

Abstracts for the 39th Human Genetics Society of Australasia Annual Scientific Meeting Perth, Western Australia August 8–11, 2015

Poster Presentations

BIOCHEMICAL GENETICS, METABOLIC AND DIET DISEASE MANAGEMENT AND NEWBORN SCREENING

1. LACTIC ACIDOSIS SECONDARY TO VITAMIN DEFICIENCY

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Thiamine and riboflavin are water soluble essential vitamins that play a critical role in energy metabolism. Thiamine pyrophosphate (TPP), the active form of thiamine, is involved in a number of enzyme complexes associated with the metabolism of carbohydrates, branched chain amino acids and fatty acids. Riboflavin is the central component of the co-factors flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD), which are involved in the metabolism of carbohydrates, lipids and proteins, are part of the electron transport chain and have an antioxidant function. We present results of biochemical genetics testing in a 4-year-old female, admitted to hospital following complications of chemotherapy for ALL. She was initially diagnosed with pancreatitis secondary to asparaginase chemotherapy, then developed a febrile neutropenia and while still unwell, developed a metabolic acidosis with lactate reaching 10 mmol/L. Her initial urinary organic acid profile showed increased lactate, branched chain amino acid metabolites, metabolites indicative of a β -oxidation defect, tyrosine and phenylalanine metabolites and an increased glutarate. Plasma acylcarnitines performed at this time were normal. When her vitamin levels were measured she was found to be deficient in thiamine (46 nmol/L, NR 67–200), Riboflavin (171 nmol/L, NR 174–471) and Vitamin B6 (32 nmol/L, NR 35–110). Following intravenous thiamine, lactate levels decreased and a second urine metabolic screen showed a decrease in the abnormal metabolites but an increased orotate excretion, possibly due to vitamin B12 or folate deficiency. Organic acid findings indicating defects in several co-factor dependent pathways should prompt investigation and treatment of vitamin deficiencies.

2. COMPARISON OF PROTEIN N-GLYCOSYLATION PROFILES AND EXPLORATION OF ASSOCIATION BETWEEN GLYCANS WITH GLUCOSE OF METABOLIC SYNDROME

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Objective: To make comparison of plasma N-glycosylation structure by age and gender as well as to explore the association between blood glycans and glucose of metabolic syndrome. **Methods:** Serum N-glycans profiles were collected from 212 residents of a certain community by High Performance Liquid Chromatography (HPLC). Two independent samples *t* test or nonparametric tests were used to compare the N-glycosylation structure between age groups divided by 35. Subjects were split into two groups according to glucose level (below 5.6 mmol/L is defined as normal) and Wilcoxon rank sum test was applied to make comparison of glycan level between two groups before impact factor analysis of glucose using logistic regression. **Results:** The average age of the 212 subjects was (37.78 \pm 17.89) years, and the sex ratio was 0.88. More digalactosylated glycans ($t = -5.91, p < .01$), trigalactosylated glycans ($t = 2.86, p < .01$), Monosialo ($t = -2.78, p < .01$), Core fucosylated glycans ($t = -3.72, p < .01$), monosialylated biantennary glycans ($t = 87.86, p < .01$) and biantennary glycans ($t = 2.86, p < .01$) were detected in younger than 35 years, whereas more non-galactosylated glycans ($t = 4.64, p < .01$), Biantennary non-galactosylated glycans ($t = 3.65, p < .01$), Trisialo ($t = 3.1, p < .01$), disialylated biantennary glycans ($t = 3.76, p < .01$), triantennary glycans ($t = 2.99, p < .01$) and tetraantennary glycans ($t = 3.1, p < .01$) were seen in 35 years and above. Galactosylation, fucosylation, Sialic glycosylation of N-glycans was significantly different ($p < .05$) between men and women: more Monogalactosylated glycans ($t = -2.06, p = .04$), Core-fucosylated glycans ($t = -2.16, p = .03$) and Monosialo ($t = -2.43, p = .02$) were detected in women, whereas more Biantennary non-galactosylated glycan ($t = 2.33, p = .02$) and Disialo ($t = 2.11, p = .04$) were seen in men. GP5, GP11 and A2 were statistically significant with OR of 0.257 (95% CI:0.098–0.678), 2.495(95% CI:1.014–6.135)and 2.655 (95% CI:1.042–6.765) respectively. **Conclusions:** The N-glycome profile

in serum is age dependent and gender dependent. GP5, GP11 and A2 are the impact factors of blood glucose.

3. EXCELLENT RESPONSE TO ENZYME REPLACEMENT THERAPY IN A PATIENT WITH SEVERE COMORBIDITIES

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Comorbidities can be an exclusion criteria for medication through the Life Saving Drugs Program in Australia. A 10-year-old girl from a non-consanguineous family was diagnosed with cystic fibrosis through newborn screening and MPS IVA (Morquio syndrome). She has had 12 months of treatment with enzyme replacement therapy (ERT) using elosulfase alfa weekly at a dose of 2 mg/kg. She had initially been excluded from the international trial due to her cystic fibrosis. She is homozygous for Δ F508 in the CFTR gene. There was no enzyme activity for N-acetylgalactosamine-6-sulphate detected on leucocytes. Each elosulfase alfa infusion was given via an infus-a-port with premedications of Cetirizine and Paracetamol. After 46 weeks of therapy she grew 0.5 cms in height, there were no changes noted in her ECG, skeletal features of MPS IV. Her glycosaminoglycans (GAG) reduced from 19 to 16 g/mol creatinine at 46 weeks of therapy. Her 3-minute stair climb improved by 24 steps (18%) and 6-minute walk test improved by 161m (86.5%). Respiratory function tests supported improved respiratory function by an increased FEV1 of 110 mLs (14%) and FVC of 80 mLs (7%). She has not required a hospital admission for more than 18 months for a chest tune-up where previously her cystic fibrosis would have been the cause of 1–2 admissions per year. Her parents have noted a dramatic increase in her level of activity. No adverse reactions were observed.

This patient demonstrates that a significant comorbidity has not stopped her benefitting greatly from ERT.

4. THE ROLE OF DIETARY MANAGEMENT IN REVERSAL OF LIVER DYSFUNCTION AND FAILURE TO THRIVE IN AN ATYPICAL CASE OF CITRIN DEFICIENCY

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Background: Citrin is a mitochondrial aspartate-glutamate carrier protein which is encoded by the SLC25A13 gene. There were previously two described phenotypes, neonatal intrahepatic cholestasis (NICCD) and citrullinemia type II (CTLN2). Recently this has expanded to include a third phenotype known as failure to thrive and dyslipidemia caused by citrin deficiency (FTTDCD). We present a 4-week-old male infant who presented with failure to thrive, prolonged hyperbilirubinemia, and other biochemical elevations suggestive of citrin deficiency. The mechanism of treatment in citrin deficiency is a lactose free diet and restriction of carbohydrate to reduce the generation of reducing equivalents when a high carbohydrate diet is administered. **Aim:** We aim to investigate reversal of faltering growth and the restoration of presenting liver dysfunction and amino acid profile. **Methods:** Structured, aggressive dietary therapy was commenced with elimination of lactose from diet, commencing on lactose-free formula along with fat supplement at 8 weeks of age; restriction of carbohydrate to 35%, protein to 20% and fat

to 45% of total energy intake when weaned off formula. **Results:** Within weeks of dietary intervention, not only was there a marked improvement in growth, reversal of liver dysfunction, reduction of galactose metabolites as well as raised amino acids; citrulline, methionine, proline and arginine respectively all to normal parameters. **Conclusion:** Dietary intervention is paramount in treating NICCD and FTTDCD patients. A protein, fat and carbohydrate (PFC) ratio of 20%:45%:35% has been effective in the treatment of this patient and in preventing the long term complications of CTLN2.

5. A MALE INFANT PRESENTING IN UTERO WITH HYDROPS FETALIS AND DYSPLASTIC KIDNEYS DUE TO PMM2-CDG (1A).

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A male baby was delivered at 37 weeks gestation via cesarian section after an antenatal diagnosis of hydrops fetalis, requiring intrauterine transfusion for fetal anemia at 32 weeks gestation, and bilateral dysplastic kidneys. At day 6 he was retrieved to the pediatric intensive care unit (PICU) due to hypertensive cardiomyopathy. The baby was generally edematous with dysmorphic facial features, bilateral inguinal hernias, micropenis and a horseshoe kidney with non-specific increased parenchymal echogenicity. The underlying cause for the baby's deterioration remained unclear during his extended stay in PICU. He exhibited persisting pericarditis, nephrotic syndrome, femoral DVT, neurological abnormalities, poor wound healing and malnutrition despite total parenteral nutrition, trophic feeds via a transyloric tube and second daily albumin transfusions. He had recurrent episodes of hypoglycemia with short fasts but it was not possible to collect blood for corresponding insulin levels due to the edema. A congenital disorder of glycosylation (CGD) was considered likely due to the complex multi-organ system involvement and presumed hyperinsulinemic hypoglycemia. Carbohydrate deficient transferrin (CDT) studies at 12 weeks of age were markedly increased and transferrin isoforms by HPLC showed a type I pattern with increased disialotransferrin and asialotransferrin and decreased tetrasialotransferrin. The clinical and laboratory findings were consistent with PMM2-CDG (1a) or PMI-CDG (1b), both disorders of N-glycosylation. Subsequent enzyme analysis of skin fibroblasts revealed a markedly reduced level of phosphomannomutase (PMM) activity, with normal phosphomannose isomerase activity therefore confirming the diagnosis of PMM2-CDG (1a) for which there is no specific treatment. The baby's condition continued to deteriorate and he died at 3 months of age.

6. AN INTERNATIONAL COMPARISON OF NEWBORN BLOODSPOT SCREENING CRITERIA: GOING BEYOND WILSON AND JUNGNER

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Newborn bloodspot screening (NBS) is an important public health initiative. Despite international adoption of NBS, no two countries' screening programs are the same. One key area causing this difference is the criteria used to assess conditions for inclusion or exclusion in NBS programs. There is value in understanding these

differences to contribute to the academic literature in this field, but also to provide essential information which supports best practice policy development. In this study we explore how conditions for NBS are assessed internationally by reviewing NBS criteria. To gain an understanding of NBS criteria, a systematic review was conducted. Five key areas that influence the assessment of conditions for NBS were identified: core criteria, scoring system, level of evidence, aim of screening, and outcome of assessment. Against these key areas, a structured comparison of policy documents from seven countries was then conducted. The comparison of the international policy documents highlights similarities and differences in the way conditions are assessed for NBS. The core criteria and scoring systems differed in the level of detail used. The types of evidence required for assessment was consistent across countries, predominantly relying upon systematic reviews combined with expert opinion. Most countries have moved on from considering solely the benefits to the child, towards a family-centered approach. The outcome categories countries used to communicate their recommendation after assessing the criteria differed significantly. The findings of this study provide essential information to those countries in the process of developing or revising their decision making processes, including Australia.

7. NEWBORN SCREENING FOR DUCHENNE MUSCULAR DYSTROPHY IN AUSTRALIA

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Duchenne muscular dystrophy (DMD) is an x-linked recessive disorder affecting about 1 in 3,500 males. Symptoms of muscle degeneration are usually apparent by the age of 3 years and progress to premature death. While there is not yet a cure, current treatments defer the severity of symptoms with earlier treatment providing the best outcome. Diagnostic tests have been based on measurement of creatine kinase (CK), an enzyme normally present in muscle fibres which has increased levels in blood after muscle damage and is significantly elevated in DMD. For those with elevated CK, mutational analysis of the dystrophin gene confirms a diagnosis. In order to investigate the optimal protocol for newborn screening in the Australian population, CK levels were determined in 4 cohorts of samples: Cohort 1: de-identified samples collected for routine newborn screening at 48–72 hours of age from 5661 males and 5,445 females; Cohort 2: de-identified samples collected at 6–7 days of age from 82 males and 61 females; Cohort 3: de-identified samples collected at 6–12 weeks of age from 65 males and 56 females; Cohort 4: current and archival samples from 19 known DMD patients. The CK levels decreased with the age of the infant, with median levels higher in males than females at each age and elevated in patients with DMD collected during a clinic visit and from their initial newborn screening sample compared to age and sex matched control samples. Screening for DMD using CK followed by mutational analysis would allow early treatment.

CLINICAL GENETICS, NEUROGENETICS AND PRENATAL DIAGNOSIS

8. FETAL PHENOTYPE OF 17Q12 MICRODELETION SYNDROME: RENAL ECHOGENICITY AND CONGENITAL DIAPHRAGMATIC HERNIA IN TWO CASES

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17q12 microdeletion syndrome is well associated with prenatal presentation of renal pathology. Congenital diaphragmatic hernia (CDH) has recently been reported in fetuses with 17q12 microdeletion. We describe two cases of prenatally detected renal echogenicity and congenital diaphragmatic hernia. 17q12 microdeletion was confirmed in both cases using high resolution chromosomal microarray. One case involved a set of identical twins with discordant phenotype. The findings further support the association of congenital diaphragmatic hernia and 17q12 microdeletion syndrome and highlight the variable expressivity of this chromosomal deletion. Prenatal diagnosis of 17q12 microdeletion has significant implications on informed decision-making and postnatal medical management.

9. A NEW CASE OF BRAIS MYOPATHY, AND A HUNT FOR THE GENE

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We report a family who presented with excruciating, post-exercise muscle cramps, associated with above average strength and muscle hypertrophy, in the setting of a normal electromyogram. Three generations were affected and inheritance appeared to be autosomal dominant. A French Canadian cohort with a similar phenotype, so-called Strongman syndrome (Brais myopathy), were studied. The analysis focused on candidate genes associated with muscle hypertrophy. Exome sequencing of one large French Canadian family discovered a novel, potentially damaging, variant in *DCST2*. Sanger sequencing of *DCST2* in our proband, did not reveal any likely pathogenic variants. Exome sequencing of the proband did not identify variants in genes associated with hypertrophy or muscle cramps: *CAV3*, *CAPN3*, *CLCN1*, *DOK7*, *GMPPB*, *RYR1* and *SCN4A*. Data analysis of the proband and exome sequencing of relatives are presented.

10. MICRODELETION OF THE IGF2 ENHANCER REGION: A NOVEL MECHANISM FOR FAMILIAL RUSSELL-SILVER SYNDROME

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Russell-Silver syndrome (RSS) is a condition characterized by prenatal and postnatal growth retardation, dysmorphic features, and

body asymmetry. Hypomethylation of the *H19* Imprinting Centre 1 on the paternal copy of 11p15 is the underlying cause in 35–60% of reported cases. This hypomethylation leads to reduced expression of *IGF2* and bi-allelic expression of *H19*, two reciprocally imprinted genes within the 11p15 region. We report a pedigree with a number of individuals diagnosed with RSS who have a novel 11p15 microdeletion on SNP array. The deletion is located telomeric with respect to *H19* and encompasses the *TNNT3* locus. Methylation studies in the proband revealed normal methylation at Imprinting Centre 1 on 11p15.5. Further investigation revealed that the deletion had been inherited from the proband's unaffected father, who in turn had inherited it from his unaffected mother. Further affected members in this family were ascertained, all with the same paternally inherited microdeletion. We surmise that it is unlikely that loss of *TNNT3* function explains the RSS phenotype in this family, but that deletion of this region on the paternally inherited chromosome removes a long-range enhancer required for paternal *IGF2* expression. Maternal inheritance of the deletion in members of this family is not associated with an RSS phenotype, which is consistent with maternal silencing of *IGF2*. Interrogation of the region by deep sequencing is in progress to identify the genomic co-ordinates of the deletion and to obtain further evidence that dissociation of *IGF2* from its enhancer produces the RSS phenotype.

