outcomes.

ASGC Oral 6
DEVELOPING A YOUTH FRIENDLY MODEL OF GENETIC COUNSELLING

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Evidence suggests that healthcare professionals trained in either adult or paediatric models of care find it difficult to provide adolescents and young adults (AYAs) services which meet their developmental and healthcare needs. Genetic counselling is no exception and anecdotal evidence suggests that it is particularly difficult

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for these professionals to provide adolescent care which meets the expectations of both clients and the counsellor. AYAs present for genetic counselling at a time when they are already grappling with the developmental challenges of adolescence. Additional anxiety due to the potential risk of a genetic disease during this life stage may overwhelm the coping resources of young people. A lack of specific models of genetic counselling and counselling strategies for working with young people who are psychosocially vulnerable compromises the quality of genetic counselling and care received by AYA clients accessing such services.

To address this problem a reference group was formed to develop a model of AYA specific genetic counselling. This group comprised experts in adolescent health and genetic counselling practice and research. A literature review was undertaken following which a youth friendly model of genetic counselling was developed. This model will be presented with particular emphasis on genetic counselling practice when working with AYAs.

ASGC Oral 7
PARTNERSHIP BETWEEN GENETIC COUNSELING AND PSYCHOLOGICAL RESEARCH: IMPLICATIONS FOR BOTH PARTNERS

S. Shiloh[1]

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The partnership between genetic counselling and psychology is unique and productive. The definition of genetic counselling embodies several key psychological processes: communication, comprehension of complex constructs like risk, choice and decision making, coping and adjustment. Genetic counselling is a rich naturalistic setting in which real life issues are discussed and core psychological processes take place, but, unlike other real life situations that tend to be chaotic, genetic counselling is relatively more structured and therefore more suitable for controlled research. This is a major asset for research psychologists whose findings are often criticized for lack of clinical validity. On the other hand, genetic counsellors often express a need for theoretical concepts and models to describe, explain, and guide their work, rather than relying solely on their clinical intuitions and judgments, as good as they often are. Academic psychology fulfils this need. I will present a few findings from my studies pertaining to risk perception and decision making as examples to support these arguments. I will also point to some implications that can be drawn from such research to psychology and genetic counselling.

ASGC Oral 8
ATTITUDES OF ADULTS WITH CYSTIC FIBROSIS TOWARDS POPULATION-BASED CYSTIC FIBROSIS CARRIER SCREENING

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Cystic fibrosis (CF) is the most common inherited, life-shortening condition in Australia, affecting 1 in 2,500 people. Most carriers are not aware of their carrier status until they have a child with CF, and thus do not have the option to make informed reproductive decisions. Population-based CF carrier screening is possible, however, a publicly funded program does not exist in Australia. Success of screening programs has been found to be dependent on acceptance by the communities involved, and consultation with stakeholders is important in this process. We ascertained the views held by 152 adults with CF attending a single institution in Victoria (52% response rate). A purpose designed questionnaire was used to assess experience of CF, knowledge of CF genetics, personal use of genetic counselling and testing, and how these views may influence their attitudes toward population-based CF carrier screening. A very high (93%) acceptance of population-based CF carrier screening was observed. Acceptance of preimplantation genetic diagnosis and prenatal diagnosis were associated with support for CF carrier screening. Participants not supportive of CF carrier screening had concerns about limited resources, reducing the motivation for improving treatment, and the potential to devalue the lives of individuals with CF. Overall, the majority of participants were supportive of screening regardless of their perception of CF severity or their progression with the disease. These findings may inform the implementation of carrier screening programs, not limited to CF carrier screening.

ASGC Oral 9
PANEL DISCUSSION ON CASCADE TESTING FOR CYSTIC FIBROSIS - THE FAMILY PERSPECTIVE

Dr David Jessup

Abstract Not Received at Time of Printing

ASGC Oral 10
COUNSELLING ISSUES RELATED TO PRENATAL DIAGNOSIS/CELL-FREE FETAL DNA

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This session will review counselling issues related to noninvasive prenatal testing utilizing detection of cell-free fetal DNA (cffDNA) in maternal serum. The speaker will discuss the experience of a busy perinatal genetics service in the US that has offered this form of prenatal testing for aneuploidy for several months.

ASGC Oral 11
GENETIC CARRIER TESTING IN HEALTHY SIBLINGS: INVESTIGATION OF CURRENT PRACTICE AND HEALTH PROFESSIONALS' VIEWS

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A set of guidelines has been developed by the HGSA to help health professionals decide when genetic testing in children is appropriate. In relation to carrier testing in healthy children who have siblings with genetic disorders, the guidelines suggest testing should only occur when the information will help provide medical benefit to the child in the immediate future. These guidelines are recommendations rather than regulations and it is unclear how they are interpreted and used in clinical practice.

In order to determine the current practices relating to carrier testing in healthy children in genetic services around Australia, in-depth interviews are being conducted via telephone with key experienced genetic health professionals in each State and Territory. This paper will present the current practices and views of these genetic counselors and clinical geneticists. Preliminary data suggests that the facilitation of carrier testing in healthy children by genetic health professionals varies between genetic services and States. Although the HGSA guidelines are taken into account, practice is also guided

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by the experience and views of the senior clinicians within the service as well as relevant literature in the field.

This exploration of current practice in genetic services around Australia is the first step in promoting a comprehensive discussion about the most appropriate way to manage parental requests for carrier testing in children.

ASGC Oral 12
SHOULD WE BE OFFERING WOMEN A CHOICE OF THE TYPES OF CHROMOSOME CONDITIONS THEY WANT PRENATALLY DIAGNOSED?

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Background: Women who have prenatal diagnosis currently receive abnormal results that include conditions spanning a large range of clinical outcomes, yet most of these women believe they are having a diagnostic test for Down syndrome.

Objective: To determine if women, who had Down syndrome screening in their current pregnancy, would choose prenatal diagnosis for other types of chromosome conditions based on short descriptions of possible clinical outcomes.

Method: A survey based on the Theory of Planned Behaviour. The types of chromosome conditions included: Down syndrome, Klinefelter syndrome, Triple X syndrome, and mosaic trisomy 20. Outcome measures were: women's intention to test, their attitude (behavioural beliefs), other people's influence (normative beliefs), and their ability to have the test (control beliefs).

Results: Women's intention to have a prenatal diagnostic test decreased as the severity of the clinical outcome decreased. The strongest unique belief predictor of an intention to test for Down syndrome was having an opportunity to terminate an affected pregnancy (behavioural belief); for Klinefelter syndrome it would make it easier to test if they had information about the accuracy of the test (control belief); for Triple X syndrome it was their partner's positive influence (normative belief); and for mosaic trisomy 20 they would test because of the range of clinical outcomes (behavioural belief).

Conclusion: These results suggest that women may prefer to choose the specific conditions for which they have prenatal diagnosis, whilst the unique belief predictors of intention to test highlight issues relevant to pre-test counselling.

ASGC Oral 13
EXPLORING BELIEFS ABOUT CAUSES AND HEREDITABILITY OF MAJOR DEPRESSIVE DISORDER AMONG CHINESE AUSTRALIANS

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The aim of this study was to explore causal attributions and beliefs about hereditability of major depressive disorder (MDD) among Chinese Australians with a family history of depression. A qualitative and ethnographic approach was most suitable for this topic, as it is an unexplored area of study. Face-to-face interviews with Chinese Australians were conducted guided by an interview schedule which included questions on causal attributions of MDD and the perceived hereditability of MDD, as well as an acculturation survey and a family history screen for depression. A total of 16 participants (11 females, 5 males) with a family history of MDD were recruited. Participants simultaneously held a mixture of traditional folk beliefs and scientific biomedical explanations of MDD. Common causal attributions of MDD related to stressful life events, academic pressure from parents, and a pessimistic personality or negative coping mechanisms. Commonly held beliefs surrounding the causes of MDD affecting multiple family members were a shared family environment and a 'contagion effect'. Highly acculturated participants were more likely to believe in genetic causes of MDD as well as 'chemical imbalances' in the brain, and were less likely to hold perceptions of stigma surrounding mental illnesses. Finally, mental health services are currently underutilised by Chinese Australians. The findings of this study should be taken into consideration when discussing MDD diagnosis with Chinese patients. A greater understanding of alternative belief systems in mental health practitioners will lead to greater cultural competence in the mental healthcare system.

ASGC Oral 14
COPING

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Helping clients cope with a genetic condition or a genetic risk in their family is one of the main goals of genetic counselling. The quest for understanding coping with stress in general and with illness in particular – including genetic conditions – has produced a large field of theoretical and empirical knowledge. A brief review of the main concepts and the most relevant theoretical approaches will be followed by a few findings from my own research on genetic counselling relating to the role of perceived personal control as a coping-related outcome of genetic counselling. Data on individual differences in coping styles, particularly information seeking strategies, and their relationship to interest in genetic testing will be presented and issues related to the functions of coping will be addressed. Parallel coping processes - danger control versus fear control - and interactions between them will be discussed within the framework of the Self-Regulation Model (Leventhal, 1970).