11. PERSONALIZED MEDICINE POSSIBLE WITH REAL-TIME INTEGRATION OF GENOMIC AND CLINICAL DATA TO INFORM CLINICAL DECISION-MAKING

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Over 14,000 genes are known to cause or contribute to disease and over 2,000 diagnostic genetic tests are now available. Despite widespread use of genomic sequencing in research, there are gaps in our understanding of the performance and provision of genomic sequencing in clinical practice. The Melbourne Genomics Health Alliance, a collaboration between seven Melbourne-based research and clinical organizations, was established to determine the feasibility, performance and impact of using genomic sequencing as a diagnostic tool, with the objective of demonstrating that personalized medicine through targeted genomic analysis is possible. The Alliance partnered with BioGrid Australia to enable the linkage of genomic sequencing, clinical treatment and outcome data for this project. BioGrid operates a secure federated data-sharing platform that enables real-time integration of record-level data across institutions and jurisdictions. This platform provides ethical access to data while protecting both privacy and intellectual property and importantly has the capability to provide an integrated view for the clinician as well as project wide reporting. This project has built an integrated dataset of genetic, clinical and patient survey information that has been used to evaluate the potential diagnostic value of genomic sequencing in routine clinical practice. This presentation will focus on the data linkage and sharing framework as well as key implementation challenges. This project allows the Alliance to facilitate the integration of genomic sequencing into clinical practice, and provide recommendations for subsequent implementation. This translational analysis provides the groundwork for further exploration of targeted approaches to personalized disease treatment.

12. KING–DENBOROUGH SYNDROME, DO WE KNOW THE MECHANISM?

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King–Denborough syndrome (KDS) is a rare condition characterized by dysmorphic features like Noonan syndrome and malignant hyperthermia susceptibility. The exact mechanism for this condition is not clear. Noonan syndrome is caused by mutations in genes in the RAS-MAPK pathway. Our 4-year-old male patient is one of three male siblings born to non-consanguineous couple with birth weight of 2.5 kg. He had bilateral ptosis and developed malignant hyperthermia while having anesthesia before surgery for ptosis. On examination, he has ptosis, low-set ears, webbed neck, pectus excavatum. His head circumference is just above 50th percentile, height and weight between 10th and 25th percentile. He does not have clinical evidence of heart disease and has a normal neurological examination. The father of our patient has been operated for scoliosis, but did not have facial features of Noonan syndrome. Our patient has a mutation in the *RYR1* gene c.7523G>A p. Arg2508His. His mother or siblings do not have this mutation. He has been advised about the risk of anesthesia and is being monitored for his growth and development. Although there is overlap between Noonan syndrome and KDS, no definite mechanism has been reported in causation of KDS. Although we do not have any proven explanation for the presence of Noonan like features in KDS, we postulate that the *RYR1* gene in combination with some other genetic modifier may be affecting the RAS-MAPK pathway. It is also possible that the similarity between KDS and Noonan syndrome is just a coincidence.

13. OUR EXPERIENCE WITH A TARGETED EXOME SEQUENCING PANEL TO INVESTIGATE GENETIC SYNDROMES WITH ABSENT SPEECH

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Massively parallel sequencing can be clinically implemented and iterated using various approaches. One approach is via targeted (to the phenotype) gene panels. Here we discuss our experience in using one of these panels, the 'absent speech/synophrys panel', for investigating children with dysmorphism and intellectual disability, with disproportionate speech delay within a clinical genomic diagnostic pipeline. This pipeline is embedded within the clinical service to help further address the diagnostic odyssey of families and children living with rare and undiagnosed diseases. The panel includes genes for overlapping syndromes such as Cornelia de Lange syndrome, Coffin-Siris syndrome and Kabuki syndrome. Clinical phenotyping was performed at Genetic Services of Western Australia and the samples were analysed at the Department of Diagnostic Genomics Laboratory, PathWest, WA, using massively parallel sequencing (MPS). Likely pathogenic variants were confirmed by Sanger sequencing. We have identified pathogenic mutations in 6

of 29 patients tested (21%). Adopting targeted exome sequencing panels is an approach to the stepwise implementation of clinical genomics. We will discuss the benefits and challenges arising from the clinical application of this approach and considerations for further developments to facilitate the integration of MPS into clinical genetic services.

14. DIFFERENTIATING ASYMMETRICAL OVERGROWTH SYNDROMES: A CASE STUDY

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Background: Asymmetrical overgrowth has many genetic causes with significant clinical overlap, including CLOVES syndrome, Proteus syndrome (PS), Beckwith-Wiedemann syndrome (BWS), PTEN-hamartoma syndrome (PHS), neurofibromatosis type 1 syndrome, hemihyperplasia — multiple lipomatous syndrome (HHML) and isolated macrodactyly (IM), often resulting in misdiagnosis. CLOVES syndrome is characterized by congenital lipomatous overgrowth, vascular malformations, epidermal nevi and scoliosis, and with HHML, forms part of the *PIK3CA*-related overgrowth spectrum (PROS). This case study aims to promote the consideration and correct diagnosis of this rare group of disorders. **Case report:** We describe a 26-month-old girl with focal overgrowth and lipomatous lesions of her left lower extremity, with epidermal pigmentation. She had a benign renal cyst, and normal intelligence and neurodevelopment. The overgrowth has not been progressive. While genetic testing was unavailable, her symptoms place her between CLOVES syndrome and HHML in the *PIK3CA* spectrum. **Discussion:** Some identifying features can help clinicians diagnose overgrowth syndromes. One feature is the natural history. Most present prenatally with proportionate progression, whereas PS presents with postnatal onset and aggressive progression. Classic signs like splaying of the feet in CLOVES syndrome, cerebriform connective tissue nevi in PS, and incidence of specific cancers in BWS and PHS also facilitate differentiation. In cases such as ours, when genetic confirmation is not easily accessible, the clinical picture can often provide clues for the discerning clinician. It is now recognized that CLOVES syndrome, HHML, megalencephaly syndromes, fibroadipose overgrowth and IM are all due to *PIK3CA* mutations and form the clinical continuum of PROS.

15. MOSAICISM FOR A PORCN MUTATION IN A WOMAN WITH GOLTZ SYNDROME

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The patient, a woman aged 27 years, was referred to the genetics clinic for reproductive counseling. She had been diagnosed at the age of 13 years by a dermatologist as having Goltz syndrome, also known as focal dermal hypoplasia. She was the only affected member of her family. She had typical features of the syndrome in her skin, teeth and nails. She was of normal intelligence. Testing of lymphocyte DNA of the *PORCN* gene at CTGT (Connective Tissue Gene Tests) in Allentown, PA, USA, showed no mutation in *PORCN*. Subsequently, a skin biopsy was taken from an affected area of the patient's left arm. Testing of the DNA extracted from the biopsy showed a c.1094G>A transition in exon 13 of the *PORCN* gene. This mutation was previously reported in association with Goltz syndrome in a female. Goltz syndrome is an X-linked dom-

inant condition and affected males are rare. Females with familial Goltz syndrome have extremely skewed X inactivation but it is less common in sporadic cases. X-inactivation studies on our patient are in progress. In sporadic cases such as the one presented here, mosaicism for a *PORCN* mutation is a more likely mechanism by which the proportion of cells carrying a *PORCN* mutation is reduced. The mutation probably arose as a post-zygotic event.

16. CONGENITAL LARYNGEAL MALFORMATION — A RARE PRESENTATION

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Background: Congenital laryngeal malformations (CLM) are rare, and include laryngomalacia, subglottic stenosis, laryngeal cleft and laryngeal webs. CLMs are associated with specific syndromes, however isolated CLM has not been previously ascribed to a Mendelian gene(s). Familial laryngeal web and deletions of 22q11.2 (with or without other features) has been described. **Case Report:** We report a four generation family with a range of CLMs. This family has been previously reported by Danks et al. (*Archives of Disease in Childhood*, 48:275, 1973). The index case is suspected of having a laryngeal cleft, given choking with eating and drinking when young. One son has a laryngeal cleft, while the other son had a laryngeal web requiring tracheostomy. Microarray analysis excluded microdeletions of 22q11.2, but identified a maternally derived 7q36.3 duplication inherited by one child. Duplications of a regulatory sequence (ZRS) located within the *LMBR1* gene in this 7q36.3 region are associated with triphalangeal thumb polysyndactyly syndrome (TPTPS) and syndactyly type IV (SD4). Aside from mild bilateral eyelid ptosis for one child, and elongated toes in the mother and both sons, there were no other distinctive clinical features. There was no abnormality on paternal microarray. **Discussion:** The pattern in this family suggests autosomal dominant inheritance, with variable presentation. We found no features consistent with TPTPS or SD4, and duplications of *LMBR1* are not expected to cause CLMs. Therefore the CNV was considered benign. We pursued exome sequencing through the University of Washington Mendelian gene discovery program. We present the findings of the exome data.

17. HOW DOES ACQUISITION OF DEVELOPMENTAL MILESTONES IN THE CDKL5 DISORDER COMPARE WITH RETT SYNDROME?

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Background: The *CDKL5* disorder is a relatively newly identified disorder caused by a mutation on the *CDKL5* gene, originally thought to be an early onset variant of Rett syndrome. Systematically collected data on the acquisition of developmental milestones is limited. **Aim:** To compare the acquisition of sitting and walking in the *CDKL5* disorder and Rett syndrome. **Methods:** Data on 127 individuals (109 females) with the *CDKL5* disorder were sourced from the International *CDKL5* Disorder Database provided they

had a pathogenic or probably pathogenic CDKL5 mutation. Data on 283 girls with Rett syndrome born since 1999 were sourced from the Australian Rett Syndrome and the InterRett databases. Kaplan-Meier time-to-event analyses investigated the occurrence of developmental milestones. **Results:** Nearly two thirds of females with the CDKL5 disorder learnt to sit independently by five years and slightly more than one quarter (29%) learnt to walk by 6 years 5 months. Approximately one third of males with the CDKL5 disorder learnt to sit by 3 years and one male (8%) learned to walk independently at 2 years. In contrast, 259 (92%) of girls with Rett syndrome learnt to sit and 46% could walk by 6 years 8 months. **Discussion:** More females with Rett syndrome acquired independent sitting and standing compared with females with the CDKL5 disorder. Males with the CDKL5 disorder had more developmental difficulties than females. The two syndromes have a different pattern of gross motor skill acquisition but there are children with particularly severe or mild presentations in each.

18. MITRAL VALVE THICKENING, MITRAL VALVE PROLAPSE, BICUSPID AORTIC VALVE AND COARCTATION OF THE AORTA IN A FATHER AND SON WITH TERMINAL DELETION OF 3P26.1 DETECTED BY COMPARATIVE GENOMIC HYBRIDIZATION MICROARRAY.

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A boy aged 1 month with coarctation of the aorta repaired at age 10 days had a CGH microarray showing a terminal deletion of chromosome 3p26.1-pter (GRCh37/hg19 93,949–4,026,397). The patient had no morphological features to suggest the 3p25 deletion or any other syndrome, developmental progress has been normal. The boy's father, who recalled he had 'a hole in the heart' as a child, has the same deletion and echocardiography showed a thickened mitral valve with moderate regurgitation and a bicuspid aortic valve. Congenital heart disease has been localized to more proximal breakpoints at 3p25 (Shuib et al., *Am J Med Genet A*, 149A:2099–2105, 2009): the aortic coarctation of a child with terminal deletion at 3p26.2 was attributed to a coexistent terminal duplication at 5q34 (Chen et al., *Genetic Counseling*, 23:405–413, 2012). Aortic coarctation was not reported in 83 patients with overlapping deletions in the DECIPHER database: most have intellectual disability and a range of physical abnormalities, while the father of our patient had normal psychomotor development. The findings in our patient's father suggest that echocardiography would have been required to detect a bicuspid aortic or left heart abnormalities in previous reports of this deletion. The CHL1, CNTN4, CNTN6, CRBN, IL5RA, LRRN1, SUMF1 and TRNT1 genes in the deleted segment are not known to be associated with cardiac disease.

19. FILAMIN A VARIANT, AORTOPATHY AND ADULT ONSET EPILEPSY.

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The Filamin A protein cross links actin filaments in the cytoskeleton and additionally binds to membrane channels, receptors, intracellular signalling proteins and transcription factors (Nakamura et al., *Cell Adhesion and Migration*, 5:160–169, 2011). This, and expression in multiple tissues at different ages and stages of development, contributes to the pleiotropic pathology involving the gene, which includes periventricular heterotopia of cerebral neurons and arterial abnormalities. Next-generation sequencing for mutations associated with aortopathy identified a hemizygous FLNA variant of unknown significance (VUS), c.7059T>G (p.Phe2353Leu) in leukocyte DNA of a 59-year-old man who had a dissecting aneurysm of the ascending aorta repaired at age 40 years. The variant was predicted to be pathogenic by analysis of the sequence on the PolyPhen2, Align GVGD, SIFT, and MutationTaster programs, while K4v predicted it to be benign. He also had a dissecting aneurysm of the brachiocephalic and left carotid artery, a pacemaker for sick sinus syndrome and adult onset epilepsy. MRI of the brain is contraindicated so whether he has periventricular heterotopia is unknown. We will describe: (a) Results of immunostaining of FLNA in the patient's cultured fibroblasts, DNA sequencing for the variant in his mother and brain MRI for his 20-year-old daughter; (b) How genetic and phenotypic characterization of the wider family and functional analysis of the cells from the proband were used in a challenging situation where complete phenotypic ascertainment is not possible in the face of a VUS.

20. A DE NOVO MUTATION IN KMT2A (MLL) IN MONOZYGOTIC TWINS WITH WIEDEMANN-STEINER SYNDROME.

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Background: A case of growth deficiency, psychomotor delay and facial dysmorphism was originally described in a male patient in 1989 by Wiedemann et al, and later in 2000 by Steiner et al. Wiedemann-Steiner syndrome (WSS) has since been described only a few times in the literature, with the phenotypic spectrum both expanding and becoming more delineated with each case reported. We report the clinical and molecular features of monozygotic twins with a de novo mutation in KMT2A. **Methods:** SNP microarray was done on both twins and whole exome sequencing was done using both parents and one of the affected twins. **Results:** SNP microarray confirmed that they were monozygotic twins. A de novo heterozygous variant (p. Arg1083*) in the KMT2A gene was identified through whole exome sequencing confirming the diagnosis of Wiedemann-Steiner Syndrome. **Conclusion:** In this study, we have identified a de novo mutation in KMT2A associated with psychomotor developmental delay, facial dysmorphism, short stature, hypertrichosis cubiti and small kidneys. This finding in monozygotic twins gives specificity to the Wiedemann-Steiner syndrome. The description of more cases of WSS is needed for further delineation of this condition. Small kidneys with normal function have not been described in this condition in the medical literature before.

21. EPIDERMOLYSIS BULLOSA: PRESENTATION OF TWO CASES AND A CLINICAL AND PATHOLOGICAL COMPARISON

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Epidermolysis bullosa (EB) is a skin disorder that is characterized by skin and mucosal membrane fragility. There are more than 30 recognized subtypes of EB and more than a dozen recognized genes. Combined, these rare conditions have an estimated prevalence of 8/million. Two cases of EB are described here; one with Herlitz-type junctional epidermolysis bullosa (JEB) and one with epidermolysis bullosa with pyloric atresia (EB-PA). Both of these disorders are inherited in an autosomal recessive manner; however, there is no history of consanguinity in either of these families and they are from different ethnic backgrounds. Skin biopsy findings and molecular genetic results are presented and contrasted, as well as clinical findings. A summary of these EB subtypes is provided.