Selected Free Communications
Session 5A
Oral 1
MITOCHONDRIAL DEFECTS IN RETT SYNDROME

W.A Gold[1], S.L. Williamson[1], S. Kaur, S[1,3], J.H Gibson[1], G.J Pelka[2], I.P Hargreaves[5], J.M Land[5], P.P.L Tam[2], J. Christodoulou[1,3,4]

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Rett syndrome (RTT) is a severe neurodevelopmental disorder, predominantly caused by mutations in the X-linked Methyl-CpG-binding protein 2 (*MECP2*) gene. RTT patients share a number of common clinical features with primary mitochondrial respiratory chain (RC) disorder patients, in addition to the abnormal neuronal mitochondrial morphology and RC function which have previously been identified in RTT patients.

We have shown evidence of RC gene dysfunction in post mortem brains of RTT patients where the mitochondrial cytochrome c oxidase I (*MTCO1*) gene was down-regulated. Mitochondrial abnormalities were also detected in the skeletal muscle from the RTT

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Mecp2^{tm1Tam} mouse model. RC enzyme activity in COII+III and COIV, complexes as well as reduced glutathione levels were significantly reduced in symptomatic mice. Microarray analysis of symptomatic mouse samples revealed a down-regulation of the nuclear encoded gene, cardiolipin synthase (*Crls1*), which codes for a protein crucial for the formation of RC super-complexes. Proteomic studies have not shown any alterations in CRLS1 expression in whole cell lysates and so we are currently examining CRLS1 expression in mitochondrial enriched lysates.

Our findings suggest that mitochondrial abnormalities in skeletal muscle may well be contributing to the pathogenesis of RTT, possibly through the dysregulation of *CRLS1*. This could in turn affect the organization and stability of RC super-complexes, and/or through the accumulation of free radicals as evidenced by the decrease in reduced glutathione. Free radical accumulation has been implicated in a number of neurological disorders and potentially, maybe a novel target area of future RTT therapeutic regimens.

Oral 2
GENOME-WIDE ANALYSIS USING NEXT-GENERATION SEQUENCING FOR DISEASE-GENE IDENTIFICATION IN GENETICALLY HETEROGENEOUS EYE DISEASES

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There is marked genetic heterogeneity in many ocular disease including developmental eye conditions such as microphthalmia, as well as diseases affecting the retina. While causative genetic factors are known in some cases, there are many patients and families with no known underlying disease gene. Next-generation sequencing provides a key advance in determining structural and sequencing variants on a genome-wide scale. In patients and families with genetically heterogeneous eye disorders, we are using mate-paired-end-tag and exome target enrichment next-generation sequencing strategies to facilitate disease-gene identification. In balanced chromosomal rearrangement patients we have detected a novel candidate disease gene affecting the development of the eye, and another leading to retinitis pigmentosa. Using exome sequencing we have successfully identified disease genes in three patients with developmental eye disease. This work underlines the utility of combined genome-wide structural and exomic analyses for disease gene identification in genetically heterogeneous conditions affecting the eye.

Oral 3
PITFALLS AND SUCCESSES OF EXOME SEQUENCING: MUTATIONS IN A NOVEL GENE CAUSE WALKER-WARBURG SYNDROME AND DEFECTIVE GLYCOSYLATION OF α-DYSTRGOGLYCAN

T. Roscioli[1,2], E-J. Kamsteeg[1], K. Buysse[1], I. Maystadt [3], J. van Reeuwijk[1], C. van den Elzen[1], E. van Beusekom[1], M. Riemersma[1,4], R. Pfundt[1], L.E.L.M. Vissers[1], M. Schraders[5], U. Altunoglu[6], M.F. Buckley[1,2], H.G. Brunner[1], B. Grisart[3], H. Zhou[1], J.A. Veltman[1], C. Gilissen[1], G.M.S. Mancini[7], P. Delrée[3], M.A. Willemsen[4], D. Petković Ramadža[8], D. Chitayat[9,10], C. Bennett[11], E. Sheridan[11], E.A.J. Peeters[12], G.M.B. Tan-Sindhunata[13], C.E. de Die-Smulders[14], K. Devriendt[15], H. Kayserili[6], O. Abd El-Fattah El-Hashash[16,17], D.L. Stemple[18], D.J. Lefeber[4,19], Y-Y. Lin[18], H. van Bokhoven[1]

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We present the results of homozygosity mapping in combination with exome sequencing identifying mutations in a novel gene as a common cause of Walker-Warburg syndrome (WWS) in addition to common false negative negative findings in next generation sequencing. WWS is an autosomal recessive multisystem disorder characterized by eye and brain abnormalities with congenital muscular dystrophy and aberrant α-dystroglycan (αDG) glycosylation. Thirty WWS patients were genotyped using the Affymetrix GeneChip Human Mapping 250K SNP NspI Array to identify copy number variants and homozygous regions. Three homozygous deletions affecting the candidate gene were detected. Concurrently, a shared a 3.5 Mb homozygous region of chromosome 7p21 containing ten genes was identified in another family. Exome sequencing and filtering based on an autosomal recessive model identified a single homozygous variant in this region of shared homozygosity. This c.647C>A transversion predicting a p.Ala216Asp substitution, showed complete segregation in the family. Additional identified mutated alleles are reported. Knockdown of the zebrafish homologue recapitulates the entire human WWS phenotype and shows hypoglycosylation of αDG. These results implicate a role for this gene in αDG glycosylation to maintain sarcolemma integrity in vertebrates. The bacterial homologue is a nucleotidyl transferase belonging to a large glycosyltransferase family, but its role in chordates is not fully understood as they lack the corresponding biosynthesis pathway.

Oral 4
MUTATIONS IN *PRRT2* CAUSE BENIGN FAMILIAL INFANTILE EPILEPSY AND INFANTILE CONVULSIONS AND CHOREOATHETOSIS SYNDROME

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Benign familial infantile epilepsy (BFIE) is an autosomal dominant seizure disorder in which seizure onset occurs at around 6 months of age and offset by 2 years of age. In some cases an adolescent onset movement disorder, paroxysmal kinesigenic choreoathetosis (PKC), follows: this is known as infantile convulsions and paroxysmal choreoathetosis (ICCA) syndrome. Both disorders map to a locus at chromosome 16p11.2-q12.1. Recently, mutations in the gene *PRRT2* located at 16p11.2 were identified in patients with PKC. This finding suggested that mutations in *PRRT2* might also cause BFIE and ICCA. To confirm this hypothesis, we screened thirty-six unrelated BFIE or ICCA patients for mutations in the coding regions of *PRRT2* by direct sequencing. Family members of mutation-positive patients and controls were tested by sequencing, high-resolution melting analysis or a mutation-specific assay. Mutations in *PRRT2* were identified in 30/36 (83%) patients with BFIE or ICCA. Five different mutations were identified: a recurrent insertion mutation present in 26 families and four private mutations. All mutations segregated with the phenotype in families and were not observed in controls. Mutations in *PRRT2* are the major molecular cause of BFIE and ICCA. *PRRT2* codes for a protein of unknown function with high expression in the brain and represents a new gene family involved in the pathogenesis of epilepsy. This finding resolves a long-standing question in epilepsy genetics, as the chromosome 16 BFIE and ICCA locus has been known for many years without the gene being identified.

Oral 5
GENOME-WIDE ANALYSIS OF SEQUENCE VARIATION UNDERLYING TISSUE-SPECIFIC TRANSCRIPTION FACTOR BINDING AND GENE EXPRESSION

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Recent studies have established that transcription factor binding can vary significantly between normal individuals, and that the majority of this variation is due to naturally occurring genomic variability, such as single nucleotide polymorphisms (SNPs). However, there are few examples where the exact functional effect of these SNPs has been analysed in detail.

We analysed genome-wide differences in the occupancy of Scl, a member of the pentameric erythroid-specific transcription factor complex, in erythroid cells from three individuals. Over 1% of sites were found to have differential occupancy between individuals. Interestingly, analysis of these variable Scl binding sites identified several examples of sequence polymorphisms lying over 100bp away from the cognate binding site. In order to understand the functional effect of such polymorphisms, we analysed one example in detail, lying within a ubiquitously-expressed gene called *NME4*.

One sequence variant within this gene results in recruitment of Scl and the pentameric complex, and as a result an erythroid-specific transcript of *NME4* (termed *eNME4*) is expressed. However, the other sequence variant results in the complete loss of all transcription factor binding and expression of *eNME4*. In this situation however, the causative polymorphism lies 65 base pairs upstream of the canonical Scl binding site. Importantly, the sequence of this SNP has no effect on *NME4* expression in non-erythroid tissues.