22. NEED FOR A NEW INTERNATIONAL RARE DISEASE DATABASE: THE MECP2 DUPLICATION SYNDROME

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Background: Individuals who have two or more copies of the MECP2 gene, located at Xq28, have been found to share clinical features and a distinct facial phenotype known as MECP2 duplication syndrome (MDS). **Aims:** To provide a preliminary snapshot of MDS to inform the development of a new international database. **Methods:** The International Rett Syndrome Database (InterRett), first established in 2002, collects data on Rett syndrome and Rett-related disorders including MDS. **Results:** Data are available on 57 cases (49 males and 8 females) with MDS. Median age at ascertainment was 7.9yrs (range 1.2–37.6 years) and at diagnosis 3 years (range 3 weeks–37 years). Only 10% had an initial diagnosis of MDS. Less than a third (30%) learned to walk (median age 30 months), while 70% learned to use babble or words (median age 15 months). Speech deterioration was reported in 37% and only 20% were able to use word approximations or better at ascertainment. The majority (85%) had been hospitalized in the first 2 years of life, often because of respiratory infections. Just under half (45%) had seizures, occurring daily in half (56%) of this group. Scoliosis affected a quarter of those aged over 7 years. The majority (90%) had gastrointestinal problems and a third had a gastrostomy. Respiratory infections and sleep apnea were common. **Conclusion:** Parents and clinicians alike need to know more about this disorder, particularly the occurrence of comorbidities and their management. These data supported by consumer consultation will inform the development of a new MDS-specific international database.

23. HOW CAN WE BEST INFORM THE NEW ERA OF GENETIC TESTING? RECENT EXPERIENCE IN THE DIAGNOSIS OF RETT SYNDROME IN AUSTRALIA.

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Background: A definitive molecular diagnosis of Rett syndrome (RTT) helps families understand the cause and course of their child's condition and facilitates access to appropriate services. Yet diagnosis can still be delayed. **Aims:** Our overall aim is to develop recommendations to improve the RTT diagnostic process. **Methods:** We developed a questionnaire to investigate clinical appropriateness of MECP2 testing in Australia. We administered it to referring clinicians and requested completion prior to notification of results. **Results:** From mid-July 2011 to mid-July 2014 there were 276 referrals where a clinician could be contacted and agreed to participate. Questionnaires were completed and available for analysis on 243/276 (88.0%). Of the 243, 211(86.8%) were female and pathogenic MECP2 mutations were identified in 14.7% and in no males (12.8% positive overall). Median age at diagnostic testing was 3.9 years (range 3 months–63.7 years) and in those with a mutation 3 years (range 1 year 5 months–46 years). When clinicians thought a RTT diagnosis was very or somewhat likely there was a positive result in 13/21 (56%) females. When thought to be somewhat or very unlikely ($n = 104$ females) exclusion was the commonest reason (in 25%) for referral followed by autism (~19%), regression (16%), stereotypies or hand flapping (11%) and parental request (~5%). In 6/104 (5.7%) of 'unlikely' cases the result was positive and in 2/6 parental request was cited as the reason for the referral. **Conclusion:** With the advent of next generation sequencing panels it is important to understand the nature of target populations to guide the benefits or otherwise of new approaches.

24. MECP2 MUTATIONS RESULT IN MICROTUBULE INSTABILITY AND TRAFFICKING DEFICITS.

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Background: Rett syndrome (RTT) is a rare, severe genetic neurodevelopmental disorder, predominantly caused by mutations in Methyl-CpG-binding protein 2 (MECP2). Despite the genetic cause being identified, the neurological pathophysiology is still largely unknown. Tubulin and the microtubule network play an essential role in neuronal function whereby the acetylation state of microtubules dictates the efficiency of synaptic targeting and molecular motor trafficking of mitochondria and Brain Derived Neurotrophic Factor containing vesicles. Recent reports showing increased tubulin acetylation and microtubule instability in Mecp2-deficient cells, suggest a link between these irregularities and the neurobiology in RTT.

Aims: To investigate the changes in microtubule dynamics, microtubule-regulated mitochondrial trafficking and to determine the efficacy of the HDAC6 inhibitor, Tubastatin A in MeCP2-mutation positive cells. **Methods:** Tubulin acetylation and HDAC6 were measured in patient fibroblasts and cortical neurons from the RTT mouse model (Mecp2T158A). Mitochondrial velocity and microtubule stability was analyzed. A mouse trial was also conducted to determine the efficacy of Tubastatin A. **Results:** Reduced acetylated tubulin and increased HDAC6 were observed in both patient cells and mouse cortical neurons. Reduced mitochondrial velocity was observed in the Mecp2T158A cortical neurons and microtubule instability was shown in the patient fibroblasts. Tubastatin A restored tubulin acetylation levels in the patient fibroblasts and improved microtubule stability. Preliminary studies in the Tubastatin A treated Mecp2T158A mice showed improved motor performance. **Summary:** Tubastatin A restores the acetylation and microtubule stability defects in MeCP2-deficient cells, leading to the restoration of microtubule molecular trafficking, providing a novel potential therapeutic option for RTT.

25. PREDICTIVE GENE TESTING FOR HUNTINGTON'S DISEASE AND OTHER NEURODEGENERATIVE DISORDERS

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Background: Controversies exist around predictive testing (PT) programs in neurodegenerative disorders. **Aims:** This study sets out to answer the following questions relating to Huntington's disease (HD) and other neurodegenerative disorders: what are the differences between these patients in their PT journeys?; why and when individuals withdraw from PT?; and what are the decision making processes regarding reproductive genetic testing? **Methods:** A case series analysis of patients having PT from the multidisciplinary Western Australian Centre for PT over the past 20 years was performed, using internationally recognized guidelines for predictive gene testing in neurodegenerative disorders. **Results:** Of 740 at-risk patients, 518 applied for PT: 466 at risk of HD; 52 at risk of other neurodegenerative disorders: spinocerebellar ataxias, hereditary prion disease and familial Alzheimer's disease. 13% withdrew from PT — 80.32% of withdrawals occurred during counseling stages. Major withdrawal reasons related to timing in the patients' lives or unknown as the patient did not disclose the reason. 38 HD individuals had reproductive genetic testing: 34 initiated prenatal testing (of which 8 withdrew from the process) and 4 initiated pre-implantation genetic diagnosis. There was no recorded or other evidence of major psychological reactions or suicides during PT. **Conclusions:** People withdrew from PT in relation to life stages and reasons that are unknown. Our findings emphasise the importance of: (1) adherence to internationally recommended guidelines for PT; (2) the role of the multidisciplinary team in risk minimization; and (3) patient selection.

26. GENETICS IN PRION DISEASES

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Background: Normal prion protein isoforms transform and aggregate into a misfolded structure — the pathogenic scrapie isoform, which results in disease. Most prion diseases are sporadic; rarely are they secondary to autosomal dominant mutations in the prion

protein gene [PRNP], which usually leads to familial Creutzfeldt-Jakob disease (fCJD). **Method:** Study of the E200K mutation of the PRNP gene in a family over 15 years revealed six patients with a mean age of onset fCJD of 58.83 yrs (*SD* 7.2) with common symptoms of memory loss, difficulty walking and hallucinations. Most frequent neurologic phenomena were rapidly progressive dementia, myoclonus and ataxia. The mean duration of onset of symptoms to death was 36 months (*SD* 1.1). Two male family members developed neurodegenerative disorders unrelated to the prion mutation: progressive supranuclear palsy and olivopontocerebellar degeneration [mean survival = 96 months]. We have also observed a novel G131V mutation in a 51-year-old man with a 9-year history of dementia and ataxia with abundant prion protein amyloid plaques and spongiform degeneration. No other family members have this mutation; his only child, a 21-year-old son, has recently requested predictive testing. We have also performed predictive testing in a 67-year-old man from a family with the P102L mutation characterized by ataxia and dementia, and in two families with fatal familial insomnia (D178N). **Conclusion:** There is phenotypic variability in prion mutations, which can present with unusual clinical manifestations, including long duration dementing disease. Members of families with prion mutations might be at risk of other neurodegenerative disorders.

27. THE PATTERNS OF INHERITANCE IN EARLY-ONSET DEMENTIA: ALZHEIMER'S DISEASE AND FRONTOTEMPORAL DEMENTIA

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Background: Known genes which contribute to autosomal dominant transmission of early-onset dementia (EOD) account for only a small proportion of total genetic load for EOD. **Aim:** To examine the proportion of patients with a family history of EOD and compare this to their mutation status. **Method:** Data was collected on gender, diagnosis, age at onset, mutation status and family history of dementia on 202 consecutive patients from 2000 to 2013 with early-onset Alzheimer's disease (EOAD; *n* = 120) and frontotemporal dementia (EOFTD; *n* = 82). Family history was characterized in two ways: having any family member affected by dementia or Goldman classification. Each participant with an autosomal dominant family history had been offered genetic testing to determine their mutation status. **Results:** The majority of participants, 72.5% with EOAD and 74.4% with EOFTD, did not have a positive family history of dementia. Of those with a suspected familial component, 1.6% of EOAD and 7.3% of EOFTD, carried a known mutation. Autosomal dominant inheritance patterns were seen in 14.2% of EOAD and 13.4% of EOFTD families; in these subgroups known mutations explained 11.8% and 54.5% respectively. A patient was identified carrying two genes known to increase the risk of EOFTD: SIGMAR1 and C9orf72. **Conclusion:** EOD does not seem to be strongly inherited in an autosomal dominant pattern. The majority of patients were sporadic and did not possess mutations; known mutations do not explain the total autosomal dominant burden. Other patterns of inheritance, including mitochondrial and oligogenic, require exploration.

28. PREDICT-HD: A DECADE OF OBSERVATION

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Background: PREDICT-HD is a multicenter observational study. **Aim:** The study aimed at identifying biomarkers that might be

useful in clinical trials of prodromal patients at risk of Huntington's disease (HD). *Methods:* Hundreds of premanifest HD patients have been followed for over 10 years with annual visits involving imaging, cognitive, movement and other measures. The UHDRS motor score, MRI detected striatal volume, speeded finger tapping, self-timed finger tapping, word list learning and odour identification predict manifest HD 15–20 years prior to neurological diagnosis. *Results:* Further analyses suggest that the transformation to manifest HD may be cognitive and behavioral with an earlier diagnosis with less motor manifestations, findings which have implications for clinical intervention in HD and diagnostic management. Furthermore, growth mixture models detect mild progression without depression and rapid progression as additional subtypes, and the CAG-Age product score and gender predictors of these subtypes. *Conclusion:* This study lays the foundation for early intervention studies in Huntington's disease.

29. EXPERIENCE OF PATIENTS RECEIVING THEIR DIAGNOSIS OF MYOTONIC DYSTROPHY AS COMPARED WITH HUNTINGTON'S DISEASE

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Receiving a genetic diagnosis has the potential to be a very traumatic experience especially when the disease is incurable, likely to cause significant morbidity and may also affect other family members as is the case for myotonic dystrophy (DM) and Huntingtons disease (HD). Patients' experience of the process of receiving a diagnosis for progressive neurogenetic disease has been described in small qualitative studies but no systematic survey has been undertaken before. The purpose of this study was to survey the whole experience of genetic testing: the patients' preparation for having the test, the time of receiving the result and the follow-up after genetic testing. We predicted that factors affecting patients experience would be the staff involved, whether the test was predictive or diagnostic, whether the test had been performed a long time ago or more recently, and also demographic factors such as age and gender. 139 patients of a neurogenetic clinic with a positive diagnosis of either HD or DM were mailed the questionnaire. A similar response rate occurred in each group 26/69 (38%) in DM and 24/70 (34%) in HD. Patients diagnosed with DM had an inferior experience relative to patients diagnosed with HD. This is likely to be due to closer adherence to a standardized protocol for HD. Better results were obtained when the diagnosis was made through genetically trained practitioners. Greater flexibility around where the patients receive their results and attention to follow up are further aspects that could be improved.

30. THE IMPACT OF NON-INVASIVE PRENATAL TESTING ON ANXIETY LEVELS IN WOMEN CONSIDERED AT HIGH OR LOW RISK FOR ANEUPLOIDY THROUGH COMBINED FIRST TRIMESTER SCREENING.

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Non-Invasive Prenatal Testing (NIPT) for fetal aneuploidy is now a revolutionary option for pregnant women seeking information about the chromosomal health of their baby without the risk of miscarriage. We aimed to (1) examine the impact of non-invasive prenatal testing (NIPT) in women receiving a high risk ($\geq 1:300$) or low risk ($\leq 1:301$) result from combined First Trimester Screening (cFTS);

and (2) to examine factors influencing anxiety and decision-making in both risk populations. Questionnaires and structured interviews were administered to low ($n = 50$) and high ($n = 63$) risk women at the time of testing (point A) and one week after receiving a low risk NIPT result (point B). Anxiety levels were measured using the State-Trait Anxiety Inventory. Both high and low risk groups demonstrated similar intrinsic (trait) anxiety levels ($36 + 10$ vs. $35 + 10$; $p = .70$). High risk women had significantly higher levels of state anxiety at point A than low risk women ($42 + 11$ vs. $36 + 11$; $p < .01$). Both groups had a statistically significant reduction ($p < .01$), to similar final levels, of state anxiety at point B ($30 + 11$ vs. $29 + 8$; $p = .61$). Both groups identified elimination of the risk of procedure related miscarriage as their primary motivation for NIPT. In conclusion, both groups benefit from a decrease in state anxiety after NIPT. High risk women, who initially have higher levels of state anxiety, continue their pregnancy with similar levels of anxiety to low risk women who have a 'negative' NIPT result. Both populations considered NIPT a valuable addition to prenatal care.

31. NON-INVASIVE PRENATAL SCREENING THROUGH VICTORIAN CLINICAL GENETICS SERVICES (VCGS) – THE FIRST 18 MONTHS

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From April 2013 until September 2014, VCGS provided Natera's Panorama Non-Invasive Prenatal Screening test (NIPS) to Victorian women. This test detects pregnancies at high risk of trisomies 21, 18, 13, monosomy X and triploidy by analysing fetal cell-free DNA in the maternal circulation. Of the 1,252 women who undertook the Panorama test through VCGS, 35 (2.8%) received a high risk result for one of the conditions (T21, 15; T18, 6; T13, 5; sex chromosome aneuploidies, 7; triploidy, 2). Twelve high risk results for trisomy 21 were confirmed by invasive testing, two women miscarried and one terminated without further testing. Three women with high risk trisomy 18 results had a normal amniocentesis, two miscarried, and one fetus had a partial tandem duplication of chromosome 18. Four women at high risk for trisomy 13 had a normal invasive test or normal baby, and one wasn't followed up. One high risk monosomy X pregnancy was confirmed (mosaic), the remaining four either miscarried, terminated or were not followed up. Two other sex chromosome aneuploidies and two cases of polyploidy were detected. Approximately 75% of women had the Panorama test before 12 weeks gestation, thus utilising NIPS as a first-tier screening test. Around 70% of women also had some form of maternal serum screening. Only 10% of women had NIPS after a high/intermediate risk result from combined first trimester screening. These data show that NIPS was successfully implemented, and raise considerations about managing false positive results, and how NIPS is incorporated into prenatal care.

32. GENETIC COUNSELING FOR VARIANTS OF UNCERTAIN CLINICAL SIGNIFICANCE IN THE DYSTROPHIN GENE IN THE PRENATAL SETTING

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Chromosome microarray (CMA) is being increasingly utilized by women undergoing prenatal diagnosis due to its increased ability to detect clinically significant chromosome abnormalities, compared

with conventional karyotype. Despite its increasing use in the prenatal setting, ethical and practical concerns remain regarding the management of variants of uncertain significance (VOUS), especially in the absence of a relevant family history or a phenotype in the fetus. The detection of VOUS in the dystrophin gene has been previously reported in the pediatric setting. We will discuss two cases where a VOUS was detected in the dystrophin gene in the context of an ongoing pregnancy. These variants were both incidental to the reason for performing the test and of uncertain clinical significance. We discuss our approach to determining the likely clinical significance of the variants, as well as the genetic counseling challenges. Using a multidisciplinary, multicenter approach, we were able to reach a conclusion that was satisfactory for our clients.