This provides an example of the tissue-specific effects which can arise from common variation, and highlights the importance of carrying out functional characterisation of common non-coding polymorphisms associated with disease risk in clinically relevant tissues.

Oral 6
THE WHOLE EXOME SEQUENCING APPROACH TO IDENTIFY NOVEL GENES IN MITOCHONDRIAL RESPIRATORY CHAIN DISORDERS

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Mitochondrial respiratory chain (MRC) disorders are a heterogeneous group of disorders due to mutations in either mitochondrial or nuclear encoded genes. Identification of causative mutations is important not only for diagnosis but also to understand the pathogenesis of these disorders. We have studied a family where consanguineous parents have had two affected children, both deceased by the age of 6 months. They had seizures, hypotonia, elevated blood and CSF lactate levels, a dramatic combined OXPHOS defect, and very marked mtDNA depletion in muscle, all indicative of a MRC disorder. We undertook whole exome sequencing in this family and the data revealed a candidate set of 35 genes. As the patient suffered from mitochondrial depletion, we focussed our data mining on variations in genes involved in mitochondrial DNA synthesis. This analysis revealed a homozygous missense mutation which leads to a substitution of an arginine to cysteine in a gene involved in the pre-mRNA splicing machinery. Sanger sequencing confirmed the variation to be homozygous in the affected siblings and heterozygous in the unaffected sibling and parents, and not listed as a common polymorphism in the dbSNP database (heterozygosity 0.002). The mutation lies in an important functional domain which is highly conserved down to *Drosophila*. One of the binding partners of this gene product has been implicated to have a role in mitochondrial biogenesis. Further

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studies are under way to investigate the expression level, stability and functionality of the putative mutant protein and its effect on mitochondrial DNA synthesis.

Oral 7
DELETION OF A NOVEL PHOSPHATASE RESULTS IN A RETT SYNDROME-LIKE PHENOTYPE

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Rett Syndrome (RTT) is a neurodevelopmental disorder principally caused by mutations in the transcriptional regulator, methyl CpG binding protein 2 (*MECP2*). Defects of the murine *Mecp2* gene recapitulate the RTT phenotype in the mouse.

We performed Comparative Genomic Hybridization (CGH) microarray analysis of twins with a RTT-like phenotype, previously shown to be negative for a *MECP2* mutation and identified a *de novo* chromosome 2 deletion that encompasses a phosphatase gene. In *Drosophila,* deletion of this gene, which serves as a phosphatase, results in aberrant neuronal circuit/axon development and maturation. Additionally, homozygous deletion of this phosphatase in mice causes impaired motor co-ordination and abnormal cerebellar synaptic plasticity.

We found significantly reduced transcript levels of this novel gene in cerebellum, hippocampus and cerebral cortex, in both presymptomatic and symptomatic *Mecp2*$^{-/y}$ mouse brain samples, compared to wild type controls. Chromatin immunoprecipitation (ChIP) studies are under way to determine if a direct MeCP2 mediated interaction exists with the promoter of this phosphatase. In addition, sequencing of *MECP2* mutation-negative RTT patients for mutations in this novel gene is being undertaken.

The apparent phenotypic similarity between the knockout mice lacking this novel phosphatase and those lacking Mecp2 suggests involvement of these genes in similar biological processes in the brain. Furthermore, the altered expression of this novel gene in the *Mecp2*$^{-/y}$ murine brain points to a direct molecular interaction between these genes. Taken together, our results suggest that the deletion of this phosphatase may be a contributing factor to atypical RTT manifestation.

Oral 8
MUTATION IN *STXBP5L* ASSOCIATED WITH AN EARLY ONSET NEURODEGENERATIVE DISORDER

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We report siblings of consanguineous parents with an early onset neurodegenerative disorder characterised by severe axonal neuropathy, optic atrophy and cognitive deficit, in association with epilepsy in one child and congenital glaucoma in the other. We used homozygosity mapping to identify an approximately 12 Mbp interval on chromosome 3q13.13-21.1, identical by descent (IBD) in the siblings with LOD score 2.31. All coding exons, microRNA and conserved sequences (based on elements with LOD > 50 from the 28 way Vertebrate Multiz alignment track from the UCSC genome browser) totalling approximately 1 Mbp of the IBD interval were enriched from genomic DNA of a single affected individual using array based sequence enrichment. The enriched DNA was sequenced using Roche GS FLX Titanium pyrosequencing and resulting data mapped to the human genome. 1533 homozygous sequence variants were identified in the IBD interval and those localized to coding sequences were filtered against dbSNP130 to reveal a single, unique, missense variant in syntaxin binding protein 5-like (*STXBP5L* c.3127G>A, p.Val1043Ile [CCDS43137.1]). The product of *STXBP5L* (Tomosyn-2) is an as yet uncharacterised protein expressed in the central and peripheral nervous systems. The closely related STXBP5 (Tomosyn-1) protein is known to inhibit neurotransmitter release by preventing the formation of the SNARE complexes between synaptic vesicles and the plasma membrane. This suggests a potential role of STXBP5L in neurotransmitter transport or release. Collectively, our clinical, genetic and molecular data suggest that mutation in *STXBP5L* provides a plausible explanation for this rare neurodegenerative disorder.

Session 5B
Oral 9
CHANGING CLINICAL INTERPRETATION OF CHROMOSOMAL MICROARRAYS OVER TIME

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Chromosomal microarray (CMA) is the first-line diagnostic test for individuals with intellectual disability, autism or multiple congenital anomalies, with a 10-20% diagnostic yield.

An ongoing challenge for the clinician and laboratory scientist is the interpretation of variants of uncertain significance (VOUS) - usually rare, unreported genetic variants. Laboratories differ in their threshold for reporting VOUS, and clinical practice varies in how this information is conveyed to the family and what follow-up is arranged.

Various workflows, websites and databases are constantly updated to aid the interpretation of VOUS. There is a growing literature reporting new microdeletion and duplication syndromes, susceptibility and modifier copy number variants (CNV). Diagnostic methods are also evolving with new array platforms and genome builds.

In 2010 67 high-resolution arrays (Affymetrix 2.7M Oligo and SNP, 50kB resolution) were performed on a community cohort of individuals with undiagnosed intellectual disability. 301 CNV were detected and analysed using contemporary resources and a simple scoring system. 14 (21%) of the arrays were assessed as pathogenic, 2 (3%) as benign and 51(76%) of uncertain clinical significance.

The CNV were re-analysed in 2012 using the contemporary interpretative resources. There was a statistically significant difference in the assessment of individual CNVs ($p < 0.0001$). An additional 7 patients were reassessed as having a pathogenic array (n = 21,

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31%) and several additional susceptibility and modifier CNV were reported.

This study highlights the complexity involved in the interpretation of CMA and that it can be subject to change over time. We discuss clinical and genetic counselling implications.

Oral 10
MANAGING THE RISKS WITH SURGERY: THE EXPERIENCES OF NZ WOMEN WITH A FAMILY HISTORY OF BREAST AND OVARIAN CANCER

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Hereditary breast and ovarian cancer syndromes are rare genetic disorders conferring a significant lifetime risk of developing breast and/or ovarian cancer. Women with a strong family history of breast and ovarian cancer, particularly those who carry a BRCA gene mutation, may opt for risk reducing surgery to very substantially reduce the risk of developing breast or ovarian cancer.

This paper draws on qualitative interview data from a group of thirty-two Pakeha New Zealand women living with an increased risk of breast and ovarian cancer. Fifteen women had had bilateral salpingo-oophorectomy and four had had bilateral mastectomy, with other women planning surgery.

Many of the New Zealand women interviewed for this study expressed a matter of fact and pragmatic approach to managing their risk, particularly when it came to managing their risk of ovarian cancer by means of risk reducing salpingo-oophorectomy. However, while they were prepared to have the surgery, in order to "get on with" their lives and to *be there* for their children, they voiced a number of concerns. This paper discusses the experience of managing the risk of ovarian and breast cancer through risk reducing surgery, considering the impact of the surgery on the identity of these women as women, mothers and partners. The language used by the women suggested a distancing or separating of themselves from parts of their body that are perceived as dangerous. This is compared with the language some of the women reported that their medical professionals used when discussing salpingo-oophorectomy with them, language that suggested that ovaries are simply dispensable body parts.