MOLECULAR GENETICS AND GENOMICS

33. MENDELIAN ERRORS ASSIST IN CALLING COPY NUMBER VARIATION FROM GENOMIC SEQUENCING DATA: AN ILLUSTRATIVE CASE OF HETEROZYGOUS FAS DELETION

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Next generation sequencing technologies can identify genomic variants which underlie disease. Recently, bioinformatics tools have been designed which allow identification of copy number variation (CNVs) from exome data, using the depth of sequenced reads that vary from the surrounding baseline. However, these methods may have a high false positive rate. *Case:* A 12-year-old boy with no relevant family history, presented early in life with splenomegaly and pancytopenia, consistent with a clinical diagnosis of Autoimmune Lymphoproliferative Syndrome (ALPS). Sanger sequencing of FAS detected no mutations and CGH array failed on two occasions. *Results:* Exome sequencing of the family trio, did not identify a causative mutation in any of the genes associated with ALPS; however, the boy was noted to have failed to inherit either of two common SNPs within the FAS gene for which his father was homozygous. Read depth analysis of exome data using the CoNIFER analysis tool, identified a heterozygous deletion within the FAS gene, which was also confirmed by an in-house analysis tool specifically designed to identify Mendelian errors as a marker of deletion CNVs. The deletion, which extended from intron 5 through exon 9, was confirmed by gene targeted CGH array. Genomic sequencing is readily applied to the identification of copy number variation. We present data that confirms that the use of 'all/nothing' Mendelian errors, which exploit the absence of variants which would be expected to be present, may be used to corroborate the presence of deletions identified by 'quantitative' read depth analysis of exome data from family trios. We do not anticipate that Mendelian errors will add to the power of read depth analysis in the identification of duplications, where there would be expected to quantitatively more DNA template, rather than the presence or absence of specific variants.

34. THE MELBOURNE GENOMICS HEALTH ALLIANCE DEMONSTRATION PROJECT: EARLY OUTCOMES OF A WHOLE OF SYSTEM APPROACH TO INTEGRATING GENOMICS INTO CLINICAL PRACTICE

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The use of next generation sequencing is transitioning into clinical care. Gene panels are increasingly available and some Australian laboratories are introducing whole exome sequencing (WES). However, the current use of WES internationally to end a patient's 'diagnostic odyssey' represents a 'grey zone' between research and clinical care. An alliance of healthcare and research organizations, the Melbourne Genomics Health Alliance, is testing a future-oriented and ethical approach to providing genomic sequencing to patients for both germline and somatic conditions. This work is resolving challenges to implementation and determining outcomes. As the barriers to integration of genomics in healthcare extend beyond the laboratory, whole-of-system change is needed. Mechanisms have been put in place to engage clinicians throughout the demonstration project and to build understanding of clinical genomics. A total of 345 adults and children are being recruited into one of five 'flagship' conditions: acute myeloid leukemia, Charcot-Marie-Tooth disease, epilepsy, childhood-onset Mendelian conditions and hereditary colorectal cancer. WES is performed in parallel with standard care by several NATA accredited laboratories. Data are analyzed through a common, highly automated bioinformatics pipeline, filtered so only genes pertinent to the patient's condition are curated and reported. In addition, variant data is linked to clinical and research datasets, and genomic data files are made available to researchers. Early results ($n = 147$) demonstrate a 30% detection rate overall (8–51%). Evaluation, including comparison to standard care, is now underway. The approach, laboratory and clinical outcomes to date and feedback from participants and clinicians will be presented.

35. A NOVEL GENE CAUSATIVE FOR DISORDERS OF SEX DEVELOPMENT AND INTELLECTUAL DISABILITY

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Disorders of sex development (DSD) are conditions that affect the development of the gonads and genitalia. Phenotypes range from hypospadias to complete sex reversal. The underlying genetic causes for up to 70% of DSD cases are yet to be identified. Like DSD, intellectual disability (ID) varies in severity. Severe ID occurs at a frequency of 1–3% and can be caused by both, genetic and

environmental factors. Both 46,XY DSD and ID disorders can be found as isolated (non-syndromic) conditions, or as part of the same syndrome. However, in the majority of cases, for combined 46,XY DSD and ID the causative genes remain unknown. Here, we describe the identification of a novel gene that causes DSD and ID in 46,XY individuals while just causing ID in 46,XX patients. Two 46,XY DSD/ID and two 46,XX ID patients from two Israeli families and their unaffected parents were subjected to whole exome sequencing. Individual linkage analysis of each of the families, as well as inferred locus heterogeneity between the families, led to the identification of SART3. In vitro, ex vivo (morpholino knock-downs), and in vivo (CRISPR knock-ins and overexpression) studies support the role of SART3 in the etiology of 46,XY DSD and ID. A targeted Massively Parallel Sequencing DSD panel identified another patient with a variant in the same gene. This study led to the identification of a novel gene causative for DSD and ID. We provide new insights into the molecular pathways leading to both 46,XY DSD and ID.

36. GENOMICS AUSTRALIA – A GENERATIONAL OPPORTUNITY

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The introduction of genomics into routine healthcare has been heralded as being of comparable significance and impact as the introduction of antibiotics and vaccination. Governments and major research institutes are committing to the promise of genomic medicine through capital investments and establishment of national programs. Global alliances for sharing data and expertise around population-scale sequencing are gaining footholds. Australia was one of the first three countries to establish capacity for population scale whole genome sequencing, through the acquisition of the Illumina HiSeq X Ten platform at the Garvan Institute of Medical Research. This capacity stimulated investment from NSW Health to sequence at least 10,000 whole human genomes over the next three years. A flagship project of this investment is the sequencing of ~4,500 individuals of more than 70 years of age and have no history of major disease, including cancer or cardiovascular disease. This cohort, for which detailed phenotypical data has also been collected, will be made publicly available as a control for the study of the thousands of other genomes currently being sequenced from disease-affected individuals and cohorts. Apart from the tremendous research potential of this scale of genome sequencing, the implementation of this technology enables assessment of the feasibility of introducing genome sequencing as a routine diagnostic test. Here we will describe Australia's genomics capabilities and discuss the opportunities for Australia to establish an integrated and world-leading genomics ecosystem through working together and sharing expertise.

37. REDUCED COMPLEXITY GENOMES FOR GENE DOSAGE AND SNP TYPING BY NGS

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SNP microarrays are the standard diagnostic tool for cytogenetic abnormalities in samples from prenatal, postnatal, and product of conception samples. We set out to investigate whether the same information (SNP and copy number), and additional methylation

information could be gained from using next generation sequencing (NGS). Can gene dosage, SNP typing and methylation information be gained from reduced complexity genomes using NGS? Can we reproducibly produce and sequence the same fragments from genome? Would this be a viable substitute for SNP microarray? Restriction enzyme digestion followed by size selection was used to reduce the complexity of the genomes from a series of patients. Illumina sequencer ready libraries were prepared from the digests, by standard adapter ligation and PCR methods, and size selected using a Blue Pippin. Samples were sequenced on an Illumina MiSeq. Following alignment the reads were analyzed using tools in the Real Time Genomic RTG Core package. Results of initial feasibility studies on a small number of patients will be presented as well as experimental design procedure. A restriction enzyme digestion and size selection is an effective and simple way of reducing the complexity of the genome, without having to sequence the entire genome, which is costly both for time and money.

38. AUTOSOMAL RECESSIVE MUTATIONS OF *GPR126* ARE RESPONSIBLE FOR SEVERE ARTHROGRYPOSIS MULTIPLEX CONGENITA

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Arthrogryposis multiplex congenita is defined by the presence of contractures across two or more major joints and results from reduced or absent fetal movement. Here we present three consanguineous families presenting with lethal arthrogryposis multiplex congenita. By whole or targeted exome sequencing it was shown that the probands each harboured a different homozygous mutation (one missense, one nonsense and one frameshift mutation) in *GPR126*. *GPR126* encodes G-protein coupled receptor 126 that is essential for myelination of axons in the peripheral nervous system in fish and mouse. A previous study reported that *Gpr126*^{-/-} mice have a lethal arthrogryposis phenotype. We have shown that peripheral nerves from affected individuals from one family lacked myelin basic protein, suggesting that the cause of disease in affected individuals was due to defective myelination of the peripheral axons during fetal development. Previous work suggests that autolytic cleavage is important to activate *GPR126* signaling. Biochemical assays indicate that the p.Val769Glu substitution impairs autolytic cleavage of *GPR126*. Our data indicate that *GPR126* is critical for myelination of peripheral nerves in humans. This study adds to the literature implicating defective axoglial function as a key cause of severe arthrogryposis multiplex congenita and suggests that *GPR126* mutations should be investigated in patients presenting with this disorder.

39. EFFICACY OF NEXT-GENERATION SEQUENCING IN MOLECULAR DIAGNOSIS OF ARCHIVED DNA SAMPLES

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Inherited neurogenetic disorders (NGDs) include some of the most debilitating genetic disorders. Their clinical heterogeneity makes diagnosis difficult without genetic screening. The recent advent of affordable next-generation DNA sequencing (NGS) now makes this fast and inexpensive. Previously undiagnosed patients with archived DNA samples predating this innovation may benefit from NGS. However, DNA may be unviable because of degradation, and new samples may not be available. This pilot study aims to test the efficacy of a validated, in-house developed NGD subexomic panel (NSES) on archived DNA samples (obtained 1995–2012) from NGD patients that received no genetic diagnosis from previous genetic testing methods. NSES has been used for prospective diagnostic samples since 2013. NSES was performed on 103 archived samples. Measurements of DNA and NGS quality were compared against prospective control NSES samples ($n = 116$, samples obtained 2013–2014). Diagnostic success was compared to prospective NSES rates. DNA and NGS quality were found to decrease slightly with age, but not enough to be a hindrance. 12% of the archived cases ($n = 12$) had a diagnosis confirmed and 9% ($n = 9$) had variants of unknown significance, currently under further investigation. This may ultimately result in a success rate comparable to the 22.5% for prospective NSES samples with prior genetic testing. Regardless, the quality metrics indicate archived DNA is viable for NGS. We recommend archival cases be systematically re-screened with this new tool, with scope for whole exome sequencing along with linkage analysis for still unsolved families with suitable pedigree structure, such as trios or multiplex families.

40. MUTATIONS IN PIGN ARE ASSOCIATED WITH DEVELOPMENTAL DELAY AND SEIZURES

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Background: Mutations in phosphatidylinositol glycan anchor biosynthesis, class N (*PIGN*) have previously been associated with congenital anomalies, hypotonia and seizures. *PIGN* encodes a protein that is involved in glycosylphosphatidylinositol (GPI)-anchor biosynthesis. **Aim:** To identify the genetic cause of developmental delay and seizures in two siblings with an undiagnosed, suspected Mendelian disorder. **Patients and Methods:** A brother and sister were born to non-consanguineous parents of Caucasian background. They had hypotonia, motor delay, developmental delay (particularly affecting speech) and partial seizures. Magnetic resonance imaging

(MRI) performed on the girl at 8 years of age revealed cerebellar atrophy, while her brother had a normal scan. Whole exome sequencing (WES) was used to screen for likely pathogenic variations followed by functional studies to confirm pathogenicity. **Results:** Using WES we identified novel compound heterozygous variations in *PIGN* (c.548_549del:p.183_183del and c.932T>G; p.Leu311Trp) in the patients. Sanger sequencing confirmed these findings in the family. These two amino acid positions are highly evolutionarily conserved and the changes predicted to be damaging to protein function. Western blotting revealed that the protein levels of *PIGN* were normal in the male sibling but increased in his sister. The expression of GPI linked protein CD59 from patients as compared to control showed no reduction in expression on fibroblasts by flow cytometry. **Conclusion:** We hypothesise that these *PIGN* variations are the cause of the disease phenotype; however, further studies are required to confirm pathogenicity.

41. CUSTOMIZED GENETIC TESTING IN PRIMARY IMMUNODEFICIENCY DISORDERS AND IMMUNOLOGICAL RELATED DISORDERS: 10-YEAR EXPERIENCE IN AUCKLAND

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Primary immunodeficiency disorders (PIDs) are rare genetic defects leading to compromised host defences. Affected patients are prone to recurrent and severe infections. Some patients develop autoimmunity and malignancy as a result of immune dysregulation. A dedicated molecular immunology section was set up at LabPLUS in 2005 to offer genetic testing in NZ. The service is International Accreditation New Zealand (IANZ) accredited. Since 2008, we have received test requests for immunological related disorders such as atypical hemolytic uremic syndrome (aHUS), hemophagocytic lymphohistiocytosis (HLH) and periodic fever syndromes. In 2005–2014, we carried out genetic testing on 228 index cases and 32 carriers. The service offers 47 gene tests for 30 genetic disorders and processes more than half of the gene tests on the test guide annually since 2008. The three most common requests were for the X-linked lymphoproliferative (XLP), Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) and HLH. Of the 32 index XLP cases, positive diagnoses were identified in 2 patients. Most of these requests (27/32) were for male individuals presenting *EBV* infection. Positive diagnoses were made in about 25% of all tests requested. Well-defined clinical characterization of patients can assist in deciding which genes to be tested. The genetic defects in 9 out of 11 patients with suspected X-linked agammaglobulinemia (XLA) were positively identified. Most of these patients were initially identified by lack of B cells and subsequently have other laboratory workup before being referred to genetic testing service.

42. NO ASSOCIATION BETWEEN INSERTION/DELETION POLYMORPHISM OF ANGIOTENSIN CONVERTING ENZYME (ACE) GENE AND HYPERTENSION IN TYPE 2 DIABETIC PATIENTS IN NORTH OF IRAN

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Type 2 diabetes (T2D) is a multifactorial chronic disease that causes significant morbidity and mortality, worldwide. The insertion/deletion polymorphism of angiotensin converting enzyme

(ACE) gene is suggested to be associated with an increased susceptibility to hypertension in T2D patients, although the results of some studies do not support any association between them. This study focused on the association between I/D polymorphism of the ACE gene and hypertension in T2D patients in North of Iran. The study groups included 100 T2D patients with hypertension as the case group and 100 T2D patients who were not suffering from hypertension as the control group. PCR technique was used to amplify I (490 bp) and D (190 bp) alleles of ACE gene. The results obtained by this study showed that the frequencies for II, ID, and DD genotypes of ACE gene were 0.18, 0.52, and 0.30 in case group, and 0.22, 0.46, and 0.22 in control group, respectively. The I and D allele frequencies were 0.45 and 0.55 among cases and 0.44 and 0.56 among controls. The chi-square test carried out between case and control groups showed no statistically significant association between hypertension and either any genotype or any allele of ACE gene among T2D patients in North of Iran. This study is in consistent with those that do not support any association between the I/D polymorphism of ACE gene and an increased risk of hypertension in T2D patients.

43. NOVEL MUTATIONS IN CARNITINE-ACYLCARNITINE TRANSLOCASE GENE IDENTIFIED WITH SUDDEN INFANT DEATH SYNDROME (SIDS) IN CHINESE PATIENTS

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Carnitine-acylcarnitine translocase (CACT) deficiency is a rare but severe autosomal recessive disease of fatty acid oxidation. It had accounted for most cases of neonatal/infantile sudden death in the Metabolic Clinic of our service hospital since its establishment in 1997 (Hui et al., *Pathology*, 2014, 46, 375–382). Two Chinese SIDS neonates and their parents had undergone molecular testing for suspected CACT mutation after initial clinical diagnosis and biochemical work-up. Mutation analysis was performed by Sanger Sequencing for all exons and their flanking splicing junction. Restriction Fragment Length Polymorphism (RFLP) method was also employed to confirm diagnosis in the family screening. DNA from healthy Chinese control subjects (e.g., $n > 80$) were also screened by RFLP for the novel mutations found. The two probands were identified with compound heterozygosity in unconanguineous and unrelated family. Both had the founder splicing mutation of IVS2–10T>G (NG_008171.1:g.19763T>G). Two other novel variant sequences p.Arg37Ter(c.109C>T) and p.Arg236Ter(c.706C>T) were also found maternally inherited in respective probands. These novel mutations were screened by RFLP without appearance in the healthy subjects tested. In silico analysis by SIFT and PolyPhen in Ensemble indicates these novel mutations being likely significant and deleterious. While acylcarnitine profiling by tandem mass spectrometry aids in differential diagnosis of fatty acid oxidation, these novel mutations in Chinese, which are found in recent literature reports and popular databases (e.g., HGMD), can obviously enhance molecular diagnostic spectrum for definite/prompt diagnosis and early treatment of such high mortality rate disease. It is also helpful in prenatal diagnosis and genetic counseling.