Oral 11
RECEIVING ENZYME REPLACEMENT THERAPY FOR A LYSOSOMAL STORAGE DISORDER; EXPLORING THE EXPERIENCES OF YOUNG PATIENTS AND THEIR FAMILIES

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For some inborn errors of metabolism such as lysosomal storage disorders (LSDs) medical intervention becomes part of life, shaping the reality of the condition for patients and families. In recent years, enzyme replacement therapy (ERT) has become available to treat some LSDs. ERT is costly and demanding, requiring frequent hospital visits to receive replacement enzymes through intravenous infusion. This qualitative study sought to explore the influences of receiving ERT for an LSD on the health related quality of life (HRQoL) of young patients and their families. Semi–structured interviews were conducted with young people and parents and siblings of young people accessing ERT for Pompe disease, Gaucher disease or mucopolysaccharidosis types I or II. Fifteen interviews were transcribed then analysed by thematic analysis. Use of the biopsychosocial model assisted in interpreting emerging themes. Findings revealed patients and families had positive attitudes towards ERT, noticing improvements in physical health and psychosocial well-being. Participants prioritised intervention over other activities and provided suggestions for improving current service delivery. Open communication with other family members and health professionals was deemed important, especially in respect to provision and transfer of information, this has significant clinical implications for working with the population. Participants recalled stressful events and challenges that arose in relation to living with an LSD and receiving ERT. Various coping strategies were described, such as positive thinking and ways of managing uncertainty. These findings provide valuable insights into the influence of living with a chronic genetic condition and receiving intensive regular treatment on HRQoL.

Oral 12
THE EXPERIENCES OF PARENTS OF CHILDREN WITH DEVELOPMENTAL DELAY, AUTISM OR INTELLECTUAL DISABILITY WHO RECEIVE AN *FMR1* GREY ZONE RESULT

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The *FMR1* gene, initially identified for its role in causing FXS, is now understood to have a broad spectrum of related conditions. The promoter region of this gene contains a CGG repeat, which is normally repeated 6-44 times. *FMR1* alleles can be divided into four categories on the basis of repeat size. Grey zone (GZ) alleles (45-54 repeats), which overlap the boundary between normal and pre mutation (PM) alleles (55-200 repeats), are associated with some instability and a small chance of expansion to PM alleles. A recent audit of *FMR1* genetic testing in Victoria indicated that although the focus of *FMR1* testing was diagnosis of FXS and identifying PM carriers, individuals with GZ alleles were also identified. Some individuals tested due to developmental delay, intellectual disability or autism were found not to have FXS but to carry GZ alleles. This was a qualitative study exploring the experiences of parents of children who have received an *FMR1* GZ result. Transcripts from 9 semi structured interviews were analysed using thematic analysis. Uncertainty was highlighted as a central component of parent's experiences. In some instances parent's interpretations of the results differed from what they had been told in clinic. Parents faced concerns about the impact of the results on their other children and on how to communicate this information to family. The results indicated that an *FMR1* GZ result was not insignificant for families and that they require support in understanding and communicating this information. This study highlights the need for further research into families' interpretation of uncertain or equivocal results.

Oral 13
ALLOPURINOL AND S-ADENOSYLMETHIONINE THERAPIES FOR LESCH NYHAN DISEASE: MALAYSIAN EXPERIENCE, INCLUDING A GIRL.

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Four Malay children, a girl and three boys from two maternally-related families, and a 21-year-old unrelated Malaysian Chinese

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man, were diagnosed with Lesch-Nyhan disease (LND). The four children had the same HPRT1 mutation of the gene (IVS8-1G>A) and all exhibited classic LND features, but differed in the penetrance of the disease, especially the severity of dystonia and the age of onset of self-mutilation behavior (from 1.5 to 6.5 years). We noted that in three of the four children, onset of self-harming behaviour followed commencement of allopurinol therapy, even in the boy who had late-onset of the disease. We propose that there may be a mechanism for exacerbating some LND features involving accumulation of abnormal orotidine and oxypurinol nucleotides. We suggest that febuxostat could be trialed in LND in lieu of allopurinol. We also trialed S-adenosyl-methionine (SAMe) therapy in all five patients and were struck by the significant reduction of self-injury and aggressive behaviour: this aspect of the SAMe response was greatly beneficial in alleviating the stress of this devastating neurological disorder for the patients and their carers. There was also a noticeable reduction of dystonia. This is the first report of LND children trialed on SAMe therapy, and the results are encouraging. SAMe therapy has been encouraging for a related purine disorder, PRPP synthetase deficiency (Arts syndrome). By its nature, reports of therapies on very rare diseases are by nature anecdotal, but we feel that SAMe therapy for LND warrants further studies.

Oral 14
COMPLEMENTATION BETWEEN SPECIFIC PHENYLALANINE HYDROXYLASE (*PAH*) MISSENSE MUTATIONS AND CORRELATION TO CLINICAL PHENOTYPE IN PHENYLKETONURIA (PKU)

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PKU, an autosomal recessive inborn error of phenylalanine metabolism, is predominantly caused by mutations in the *PAH* gene, and shows marked genetic heterogeneity. Most PKU patients are compound heterozygotes for two distinct mutations. Genotype-phenotype correlations are hampered by complex interactions between protein subunits arising from the two different alleles. *In vitro* studies of missense mutations show a strong correlation between enzymatic activity and clinical phenotype. However, these have mostly been carried out with only a single mutation at any instance, being more reflective of a homozygous genotype.

We expressed thirteen different missense mutation pairings from our patient cohort in a COS-7 cell line, measuring enzymatic activity in the pairing as well as for each of the individual mutations making up the pair. Positive complementation (enzymatic activity in the pairing being greater than the average of the individual mutations) was observed in six of the thirteen pairings.

Comparison between the *in vitro* enzymatic activity and clinical phenotype of the patients showed varying predictive value. In particular, the pairing p.I65T and p.R408W showed marked increase in enzymatic activity relative to the average of the activities of p.I65T and p.R408W alone, approaching that associated with a mild PKU phenotype. However, a patient with this genotype had classical PKU. For other pairings the results more accurately matched clinical phenotypes.

Complementation between missense *PAH* mutations may occur fairly frequently. Care must be taken when predicting clinical phenotype from *in vitro* expression data of single missense mutations and the possibility of interallelic complementation should be considered.

Oral 15
A GENETIC APPROACH TO THE PROBLEM OF MONITORING KIDNEY TRANSPLANT REJECTION

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The surveillance of transplanted organ health, particularly to detect the onset of transplant rejection, is essential for the long-term survival of organ transplant recipients. The mainstay of monitoring is the 'gold standard' histological assessment of regular so-called protocol biopsies and biopsies prompted on clinical grounds. This is not ideal as biopsies are invasive and have the potential for secondary complications. Therefore, development of a sensitive, non-invasive test that may be used on a daily basis has been identified within the field as the highest priority research need. We are developing a novel and extremely simple diagnostic test, which can be used frequently with a small volume of blood sample. Our test is based on copy number variants (CNV), which are a major type of genomic variation that exists in everyone's DNA. These CNV markers can be used to distinguish recipient and donor DNA in plasma samples. We hypothesise that rejection elicits release of DNA from the transplant organ into the recipient's plasma as a result of apoptosis and/or necrosis and transplant organ health can be monitored by measuring the level of donor DNA in plasma. As a proof of principle approach, we used plasma samples from rejection and stable transplant recipients to demonstrate the presence of donor DNA in recipient plasma samples. We identified several informative markers for each sample and successfully detected significant amounts of donor DNA in rejection samples. Currently we are performing a validation study to assess the performance of our proposed non-invasive 'Organ-Health' assay, which will hopefully provide an early warning for organ rejection.

Oral 16
MOUSE MODELS OF HUMAN SKELETAL DYSMORPHOLOGIES

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Birth defects are structural or biochemical abnormalities that are present at birth, and are the leading cause of infant morbidity and mortality, affecting 3-5% of live births. Approximately one third of all congenital abnormalities involve the craniofacial structures, where they are frequently associated with other clinical characteristics such as defects in the limbs and/or other organ systems. Mouse N-ethyl-N-nitrosourea (ENU) mutagenesis screens have proven to be an invaluable tool for the functional identification of novel disease genes, and to underpin our studies on the genetic control of morphogenesis and congenital malformation in humans we undertook a comprehensive recessive mutagenesis screen to identify novel mouse models of human dysmorphology. We have identified a number of ENU mice that recapitulate phenotypes often seen in humans. BFB mutant mice mimic the human condition Fraser syndrome (OMIM 219000), and exhibit phenotypes including cryptothalmia, polydactyly and skin blisters. We have found additional phenotypes in the palate and sternum that that have not previously been reported in Fraser syndrome patients and may

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indicate the existence of undetected phenotypes in these patients. Our KANYON strain has a mid-facial cleft, variable mid-brain excencephaly and shows abnormal sternum and rib phenotypes. These phenotypes are similar to those seen in a group of conditions known as frontonasal dysplasias (OMIM 136760). Characterisation of these ENU mouse mutant strains will highlight the biochemical outcome of particular mutations and the fundamental mechanisms responsible for normal skeletal development, that will facilitate the identification of underlying mutations in corresponding human conditions.

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