44. VALIDATION OF THE ILLUMINA TRUSIGHT CANCER SEQUENCING PANEL FOR DIAGNOSTIC TESTING

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The Illumina TruSight Cancer Panel targets 94 inherited cancer genes. At PathWest we routinely test 25 of these genes by conventional Sanger Sequencing. Transition to this panel would provide a more streamlined workflow, reduction in labor and consumable costs in addition to an increased turn-around time. We therefore undertook a validation study to assess sensitivity, specificity and gene coverage. We tested 70 DNA samples with mutations in 30 different cancer genes. The workflow allows 24 samples to be processed together for a single MiSeq run. Data was analyzed with MiSeq Reporter software using BWA-MEM alignment and GATK variant analysis. VCF files were annotated through Cartagenia Bench software. A minimum threshold of 30-fold read depth was set for exonic and flanking intronic sequences. Read depth was assessed by viewing BAM files through AlaMut Visual. Results showed 93% of mutations to be detected. 6% of variants were missed due to location in regions of poor coverage. It was estimated that approximately 6% of all exons would require Sanger sequencing to 'gap fill'. A 13bp deletion in STK11 was not detected in a region of high coverage. Overall, with a gap fill approach, the test sensitivity was estimated to be greater than 98%. The false positive rate was observed to be very low. Following discussion with referring clinicians, we propose to use this approach to replace Sanger sequencing. All reported variants will be confirmed by Sanger and areas of low coverage 'gap filled'. This panel also has the advantage of being able test for additional cancer predisposition genes not previously available.

45. DIAGNOSIS OF MOSAIC ANGELMAN SYNDROME BY METHYLATION SPECIFIC MULTIPLEX LIGATION-DEPENDENT PROBE AMPLIFICATION (MS-MLPA)

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Angelman syndrome (AS, OMIM# 105830) is characterized by severe developmental delay, absent or severely limited speech, gait ataxia, and a unique behavioral phenotype, with a happy demeanour that includes frequent and sometimes inappropriate laughter, smiling, and excitability. Disease mechanisms for AS include de novo maternally derived deletions of 15q11-q13 (70–75% of cases), pathogenic variants in the maternally inherited/expressed *UBE3A* gene (~10% of cases), paternal uniparental disomy of chromosome 15 (UPD; 3–7%), and imprinting defects affecting the maternal chromosome 15 (2–3%). More than 40% of AS patients with an imprinting are mosaic for the defect. Patients with mosaic Angelman syndrome may have a milder or atypical phenotype. Here we present two patients diagnosed with mosaic AS due to two different genetic mechanisms. Both patients presented with atypical clinical features, including absence of seizures and ataxia. Furthermore, both were also in the upper percentile for weight, which is uncharacteristic for AS. Using methylation specific multiplex ligation-dependent probe amplification (MS-MLPA), methylation testing at 15q11–13 showed incomplete loss of the maternal allele methylation pattern, consistent with mosaic Angelman syndrome. The first patient's SNP microarray result identified long continuous stretches of homozygosity (LCSH) across chromosome 15. In combination with the

MS-MLPA result, this suggests AS due to mosaic uniparental disomy (UPD) for chromosome 15. The second patient had a normal SNP microarray result. In combination with the MS-MLPA result, this suggests Angelman syndrome due to a mosaic imprinting defect.

46. VALIDATION OF A MASSIVELY PARALLEL SEQUENCING PANEL FOR ANGELMAN SYNDROME AND RELATED DISORDERS

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Angelman syndrome (AS, OMIM# 105830) is characterized by severe developmental delay, absent or severely limited speech, gait ataxia and a unique behavioral phenotype, with a happy demeanour that includes frequent and sometimes inappropriate laughter, smiling, and excitability. Disease mechanisms for AS include de novo maternally-derived deletions of 15q11-q13 (70–75% of cases), paternal uniparental disomy of chromosome 15 (UPD; 3–7%), imprinting defects affecting the maternal chromosome 15 (2–3%), and pathogenic variants in the maternally-inherited/expressed *UBE3A* gene (~10% of cases). The remaining 5–10% of patients with the major clinical features of AS who do not have any identifiable genetic abnormality may have a disorder with overlapping clinical features including epilepsy, developmental delay and intellectual disability. This includes Rett/atypical Rett syndrome (*MECP2*, *CDKL5*, *FOXG1*, *MBD5* and *MEF2C* genes), Angelman-like syndrome (*SLC9A6* gene), Pitt-Hopkins syndrome (*TCF4*, *NRXN1* and *CNTNAP2*) and Mowat-Wilson syndrome (*ZEB* gene). Massively parallel sequencing offers a rapid, comprehensive and cost-effective method for simultaneous assessment for pathogenic sequence variants in a panel of 18 genes associated with AS and related disorders. Here we present the laboratory's experience with the AS panel, which utilises the Illumina TruSight Autism Rapid Capture and MiSeq sequencer. All coding exons and flanking intronic regions were targeted for hybridization capture enrichment. Coverage of targeted bases in the regions-of-interest at a depth of at least 25 fold was >97.5%. This extended AS panel provides a cost-effective method for testing the genes associated with AS and clinically similar disorders.

47. ASSESSMENT OF GENOME-WIDE METHYLATION IN PLACENTAS FROM WOMEN WITH PREECLAMPSIA COMPARED WITH NORMOTENSIVE CONTROLS

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Preeclampsia (PE) is a hypertensive disorder of pregnancy and is a leading cause of maternal and fetal morbidity and mortality worldwide. While multiple studies have investigated gene expression changes in preeclampsia, few have looked at epigenetic changes. The aim of this study was to compare DNA methylation profiles in preeclamptic and normotensive placentas. Genomic DNA was extracted from placental samples of PE ($n = 8$), and normotensive pregnancies ($n = 16$). The Illumina Infinium HumanMethylation450K BeadChip was used to assess DNA methylation at > 480 000 CpG sites. All analyses were conducted using publically available bio-conductor packages in R. Following standard quality control and processing steps, linear regression models were used to assess the association between methylation and case-control status at each CpG site. The DMRcate package was used to identify regions of differen-

tial methylation. There were 303 gene regions found to be differentially methylated (214 hypermethylated, 89 hypomethylated) in the PE placentas compared to controls (absolute beta difference >5% and FDR value <0.05), after adjusting for gestational age at delivery. From these, five gene regions were selected for validation using pyrosequencing (*SPESPI*, *WNT2*, *ALCAM*, *ADORA2B*, and *ASB3*). Three of these gene regions, namely, *SPESPI*, *WNT2*, and *ALCAM* showed significant changes in methylation by pyrosequencing between control and PE placentas. This study identified genome-wide changes to DNA methylation profiles in placentas from women with PE that may be associated with changes in placental development and function. Functional characterization of genes identified to be differentially methylated in diseased placentas is required.

48. ARE SHORT TELOMERES A CAUSE OR CONSEQUENCE OF HYPERTENSION IN SPONTANEOUSLY HYPERTENSIVE MICE?

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Clinical studies have reported associations between reduced telomere length and hypertension, however, the role of telomere length in the pathogenesis of hypertension remains unknown. The aim of this study was to determine whether telomere shortening occurred prior to the onset of disease in spontaneously hypertensive mice. Spontaneously hypertensive Schlager mice (BPH/2J) and their normotensive controls (BPN/3J) were used in this study. Genomic DNA was extracted from kidney tissue of 4-, 12- and 20-week-old male BPH/2J and BPN/3J mice ($n = 10$ /group). Relative telomere length (T/S) was measured using quantitative PCR. Linear correlation estimates were performed to analyze telomere length over time within a strain. A general linear model with repeat measures testing was used to compare rate of telomere shortening between groups. A general linear model was used to compare relative telomere lengths and gene expression between groups. In 4 week old pre-disease animals no difference in T/S was observed between BPH/2J and BPN/3J animals ($p = .09$). The rate of telomere attrition between BPH/2J and BPN/3J was significantly different ($p = .001$). At 12 and 20 weeks, established disease, BPH/2J animals had significantly shorter telomeres when compared to their age-matched controls (12 weeks $p = .001$ and 20 weeks $p = .004$). This is the first study to show that reduced telomere length occurs after the development hypertension, indicating that this is not the cause of hypertension in spontaneously hypertensive mice. Further studies are needed to determine the mechanisms which lead to the development of hypertension and the shortening of telomeres in these animals.

49. CONFIRMING A DIAGNOSIS OF SPINAL MUSCULAR ATROPHY: WHAT COMES AFTER DELETION AND POINT MUTATION ANALYSIS?

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Spinal muscular atrophy (SMA), an autosomal recessive disorder, is the most frequent genetic cause of infant mortality. Mutations in the survival motor neuron gene 1 (SMN1) are responsible for SMA. This gene is highly homologous to the pseudogene SMN2. Approximately 95% of SMA cases result from a homozygous deletion of the SMN1 gene. The remaining patients are compound heterozygous for a SMN1 deletion and a SMN1 point mutation. However, the diagnosis of SMA cannot be confirmed for many patients when no mutations are identified in SMN1. We present two such cases. Case 1 is a symptomatic patient with one copy of SMN1 and no

coding sequence mutation identified. Quantitation of full length SMN mRNA indicated that this patient had zero expression level of full length SMN mRNA. This is consistent with the level of expression seen in SMA patients with homozygous deletion of SMN1 and supports the diagnosis of SMA linked to SMN1 gene in this patient. Case 2 is a symptomatic patient in whom a heterozygous SMN1 deletion and a SMN point mutation had been identified. However due to high homologies between SMN1 and SMN2, it was unclear which gene carried the point mutation. Quantitation of full length mRNA showed an expression level consistent with that seen in affected SMA individuals. This result provided a more conclusive diagnosis of SMA linked to SMN1 for this patient. Both these cases highlight that mRNA quantitation, with appropriate controls, is a more definitive method for confirming diagnosis of SMA.

50. OUTCOMES OF REPRODUCTIVE GENETIC CARRIER SCREENING IN VICTORIA

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The Victorian Clinical Genetics Services (VCGS) provides a range of population screening programs with the vision of reducing disease incidence in children and assisting parents with reproductive choices. This presentation focuses on the outcomes of providing Reproductive Genetic Carrier Screening (RGCS) for 3 years. RGCS includes screening for Cystic Fibrosis (CF), spinal muscular atrophy (SMA) and fragile X syndrome (FXS) because of the high carrier frequency in the general population and the significant impact these disorders have on families. It is offered to women and couples planning or in early pregnancy and includes partner testing and prenatal diagnosis for high risk couples. Our data shows a carrier frequency of 1 in 20 for at least one of the conditions tested. Of 294 carriers identified, there were 168 CF carriers (57%), 16 FXS carriers (5%), 117 SMA carriers (40%) and 7 carrying two conditions (2%). Of couples at increased risk of having an affected child (6 CF carrier couples, 16 FXS premutation (PM) carriers), 73% were pregnant at the time of testing. All CF carrier couples and all FXS PM carriers opted for prenatal diagnosis (CF: 1 affected fetus, 3 carriers, 1 non-carrier; FXS: 1 affected fetus, 4 PMs stably inherited, 2 PMs within expanded range and 2 non-carriers). The number of patients screened is less than 7% of total births in Victoria. Clinical outcomes of our service highlight that more patients should be given the opportunity to make reproductive choices to reducing disease incidence of these conditions in children.

51. COMPARISON OF METHODS TO DETERMINE SPERM DNA QUALITY DURING ASSISTED REPRODUCTIVE TECHNOLOGY

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Measurement of DNA damage in human spermatozoa is a key diagnostic tool for the infertile couple. The aim of this study was to determine whether the addition of dithiothreitol (DTT) treatment and LIVE/DEAD cell differential staining in the TUNEL assay for sperm DNA fragmentation, and 8OHdG assays for oxidative damage, will improve the assessment of sperm DNA quality. Patients were recruited at Fertility First, Sydney, who were undertaking their

third cycle or less for either an Intrauterine Insemination (IUI) or an Intra-Cytoplasmic Sperm Injection (ICSI) treatment. Approximately 200µl of the spermatozoa sample used for IUI or ICSI was analyzed for sperm DNA fragmentation and oxidative damage using existing and updated assays simultaneously. The new protocol incorporates two new steps into the existing assays. DTT was added, which has been shown to relax the tight structure of the chromatin, allowing better access to the DNA breaks deep within the nucleus. A LIVE/DEAD stain was also incorporated to examine whether TUNEL assays are influenced by the vitality of the sperm. Eighty patients have been recruited to date, 29 underwent IUI treatment and 51 patients underwent ICSI. There was no significant difference between the standard TUNEL and 8OHdG Assays when compared to the new assays for detecting sperm DNA quality. Regular review of the methods used to assess sperm DNA quality are necessary to ensure the treatment most likely to succeed is offered to infertile couples. The results of this study show that the standard protocol for measuring sperm DNA quality is sufficient.

52. A CUSTOM NEXT GENERATION SEQUENCING PANEL TO IDENTIFY THE CAUSE OF MONOGENIC DISORDERS OF INSULIN SECRETION, DISORDERS OF SEXUAL DEVELOPMENT AND NOONAN SYNDROME

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Next Generation Sequencing (NGS) is a high throughput sequencing technology that has emerged in recent years, and is increasingly being used in the clinical laboratory. It offers a fast and cost effective approach to test for both common and rare disorders where there are a large number of potential candidate genes. The Molecular Genetics Department has designed a custom NGS panel to detect the cause of Monogenic Disorders of Insulin Secretion (MDOIS), Disorders of Sexual (DSD) and Noonan Syndrome (NS). MDOIS encompasses maturity onset diabetes of the young (MODY), permanent neonatal diabetes (PND) and hyperinsulinism (HI). The custom panel contains probes for a total of 61 genes: 29 DSD, 19 MDOIS and 13 NS. Previously the laboratory had employed Sanger sequencing to test 4 DSD, 8 MDOIS and 3 NS genes. Target enrichment is carried out using a custom Illumina Nextera Rapid Capture probe set, followed by sequencing on an Illumina MiSeq. Data analysis is performed by CLC Genomics Workbench and genetic variants are annotated using Cartagenia software. The mean depth of coverage is approximately 800X, and >99% of the targeted bases have a minimum of 25X. To date, pathogenic variants associated with DSD (*SRD5A2*, *HSD17B3*, *NR5A1*, *AR*), HI (*GLUD1*), MODY (*ABCC8*, *GCK*, *GLUD1*, *HNF1A*, *HNF4A*, *HNF1B*, *INS*, *INSR*, *PAX4*) and NS (*PTPN11*, *RAF1*, *BRAF*) have been detected.

53. COPY NUMBER DETERMINATION BY MASSIVELY PARALLEL SEQUENCING USING HYBRIDIZATION ENRICHMENT GENE PANELS.

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The use of gene panels with massively parallel sequencing (MPS) technologies has become a routine approach in diagnostic genetic labs for the detection of single nucleotide variants (SNVs) and small indels. Array-based tests are widely used for the detection of copy number variations (CNVs), usually larger than 200 kb. For higher resolution CNV detection, Multiplex Ligation dependent Probe Amplification (MLPA) is often employed. The use of a combination of sequencing, microarrays and MLPA to obtain SNV, Indel and

CNV information is expensive, inefficient and often incomplete for all genes of interest. Recent publications have demonstrated exonic level detection of CNVs through read depth analysis that allows for concurrent detection of copy number and sequence variants in all tested genes. Enrichment hybridization library preparation followed by MPS yields highly reproducible sequencing profiles that allow for simplified CNV detection through normalized exonic read depth analysis. Here we report various duplications and deletions detected in patients tested at our laboratory using a custom designed gene panel for monogenic disorders of insulin secretion (MDOIS), disorders of sex development (DSD) and Noonan syndrome and related disorders.

54. MOLECULAR GENETICS QUALITY ASSURANCE PROGRAM REVIEW FOR INHERITED DISEASES

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in association with the HGSA

The RCPAQAP (Royal College of Pathologists of Australasia Quality Assurance Programs) Molecular Genetics* discipline offers proficiency testing (PT) in the Australasia region for the molecular analysis of various inherited and somatic diseases. Technical modules are also produced for such techniques as DNA sequencing and maternal cell contamination. The discipline has expanded more recently in terms of the scope of molecular genetics quality assurance modules offered and participation in these modules has steadily increased. This report presents the survey outcomes over 3 years, from 2012 to 2015, of inherited disease PT modules, specifically mitochondrial myopathy and fragile X PCR screening. The laboratories consisted of Australian and international laboratories from New Zealand, Singapore and Hong Kong, with numbers ranging from 10 to 13 participating laboratories. An identical set of samples were sent to laboratories for testing using their routine standard operating procedures. The mitochondrial myopathy module includes samples for Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke-like episodes (MELAS), Myoclonic Epilepsy with Ragged-Red Fibres (MERFF), Leigh syndrome and Leber Hereditary Optic Neuropathy (LHON). The Fragile X PCR screening module focuses on premutation status and it aims to provide laboratories with a broad range of expansions to assess their ability to detect those lengths. Following data analysis, individual responses were collated and laboratories were assessed on the accuracy of genotyping and interpretation. This forms a significant part of the report that is forwarded to a referring clinician. Key discussion points will include laboratory performance, methods utilized and areas for improvement.

CANCER GENETICS

55. ASSOCIATION OF CONGENITAL TERATOMA WITH NEUROFIBROMATOSIS TYPE 1

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Neurofibromatosis type-1 (NF1) is a genetic disorder caused by mutations in the tumor suppressor gene, *NF1*. The increased risk for benign and malignant tumors in affected individuals is well-established, caused by biallelic *NF1* inactivation due to loss of heterozygosity. Pediatric teratoma, a germ cell tumor has not been reported in NF1 patients previously. We report a case of congenital teratoma in an infant with a heterozygous maternally inherited pathogenic *NF1* mutation (c.[1756_1759delACTA].p.[Thr586Valfs*18]). The antenatally detected retroperitoneal tumor was resected postnatally and histopathology showed immature teratoma. Patient was monitored with MRI scans and alpha-fetoprotein. A recurrence in the right paraspinal region, right iliac crest and right lung was detected on MRI scan at 6 months post-resection. Lesions were not responsive to two cycles of chemotherapy with carboplatin, etoposide and bleomycin. Resection of right lung lesion and biopsy of other lesions showed mature teratoma with no immature malignant elements. Physical findings of NF1 include multiple café-au-lait macules (>6, measuring >0.5 cm) and bilateral tibial bowing at 12 months old. The pathogenic *NF1* mutation was also detected in the tumor tissue with loss of heterozygosity in the *NF1* locus. Mosaic whole *NF1* gene deletion was detected in the tumor tissue using MLPA kits P081 and P082 (MRC Holland). The loss of heterozygosity in the tumor tissue confirmed the somatic mutation ('second-hit'), supporting the hypothesis of *NF1* involvement in the pathogenesis of congenital teratoma. This is the first definitive confirmation of a direct pathogenetic link between congenital teratoma and loss of *NF1* tumor suppressor function.

56. NO ASSOCIATION BETWEEN PROSTATE CANCER AND Y-CHROMOSOME HAPLOGROUPS AMONG IRANIAN SUBJECTS

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Evidence shows a large difference in disease prevalence of prostate cancer among populations of varying ethnic backgrounds. It is supposed that there are some underlying genetic factors in some genetic lineages that would potentially increase the susceptibility or resistance to develop prostate cancer. In this study, we examined 10 Y-chromosome binary loci including M20, M35, M96, M120, M172, M201, M207, M217, M231, and M258 for their ancient and new alleles, and respective haplogroup frequencies among Iranian prostate cancer patient and healthy control groups to determine whether belonging to any of these haplogroups would potentially increase the level of either susceptibility or resistance to prostate cancer. The study group included a total of 396 subjects comprising 196 men with prostate cancer and 200 healthy male individuals as controls. Allele Specific PCR method was recruited to genotype all above mentioned binary loci. Y-chromosomal binary haplogroups for all samples of prostate cancer cases and healthy controls were defined by the analysis of all 10 binary polymorphisms. The nomenclature of the haplogroups followed that of the Y chromosome consortium (YCC). Based on the results obtained by this study, no statistically significant difference was observed between haplotypes frequencies of prostate cancer patients and healthy controls. These findings do not support any association between either susceptibility or resistance to prostate cancer with Y chromosomal haplogroups.

57. INTRODUCING THE TRUSIGHT TUMOR ASSAY INTO A DIAGNOSTIC LABORATORY FOR SOMATIC MUTATION TESTING OF FFPE SPECIMENS

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The TruSight Tumor (Illumina) NGS methodology was introduced to improve detection limit, range of mutations detected, number of genes tested and potentially improve throughput for the detection of somatic mutations, when compared to the existing real-time PCR methods. Validation was performed using 96 DNA samples from previously tested patient samples and commercial reference standards over six independent library preparation and sequencing runs. Amplicon coverage, variant read depth (vertical coverage), average base call quality and percentage of targeted coverage were all measured. Suboptimal samples were included in the trial to represent the full range of DNA quality from extracted FFPE specimens and to help define sample requirements for NGS and establish QC parameters. We used two independent NGS software programmes, VariantStudio™ v2.2 (Illumina) and NextGENe v2.3.4.2 (Softgenetics) to evaluate all data. The TruSight Tumor workflow sequences both strands independently in both directions and variants are only called if found on both strands. It was necessary to reduce the allele frequency threshold cut-off from the default setting of 3% to 1%, in order to detect some of the expected variants. The Illumina TruSight Tumor NGS assay performed well and produced consistent and reliable good quality libraries that were fit for the purpose of *EGFR*, *BRAF* and *KRAS* somatic variant detection in FFPE extracted DNA specimens. Details of the results of our TruSight Tumor validation process are presented.

58. FACTORS AFFECTING THE PENETRANCE AND SEVERITY OF HEREDITARY PHEOCHROMOCYTOMA AND PARANGLIOMA

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Introduction: Pheochromocytomas (PC) and paragangliomas (PGL) are rare and highly heritable, with 40% of subjects found to have a germline mutation. Mutations in genes encoding subunits of succinate dehydrogenase (SDH) are associated with PC/PGL, and the penetrance of these tumors in SDH-associated families is extremely variable. Some individuals develop tumors during childhood while others, within the same family with the same mutation, remain tumor-free. Environmental factors may play a role in this variable penetrance. The aim of this study is to determine whether there is a relationship between hypoxic environmental factors and penetrance of these tumors. **Methods:** Environmental (smoking status) and clinical data was collected by way of interview and patient medical records from consenting SDH-associated patients. This study forms part of a larger study, the Australian Succinate Dehydrogenase Consortium. **Results:** Forty-seven individuals from 20 families are represented in this study, reflecting *SDHA* ($n = 1$), *SDHB* ($n = 11$), *SDHC* ($n = 1$) and *SDHD* ($n = 7$) mutations. Of these, 27 (40%) individuals had developed tumors (PC, $n = 5$, PGL, $n = 22$), with the youngest age of tumor presentation 12 years (*SDHB* carrier) and oldest, 63 years (*SDHD* carrier). One individual had died of disease-related causes. Of the 47 interviewed, 13 (28%) had reported smoking. Analysis of smoking (pack-years) and tumor development are ongoing and will be presented. **Conclusions:** Our

preliminary data indicates that there may be differences in disease penetrance between smokers and non-smokers with an SDH mutation. Improved knowledge of environmental factors influencing tumor development in this Australian population will aid clinical management and genetic counseling.

59. EXPLORING CLINICIANS' ATTITUDES ABOUT USING ASPIRIN FOR RISK REDUCTION IN PEOPLE WITH LYNCH SYNDROME (LS) WITHOUT PERSONAL DIAGNOSIS OF COLORECTAL CANCER (CRC)

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Background: Recent research has shown that aspirin reduces the risk of LS-associated cancers. However, uncertainty exists around the optimal dosage, treatment duration and whether the benefits of aspirin as a risk-reducing medication (RRM) outweigh the adverse risks. Little is known about clinicians' attitudes, current practice and perceived barriers to recommending aspirin as a RRM. **Aim:** To explore the attitudes of Australian clinicians who discuss risk management options with LS patients towards using aspirin as a RRM. **Methods:** Clinicians were invited to complete an online survey. Topics included their LS clinical experience, views and practice of recommending aspirin as a RRM, and knowledge about clinical risk management guidelines for LS. **Results:** Data collection is ongoing. As of March 10, 2015, 122 respondents: 8 medical oncologists, 7 clinical geneticists, 24 genetic counselors, 19 colorectal surgeons, 45 gastroenterologists, 7 nurses and 12 other health professionals completed the survey. While most (82%) considered aspirin to be an effective RRM, 87% still want new trials in LS patients, 81% were confident about discussing aspirin, 72% would discuss aspirin as a RRM with their patients and 56% had engaged in discussion. The majority (64%) indicated that patient educational materials would be helpful. **Discussion:** Although most clinicians consider aspirin to be an effective RRM and are confident about discussing it, they consider further research is needed around dose and toxicity. The interest expressed towards patient educational materials suggests that it may be needed to facilitate informed choices in patients.

CYTOGENETICS

60. A RARE T(X;22;14) IN A PATIENT WITH NEUROFIBROMATOSIS 2

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This poster is a case study from a recent referral from Royal North Shore Genetics Service of a female patient aged 23 years investigating neurofibromatosis type 2 (NF2). Clinical notes indicated the presence of bilateral acoustic neuromas and a previous negative report for mutation analysis for NF2 on patient blood

lymphocytes. The referral indicated cytogenetic analysis to exclude a translocation or ring chromosome. Cytogenetic analysis of blood lymphocytes detected a novel three way translocation t(X;14;22)(p11.22;q32.2;q12.2). No abnormality was detected by aCGH. Two possible mechanisms are hypothesized for this abnormality to result in NF2. The translocation disrupts the NF2 gene at 22q12.2 or, alternatively, X inactivation of the der(X) could also inactivate the chromosome 22q material causing an effective loss of NF2. FISH testing will be undertaken to investigate these possibilities. NF2 is characterized by vestibular schwannoma (also known as acoustic neuromas), which is an almost universal feature of the condition. Meningioma and spinal tumors are also very common features. Schwannomas of other cranial nerves also occur and while there may be skin tumors, there are less than in patients with Neurofibromatosis 1. NF2 typically follows a pattern of progressive hearing loss, leading to affected balance, facial palsy and loss of sight. Diagnosis usually occurs several years after symptoms begin in late teens to early twenties and in the more severe cases, death occurs at an average of age 36.

61. INVESTIGATION OF LONG RUNS OF HOMOZYGOSITY (ROH) THRESHOLD LIMITS FOR CYTOSNP-12 [300K] MICROARRAY USING BLUEFUSE MULTI V4 SOFTWARE.

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Thresholds for ROH are set ~0.5–1Mb in genome-wide association studies but more conservatively at 3–10Mb for clinical diagnostics. A 5Mb threshold correlates well with the inbreeding coefficient (F) for parental relatedness (McQuillon et al., *Am J Hum Genet* 83:359–372, 2008); however, smaller thresholds may be desirable depending on the clinical or research interest. ROH thresholds were investigated for the CytoSNP-12 [300K] array by comparing with CytoSNP-850K array (Illumina) using a consanguineous sample with 6.3% autozygosity: 177.1 Mb ROH found previously using 180K CGH+SNP array (Agilent). Bluefuse Multi v4 (Bluegenome) parameters defined ROH as 50 homozygous SNPs, minimum size 0.5Mb, LOH-score >200, and filtered to include autosomes only. Scatter-plot analysis compared 300K vs 850K ROH calls. There were 21 ROH tracts >0.5Mb detected by 300K array totalling 187.3Mb [range: 0.92–35.93Mb] (6.7% autozygosity) of which 11 tracts >5Mb totalled 162.4Mb (6.0% autozygosity). All 300K ROH tracts were detected by 850K array and all >5Mb were concordant. However, another 16 tracts <5Mb were found on the 850K array and total ROH was 214.9Mb (range: 0.51–35.94Mb; 8.0% autozygosity). Scatter-plot and linear correlation ($R^2 = .9777$) analysis showed ROH size (>0.5Mb) and chromosomal location highly correlated. This data shows ROH tracts as small as ~1Mb size are detectable on the CytoSNP-12 array using the above parameters, however ROH <5Mb tends to inflate autozygosity estimates and this trade-off needs consideration during autozygosity mapping analysis.

62. FISH DETECTION OF ANEUPLOIDY USING FETAL LUNG IMPRINTS RATHER THAN FFPE TISSUE.

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Aneuploidy detection after fetal death in-utero (FDIU) or stillbirth has been performed by formalin fixed paraffin embedded tissue

(FFPE) FISH, which can be lengthy and technically challenging technique. However, in our laboratory, we perform FISH testing on lung touch-imprint slides when referred from the histopathology laboratory for investigation of possible chromosomes aneuploidy. The aim of this study was to retrospectively review 9 years of data to evaluate the utility of FISH in detecting the most common trisomies and monosomies on touch-imprints of lung tissue. A total of 378 samples were received between the years 2006 and 2014 from the wider Western Sydney Metropolitan region, following autopsy for FDIU or stillbirth. FISH Aneuploidy detection for chromosomes 13, 18, 21, X and Y was performed using the AneuVysion kit (Vysis, Abbott Molecular). Lung-imprint FISH takes 1.5hrs compared to 6–7 hrs for FFPE FISH and we successfully processed 374/378 (99%) specimens. Abnormalities were found in 45/378 (12%) samples: Trisomy 21, 14 (6.3%); Monosomy X, 11 (5%); Trisomy 13, 7 (3.2%); Triploidy, 6 (2.7%); Trisomy 18, 3 (1.4%); Sex reversal, 2 (0.9%); XX/XY mosaicism, 2 (0.9%); X/XY mosaicism, 1 (.5%). Interphase FISH on lung touch imprints is a rapid (1.5 hours) and reliable method for detecting aneuploidy with a high success rate (~99%).

63. TRANSIENT MYELOPROLIFERATIVE DISORDER WITH 47,XY,+21 KARYOTYPE IN A NEWBORN WITHOUT DOWN SYNDROME: ACQUIRED ABNORMALITY OR EVIDENCE OF MOSAICISM?

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Chromosome analysis was performed on amniotic fluid from a 21+3 week gestation pregnancy for increased risk of trisomy 21. Fifteen G-banded metaphase preparations showed a 46,XY karyotype. The pregnancy continued. At birth, blood and bone marrow was received from this baby to exclude congenital leukemia. Bone marrow chromosome analysis showed the karyotype: 47,XY,+21[7]/46,XY[13].nuc ish(CRLF2x2)[200],(D4Z1, D10Z1, D17Z1)x2[200],(ABL1, BCR)x2[200],(KMT2Ax2)[350],(ETV6x2, RUNX1x3)[45/200],(TCF3x2)[200]. Approximately 30% of bone marrow cells examined showed trisomy 21 with no other abnormalities detected using the above probe panel. Neonatal blood examination showed trisomy 21 in all 23 unstimulated cells examined. These findings were consistent with a clonal disorder. Trisomy 21 is seen in a range of hematological disorders including AML and ALL. While trisomy 21 can be seen as an acquired hematological abnormality, it may also represent constitutional mosaicism. Given these findings, the prenatal specimen was re-examined. There was no evidence of trisomy 21 in the established amniotic fluid cultures or in fixed interphase cell preparations using the Vysis Aneuvysion FISH probe set. To further investigate the possibility of low level mosaicism, interphase cells from a buccal swab and urine sample were analyzed with the 13/21 Vysis Aneuvysion probe set. There was no evidence of trisomy 21 in these specimen types. Transient neonatal leukemia occurs almost exclusively in Down syndrome babies. Literature review has identified cases of transient neonatal leukemia in non-Down syndrome babies. A review of the literature and suggested pathomechanisms of transient neonatal leukemia will be presented.

64. CHARACTERIZATION OF A COMPLEX MOSAIC MARKER CHROMOSOME USING ARRAY, FISH AND CONVENTIONAL KARYOTYPING

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A 2-month-old female infant was referred for array testing. She presented with hypotonia, required aspiration, and was noted to have widely spaced nipples, prominent forehead and umbilical hernia. SNP array studies indicated a complex terminal duplication of part of the short arm of chromosome 8. This consisted of a mosaic duplication of 8p23.1 of 3.7MB, which was proximal to a 6.7Mb non mosaic interstitial duplication involving the bands 8p23.1–p23.3. Classical cytogenetic studies were undertaken to clarify this observation. G-banded chromosomal studies revealed a female karyotype with a supernumerary marker chromosome in 70% of metaphases examined. FISH studies profiling the marker chromosome indicated two copies of the chromosome 8p subtelomere region, and one copy of the proximal flanking 8p23.1 duplication. FISH for the chromosome 8 centromere was negative. The formation of a neocentromere has been hypothesized. A review of the literature provides evidence that this region is a hotspot for the formation of neocentromeres with four documented cases published (Amor et al., *Am J Hum Genet* 71:695–714, 2002). The marker chromosome involves approximately 18Mb of DNA and contains over 30 OMIM genes. It is overlapping but larger than the 8p23.1 duplication syndrome region. Parental studies showed this marker was de novo in origin.

65. CYTOGENOMIC EVALUATION OF SUBJECTS WITH SYNDROMIC AND NON-SYNDROMIC CONOTRUNCAL HEART DEFECTS

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Despite considerable advances in the detection of genomic abnormalities in congenital heart disease (CHD), the etiology of CHD remains largely unknown. CHD is the most common birth defect and is a major cause of infant morbidity and mortality, and conotruncal defects constitute 20% of all CHD cases. We used array comparative genomic hybridization (array-CGH) to retrospectively study 60 subjects with conotruncal defects and identify genomic imbalances. The DNA copy number variations (CNVs) detected were matched with data from genomic databases, and their clinical significance was evaluated. We found that 38.3% (23/60) of CHD cases possessed genomic imbalances. In 8.3% (5/60) of these cases, the imbalances were causal CNVs; in 8.3% (5/60), unclassified CNVs were identified; and in 21.6% (13/60), common variants were detected. Although the interpretation of the results must be refined, and there is not yet a consensus regarding the types of CHD cases in which array-CGH should be used as a first-line test, the identification of these CNVs can assist in the evaluation and management of CHD. The results of such studies emphasize the growing importance of the use of genome-wide assays in subjects with CHD to increase the number of genomic data sets associated with this condition.

GENETIC COUNSELING

66. LONG-TERM GENETIC COUNSELING – IS IT GENETIC COUNSELING, PSYCHOTHERAPY OR A BIT OF BOTH?

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There has been longstanding debate about the role of genetic counselors in long-term follow-up of families for psychosocial support. Issues of clinical service delivery models, resourcing, professional competencies and personal opinion have clouded the topic for some time. A case study will be utilized to highlight the lack of clear professional boundaries in long term genetic counseling and the opportunities and possible pitfalls that may arise.

67. THE EXPERIENCE OF A LARGE HEREDITARY DIFFUSE GASTRIC CANCER FAMILY AT THE ROYAL MELBOURNE HOSPITAL FAMILIAL CANCER CENTRE: EXAMINING THE COUNSELING AND CLINICAL ISSUES

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Background: Hereditary diffuse gastric cancer (HDGC) is an inherited cancer syndrome caused by mutations in the *CDH1* gene. National guidelines recommend prophylactic total gastrectomy for *CDH1* mutation carriers based on published estimates of 80% lifetime risk of advanced gastric cancer. This case study examines genetic counseling and clinical issues arising within a large family with HDGC. **Methods:** The pedigree and genetic results are presented, along with a review of clinic database notes, including information about cascade testing, risk management decisions and cancer diagnoses. Genetic counseling issues were considered collaboratively by the investigative team. **Results:** At present, 8 family members are known mutation carriers; 6 are unaffected (45–80 years) and 2 have died from gastric cancer (41 years, 51 years). This family's experience encompasses the full range of severity of HDGC: early death, as well as mutation carriers unaffected in the ninth decade. One mutation carrier presented with gastrointestinal co-morbidities. **Conclusion:** This family's experience of *CDH1* penetrance does not reflect the published 80% lifetime risk. This experiential risk perception within the family coupled with the life-changing risk management options (total gastrectomy vs. 'wait and see') has raised unique counseling issues. These considerations can be used in a broader context as cascade testing continues, as well as in other *CDH1* families where the lived experience does not reflect published risk estimates. We suggest a possible extension of the *CDH1* phenotype based on gastrointestinal comorbidities within the family. Finally, data from larger prospective cohorts is needed to produce more robust penetrance figures for *CDH1* mutation carriers.

68. AN EXPLORATION OF AUSTRALASIAN GENETIC COUNSELORS' ATTITUDES TOWARDS COMPASSION FATIGUE, MINDFULNESS AND GENETIC COUNSELING

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Genetic counseling is a caring profession. It has been known for some time that genetic counselors are susceptible to clinical burnout and/or compassion fatigue. Recent studies have shown that mindfulness may help health care professionals with their experience of burnout. It is hypothesized that mindful awareness may be useful in ameliorating these symptoms of burnout in genetic counselors. The present study aims to collect information about the experiences of Australasian genetic counselors in relation to compassion fatigue and mindfulness. This study is an online questionnaire open to practicing Australasian genetic counselors. The survey is in three parts. The first part collects demographic information about the genetic counselor completing the questionnaire. The second part of the survey is the Professional Quality of Life Scale, Compassion Satisfaction and Fatigue Subscales — Revision IV. The final part of the questionnaire is the Mindful Attention Awareness Scale. Both scales are validated. Descriptive analyses will generate frequency data to elicit a description of participants and the responses obtained. Analysis of categorical measures will be undertaken using chi-squared analysis to determine if there are any differences in responses. For continuous variables, differences in means between groups will be assessed using *t*-tests. Qualitative content analysis (inductive approach) will be utilized to analyze open-ended responses. The results of this questionnaire will provide important data about clinical burnout and compassion fatigue among genetic counselors and will enable recommendations about the use of mindfulness to minimize the impact of these on those in this profession.

69. THE IMPACT OF GENOMICS ON GENETIC COUNSELING: AN EXPLORATION OF AUSTRALIAN STAKEHOLDER VIEWS

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There is agreement among clinicians and healthcare providers that genomic technology — specifically in the context of sequencing large panels of genes or whole genomes — will have a wide impact on many health professionals, particularly genetic counselors. The way in which pre- and post-test counseling sessions are conducted is likely to require modification, including the need to address, during consent, the increased likelihood of identifying incidental findings and variants of uncertain significance (VOUS), and related personal and familial implications. While there has been much debate about the transition to genomic counseling in Europe and the United States, there has been little exploration of professional views in Australia. To address this gap, this research study aims to characterize the similarities and differences between a genetic counseling session and a genomic counseling session, and to answer the following questions: What should genomic counseling involve? Is it adapted from, or a significant departure from genetic counseling? What training is required for genetic counselors? Seventeen genetic counselors and clinical geneticists have agreed to participate (RR =

53%), and 12 interviews have been conducted. The semi-structured telephone interviews are based around five hypothetical scenarios of the unexpected identification of: carrier status in a pregnancy, an inherited cancer predisposition, a finding with no corresponding phenotype, and prediction of a newborn's health complications. Interviews are being transcribed, de-identified, coded and analyzed for salient themes, and these will be reported. These results will inform the development of frameworks to guide genetics professionals transitioning into the genomic era.

70. INVESTIGATING DIFFERENT MODES OF INFORMATION DELIVERY IN A GENETIC COUNSELING ENVIRONMENT

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Traditionally, hard-copy resources such as diagrams and fact sheets have been used to represent inheritance patterns. However, research into multimedia-based methods of information delivery has yielded increased levels of patient knowledge. The aim of this study is to investigate the effectiveness of an animation explaining autosomal recessive inheritance: to assess changes in client knowledge and attitudes, as well as the perceived effectiveness that clinicians attribute to the animation. It is hypothesized that the animation will be at least as effective as traditional methods in achieving increased knowledge, as well as a more positive attitude towards the overall counseling session. Individuals attending their first genetic counseling session for an autosomal recessive condition are being recruited from four sites in the Hunter Genetics service. They are assigned to an intervention group, who view the animation in conjunction with their counseling session, or a control group, who receive traditional genetic counseling. Participants complete pre- and post-session questionnaires to assess their knowledge of autosomal recessive inheritance and views on the animation. Participating clinicians are also being interviewed to investigate their attitudes towards the use of the animation in a clinical setting. Total recruitment will include 50 clients and 6 clinicians. This intervention may lead to increased client understanding of the underlying inheritance of autosomal recessive conditions, as well as aid communication to other at-risk family members. If the animation is successful there is the potential for continued clinical use, and development of further animations for use in other areas of genetics.

71. NON-INVASIVE PRENATAL TESTING FOR FETAL CHROMOSOMAL ABNORMALITIES: INVESTIGATING THE EXPERIENCES OF PREGNANT WOMEN AND PARTNERS WITH VARYING LEVELS OF HEALTH LITERACY

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Non-Invasive Prenatal Testing (NIPT) uses cell free fetal DNA, found circulating in maternal blood, to screen for the most common aneuploidies. NIPT is progressively being introduced into the prenatal setting in Australia. It is important that expectant parents make decisions about prenatal screening in the context of clear and comprehensible information which facilitates an understanding of the sensitivity, specificity and limitations of the test. However, making an informed decision about NIPT may be particularly challenging for those with lower health literacy skills, commonly defined as the

ability to access, understand, appraise and apply health information. This study aims to explore (1) comprehension and interpretations of NIPT as a new prenatal screening technology, and (2) the process of decision-making about NIPT in a population of pregnant women and their partners with varying levels of health literacy. Pregnant women and their partners who undertook NIPT through a genetics service and receive a 'low-risk' result are recruited into the interview study. The 15 pregnant women and 15 partners complete a self-report on their self-perceived functional health literacy skills prior to the semi-structured exploratory interview, which explores perceptions, understanding, information seeking behaviors, knowledge, decision-making and communication needs and experiences in the context of NIPT. The findings will inform clinical practice by guiding how best to communicate information about NIPT in a manner appropriate to women and couples with varying levels of health literacy.

72. ESTABLISHING A PRENATAL GENETICS SERVICE AT THE NORTHERN HOSPITAL IN MELBOURNE

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Austin Health Genetics Department have conducted monthly Familial Cancer Clinics at Northern Health since 2013. In June 2014, Austin Health expanded this service to include a Prenatal Genetics Service; the result of a partnership between Austin Health Genetics, The Mercy Hospital for Women (MHW) and Northern Health. We aim to present an overview of the first 8 months of the new service at Northern Health and to describe some of the challenges encountered. Between June 2014 and March 2015, 103 patients were referred to the service. 81 patients attended an initial appointment, and 13 of those attended for a review appointment. 53 prenatal genetic tests have been coordinated. Altogether, 29 women were referred for termination of pregnancy (TOP), following the identification of structural fetal abnormality or a specific genetic diagnosis. Challenges have included working across 3 hospital sites, providing care to a diverse ethnic population and defining appropriate patient referral pathways. As a Catholic institution, MHW does not provide TOP services, therefore co-ordination and referral for appropriate care for couples that request TOP is a critical aspect of the genetic counselor's role. The Prenatal Genetics Service at Northern Health has streamlined care for women in the North East of Melbourne who require genetic advice in pregnancy. The ultimate goal is to establish a multidisciplinary team at Northern Health, consisting of clinical and research staff. Relationships between service providers at Northern Health, MHW and Austin Health are critical to the successful development of this service.

73. AN EVALUATION OF PRE-SYMPTOMATIC TESTING SERVICES FOR HUNTINGTON DISEASE IN AUSTRALIA (2009–2014)

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Huntington disease (HD) is a late-onset neurodegenerative condition with no available cure or treatment. Individuals at risk of the

condition can undertake genetic counseling and pre-symptomatic testing (PST), and if they choose, ascertain if they have inherited the HD mutation. International guidelines governing the provision of these services were updated in 2012 (McLeod et al., 2012). The views of those who have had PST for HD and their support persons are important in reviewing and informing Australian genetics service provision in the context of these guidelines. A recent qualitative study with individuals who have had PST through one Australian genetics service demonstrated overall satisfaction with service provision. It also identified some areas that required further exploration, including the need for follow up regardless of the test result and the importance of the role and needs of the support person. It is hypothesized that this study will confirm these findings. Separate surveys informed by the qualitative study were developed for individuals who had PST for HD and their support persons in Australia (2009–2014). Participants were recruited through promotion of the surveys in both online and paper-based formats by Huntington's disease statewide associations. Data items included demographic details, test results, client and support persons' needs, and their experiences pre- and post-testing. Understanding the needs and experience of those undertaking PST and their support persons has the potential to further inform Australian PST guidelines for optimal service provision for HD and other similar conditions. These findings are also relevant internationally.

74. PERSPECTIVES OF A CANCER SUPPORT GROUP ON CONSENT FOR TUMOR BANKING FOR FUTURE RESEARCH

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Background: Human biological material stored in biobanks is an important resource for translational biomedical research. Donors to biobanks are invited to give informed consent for the storage and use of their donated biomaterial for future ethically approved research. The advent of next generation sequencing has signalled a potential explosion of genomic data from biomaterial acquired from biobanks for research — giving rise to ethical questions over whether, when and how to return research results (including incidental findings) to donors. **Aim:** This study explores stakeholders' views concerning ethical and governance issues in the return of research results and linkage of health data to donated biospecimens. **Method:** This study uses focus groups to evaluate the views of patients, their carers and/or families on consent for tumor banking at the Kolling Tumour Banks, Royal North Shore Hospital (RNSH). Study participants were recruited by invitation through a RNSH cancer support group (Cansupport) and allocated to focus groups of 6–8 people based on responses to an initial on-line questionnaire. The participants' views on linkage of health information to samples held in biobanks and the implications of the return of research results for biobank donors and their families are explored using hypothetical scenarios provided as a booklet of stories. Transcribed recordings of the focus groups will be analyzed thematically. **Conclusion:** This study will help to inform ethical consideration and policy-making regarding consent to biobanking and may highlight a role for genetic counselors in the return of research results in the future.

GENETIC EDUCATION

75. PREPARING FOR THE IMPACT — EDUCATIONAL NEEDS OF MEDICAL SPECIALISTS ORDERING GENOMIC TESTING

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The translation of genomics into mainstream medicine presents significant challenges. There is considerable potential for misunderstanding by health professionals of the clinical application of testing and interpretation of results, a lack of preparedness for the impact of genomics and potential for missed opportunities for improved patient outcomes. Engaging non-genetics medical specialists in education in this field has historically been difficult. The introduction of high-speed genome sequencing by the Garvan Institute of Medical Research and the NSW Genomics Collaborative Grants Program in 2014 has created momentum and a unique opportunity to identify early adopters of genomic testing. Furthermore, the Centre for Genetics Education, in partnership with the Office for Health and Medical Research, NSW Ministry of Health, has recognized non-genetics medical specialists ordering genomic testing as a priority group for genomic education. A qualitative pilot study to explore the attitudes, experiences, and educational support needs of medical specialists has consequently been undertaken. Semi-structured interviews with non-genetics medical specialists who have had clinical research participants sequenced through the Kinghorn Centre for Clinical Genomics, Garvan Institute (KCCG); or from a laboratory other than KCCG recruited through professional organizations; and with NSW clinical geneticists who have utilized genomic testing in the past 12 months, have been conducted and results analyzed for recurrent themes. Findings will inform a first step in the development of urgently needed support and educational resources for non-genetics medical specialists utilizing genomic testing in clinical care.

76. GENETIC HEALTH PROFESSIONALS' PERCEPTIONS OF INTEGRATING GENETICS INTO PRIMARY CARE

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As uptake of genetic testing increases, general practitioners (GPs) are expected to have an expanded role in delivering genetics services. This research aimed to explore the views of genetic health professionals regarding genetics service delivery, their perceptions of the impact new genetic technologies may have on primary care, and potential new models of service. Clinical geneticists and genetic counselors were recruited and semi-structured interviews with 22 individuals were conducted. Qualitative data were analyzed inductively, with independent coding and iterative development of themes. Most participants perceived that often GP referrals are inappropriate and that, overall, GPs' knowledge of genetics is poor. Most were unaware of guidelines for general practitioners for general genetic conditions (e.g., the *Red Book, Genetics in Family Medicine*). Almost all believed that new technologies will impact GPs and there is a need to better integrate genetics into primary care. There was a consensus among participants that GP education is a necessary first step; however, previous research suggests this is not sufficient and other approaches should be investigated. New service models

considered in the interviews included telephone service support, genetic counselors located in primary care or working privately. The greatest perceived barriers for integration were supervision for genetic counselors and lack of financial model. Despite advances in genetic technology and the promises of the impact on healthcare, the relationship between genetic health professionals and GPs has not changed in over 10 years. This research suggests that genetic health professionals' involvement in developing initiatives for integrating genetics into primary care would be beneficial.

GENETIC EPIDEMIOLOGY

77. GENETIC SUSCEPTIBILITY OF JAZF1, CDKAL1 AND IGF1 TO TYPE 2 DIABETES IN UYGHUR POPULATION

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Background: More than 40 genetic loci have been identified to be associated with type 2 diabetes (T2D) in Caucasian and Asian populations, but it remains unclear whether those susceptibility loci for T2D are also the risk factors for the unique Uyghur ethnic population, settled in Xinjiang, a north-western frontier area of China, with its own language, religious beliefs, lifestyles and special genomic structure. **Aim:** This case-control study aimed to investigate the genetic susceptibility of 16 T2D related loci in a Uyghur population sample. **Method:** Sixteen previously reported SNPs for T2D (*JAZF1*, *CDKAL1*, *CDKN2A/B*, *ADRA2A*, *CDC123/CAMK1D*, *SLC30A8*, *FADS1*, *PPARG*, *DGKB*, *IGF1*, *IGF2BP2*, *GCK*, *IRS1*, *GCKR*, *TCF7L2* and *TSPAN8*) were selected and genotyped in 102 Uyghur participants (51 T2D patients and 51 controls). **Results:** Among the 16 loci genotyped, *JAZF1* (rs864745), *CDKAL1* (rs7754840) and *IGF1* (rs35767) were associated with T2D in the Uyghur population (OR: 2.09, 95%CI: 1.07–4.10, $p = .032$; OR: 2.32, 95%CI: 1.19–4.54, $p = .014$; OR: 0.49, 95%CI: 0.24–0.98, $p = .044$, respectively) between Uyghur subjects with T2D and controls ($p > .05$). The cumulative risk allele scores (cases: 17.1 ± 8.1 , controls: 15.4 ± 7.3) of these 16 SNPs were associated with T2D in the Uyghur population (OR: 1.27, 95%CI: 1.07–1.50, $p = .007$). **Conclusion:** This study was the first attempt to evaluate a cohort of SNPs in or near 16 susceptibility loci for T2D in a Uyghur population and showed that rs864745 (*JAZF1*), rs7754840 (*CDKAL1*) and rs35767 (*IGF1*) were potential susceptible loci, whereas the CC genotype at rs864745 (*JAZF1*) indicated potential protective effect on T2D in Uyghur population.

PUBLIC HEALTH GENETICS

78. N-GLYCAN BIOMARKER PROFILING AS A RISK STRATIFICATION TOOL TOWARDS CHRONIC DISEASE PREVENTION

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Suboptimal health status (SHS) is characterized by ambiguous health complaints, general weakness, and lack of vitality, and it has become a new public health challenge. SHS is believed to be a subclinical, reversible stage of chronic disease. As studies of intervention and prognosis for SHS are expected to become increasingly important, a reliable and valid instrument for its assessment is essential. A questionnaire for measuring SHS in urban Chinese was developed based on focus group discussions and a literature review. Questionnaire validity and reliability were evaluated in a small pilot study and then in a cross-sectional study of 3,000 individuals. The analyses included tests for reliability and internal consistency, exploratory and confirmatory factor analysis, and tests for discriminative ability and convergent validity. The final questionnaire incorporated 25 items on SHS (SHSQ-25), and encompassed 5 subscales: fatigue, cardiovascular system, digestive tract, immune system, and mental status. The SHSQ-25 has proved to be a reliable and valid instrument for measuring subhealth status in urban Chinese. The progress of a combined genomics and glycomics study for screening biomarkers and exploring SHS as a preventive tool for non-communicable disease control and management from Australian Context will be presented.

79. A POPULATION-BASED COHORT STUDY OF WESTERN AUSTRALIANS WITH RARE DISEASE

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Rare diseases are those which occur in Australia in less than 5 in 10,000 people. There are estimated to be 5,000–8,000 rare diseases, and while each disease affects relatively few people, collectively, it has been estimated that they affect 6–8% of the population. The rarity and diversity of rare diseases pose specific challenges for healthcare provision and research, and for the development and marketing of therapies. The collective prevalence, high personal burden and unmet needs of people living with rare disease impacts the Australian community and is recognized internationally as a high-priority public health issue that needs to be addressed through high-level policy and planning. Collating data on rare diseases is significantly hampered by the inadequate coding specific for each disease within the International Classification of Disease (ICD) coding system and the diagnosis of rare diseases in the health system. Here we describe a unique rare disease population-based cohort study of people living in Western Australia over an 11-year period. This study aimed to describe the impact of rare diseases on the WA health system using linked data from health service and mortality records. In 2010, point prevalence of the cohort was approximately 4% of the WA population. Analysis of the cohort indicate that people living with rare disease account for a higher than expected portion of WA hospitalizations, emergency department presentations and pediatric deaths. Information from this study will begin to inform state and national planning for improved management of rare diseases in Australia.

80. HEALTHCARE EXPERIENCES OF AUSTRALIAN ADULTS LIVING WITH RARE DISEASES AND THE OPPORTUNITIES FOR CLINICAL PRACTICE

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In Australia, evidence is needed to inform clinical practice in relation to rare diseases, including from the perspective of people living with rare diseases. This study aimed to explore the healthcare experiences of Australian adults living with rare diseases, including at the time of diagnosis, health service use and willingness to be involved in research. An online survey was conducted in July–September 2014. Respondents were recruited from the databases of peak organizations in the rare diseases sector. 810 adults living with a rare disease completed the survey. Most respondents saw multiple doctors prior to receiving a confirmed diagnosis. Half had received an inaccurate diagnosis. One fifth did not receive any information at the time of diagnosis. Among those who did, many perceived they did not receive enough information and/or did not understand the information. Health service use in the 12 months prior to the survey ranged from a mean of 1.4 visits to dental services through to 8.7 visits to general practitioners. Most were willing to participate in research about their condition. Opportunities exist to enhance clinical care for people living with a rare disease, in areas such as patient access to timely, accurate diagnosis and information, the structure of health services to meet the needs of people living with a rare disease and the collection of evidence to understand the impact of rare diseases on the health system. It also demonstrates the principle of placing people living with a rare disease at the center of clinical care for rare diseases.

81. AWARENESS OF RARE DISEASES AMONG THE GENERAL PUBLIC OF WESTERN AUSTRALIA

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An online survey was developed to assess awareness in the general public of Western Australia (WA) about issues surrounding rare diseases and to gauge support for possible policy initiatives. A total of 1033 responses to the survey were received from Western Australians aged 18 years and over. Respondents were generally aware of a range of issues facing people living with rare diseases. These included a perceived lack of knowledge about rare diseases among general practitioners and the public, the need for highly specialized medical care, and the emotional and financial stress on families. Some key issues that were not well recognized by the WA public include the lack of cures and treatments, potential for increased use of medical services and the association between rare diseases and intellectual or physical disability. These results were consistent across different socio-demographic groups. There was widespread support among respondents for government spending to help people affected by rare diseases. This support was highest among those with

greater awareness of rare diseases. When asked to make a choice, most respondents indicated a preference for spending on common diseases such as cancer and heart disease over spending on rare diseases. However, there was strong support for public funding of potentially expensive tests and treatments for rare diseases. Taken together, the findings presented here, suggest the Western Australian public would likely support a range of public health policy options in the area of rare diseases.

82. CHILDREN LIVING WITH A GENETIC METABOLIC DISORDER: IMPACT ON TERTIARY IN-PATIENT SERVICES

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Background and aim: Genetic metabolic disorders are rare, chronic, clinically complex, and have significant impacts on the patient, their family and on health services. Few studies have estimated the in-patient costs associated with these disorders. **Aim:** To describe the burden and associated in-patient cost of rare genetic metabolic disorders in children treated by Genetic Metabolic Disorders Service (GMDS) at the Children's Hospital at Westmead (CHW). **Methods:** A cohort of children aged ≤ 18 years using the GMDS (July 2004–June 2013) represented 125 different genetic metabolic disorders. The Management Support Analysis Unit at CHW provided a detailed dataset describing occasions of service including inpatient, outpatient and emergency department (ED) encounters, and costs associated with in-patient encounters. **Results:** There were 791 patients engaged with the GMDS (434M; 357F); 272 patients presented to ED (1,571 ED encounters); 716 attended outpatients (17,254 outpatient encounters); 385 patients were admitted to CHW and (3,036 admissions). The average number of admissions per year was 338; average length of stay 3.2 days (range 1–180). The average direct cost per admission was \$7,668; total cost for the 385 patients over 8 years was \$23,281,396 for admissions alone. **Conclusion:** Children living with genetic metabolic disorders use tertiary/quaternary health services frequently, resulting in a significant health cost burden. Our unique data support the need for coordinated care planning and appropriate health service financing to meet the complex needs of these children. Further research is needed to determine health service costs for other groups of rare diseases.

83. FREQUENT USE OF SPECIALIST, ALLIED HEALTH AND HOSPITAL SERVICES BY AUSTRALIAN CHILDREN LIVING WITH RARE DISEASES

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Background: Rare diseases are chronic, complex, commonly diagnosed in childhood and require on-going medical care throughout the lifespan. The experiences of health service use among families who have a child living with a rare disease are rarely described. **Aim:** To describe health services use among Australian families living with a child who has a rare disease. **Methods:** A comprehensive questionnaire which embedded validated tools was sent to families recruited from partner organizations including the Australian

Genetic Alliance, The Steve Waugh Foundation, Variety and the Genetic Metabolic Disorders Service at the Children's Hospital at Westmead. **Results:** 462 families representing children with ~270 different rare diseases responded. Families experienced diagnostic delays — 30% consulted 6–20 doctors before getting the right diagnosis. Two thirds of children were admitted to hospital at least once in the previous year for a total of 1,075 admissions; 50% presented to the emergency department. In the previous year each child averaged 9 visits to specialists, 10 visits to a general practitioner, 24 visits to an allied health professional. Most needed care from multidisciplinary teams but only 44% had a health care coordinator. 70% would like their general practitioner to coordinate care but only 43% felt that their GP had adequate knowledge about the child's rare disease. Most families (89%) indicated that electronic medical records would improve their interactions with the health system. **Conclusion:** Families report frequent use of many different specialist and allied health services supporting a need for better coordination, planning and integration of health services.

84. A PUBLIC HEALTH-BASED SCREENING PROJECT FOR β-THALASSEMIA AND OTHER BIRTH DEFECTS IN UTTARAKHAND, INDIA

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The State of Uttarakhand has a population of 10.1 million, comprising major north Indian and local tribal population groups, with 9 of the 13 state districts located in the foothills of the Himalayas. The literacy rate is quite high, 88.3% in males and 77.0% in females, and the IMR is 32/1,000 by comparison with the national average of 40/1,000. The Action on Birth Defects Project has been piloted in Uttarakhand since 2012, with the objective of establishing a framework for birth defects within the state public health system. The initial steps in the project have involved the development and implementation of screening protocols for β-thalassemia carrier status, and newborn screening for G6PD deficiency and congenital hypothyroidism. In 2013, as part of the national health and family welfare program, Rashtriya Bal Swasthya Karyakram (RBSK), Child Health Screening and Intervention Services were initiated to address community needs in Birth Defects and Developmental Delays for an estimated target population of 270 million, aged 0–18 years. The Uttarakhand Project was amended to match these national aims by combining β-thalassemia carrier screening and screening for anemia. The target group selected was government school students aged 15–18 years, estimated to number 191,000 in the four state districts selected for the study. To date, 67,343 adolescents and 15,622 newborns have been tested in Uttarakhand. The Project has been incorporated into national screening and intervention guidelines for β-thalassemia, G6PD deficiency and congenital hypothyroidism, including genetic education, care and counseling, and laboratory services, for implementation under the RBSK.

85. CASE REPORT: A RARE AND IMPORTANT DIFFERENTIAL DIAGNOSIS FOR FACIAL NERVE PALSY

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We present a 4-year-old boy with a 3-year history of recurrent facial nerve palsy. Prior to our assessment, he had been extensively investigated for infective, inflammatory and genetic causes of neuropathy without success. We recognized facial dysmorphism, bony finger syndactyly and temporal bone hyperostosis and sclerosis on CT scan, which led us to the diagnosis of sclerosteosis. Recurrent facial nerve palsy is a common presenting feature of this condition and can be treated with facial nerve decompression surgery. Sclerosteosis is a rare skeletal dysplasia that causes increased bone growth and bone density and this is the first reported case in a Sri Lankan family. It is caused by loss-of-function mutations in the *SOST* gene, which encodes the regulatory protein sclerostin that is involved in

bone remodeling. The role of sclerostin in relation to bone mineral density formation is currently of great research interest with respect to the pathogenesis and potential treatment of osteoporosis. Facial nerve palsy impacts significantly on a child's quality of life due to impaired facial expression, verbal communication, oral competence, taste and protection of the eye. It is important to identify a specific cause for this presentation so that appropriate treatment can be provided and any underlying disorder is identified. Sclerosteosis should be considered in the differential diagnosis of facial nerve palsy in a child as the cause of the facial nerve palsy in this condition is treatable and bony overgrowth of the skull must be monitored in order to prevent raised intracranial pressure and sudden death.
