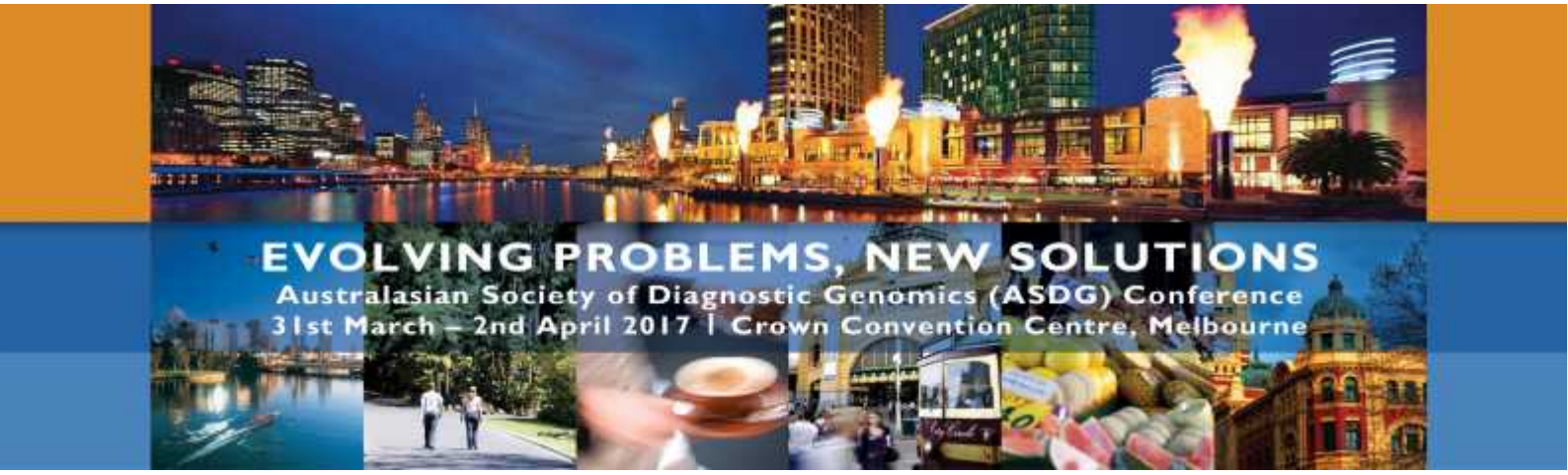

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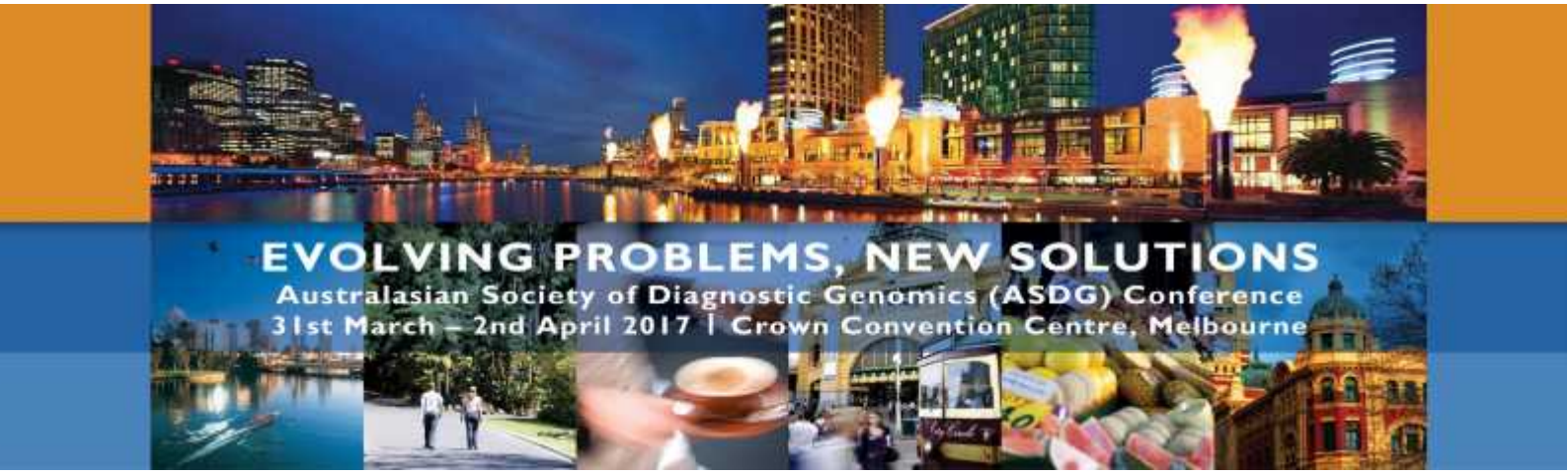

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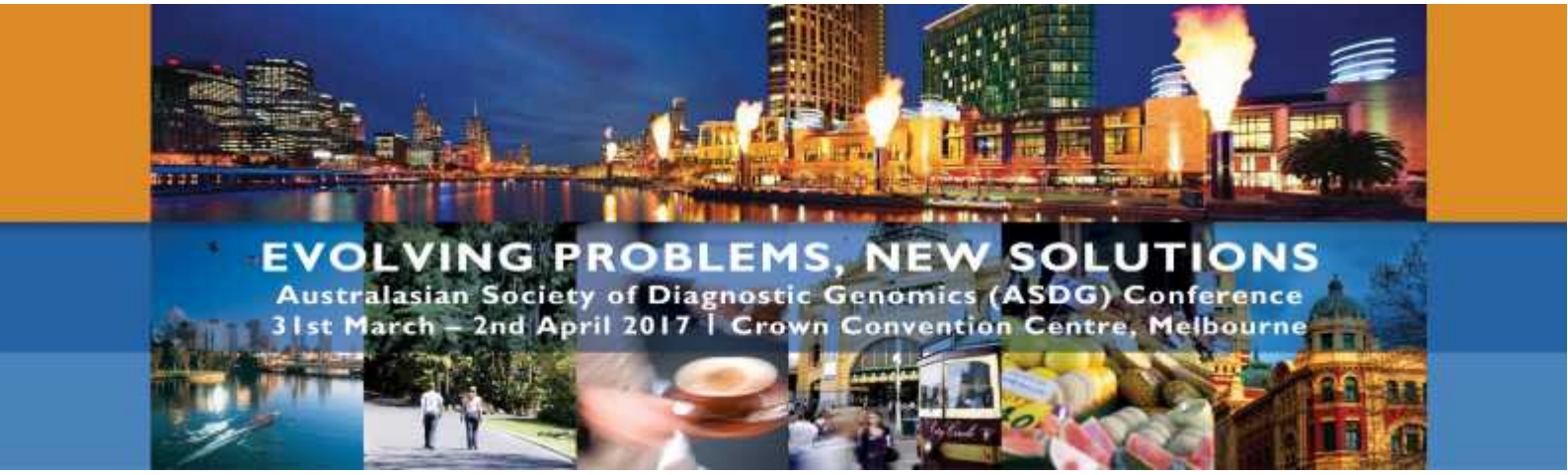

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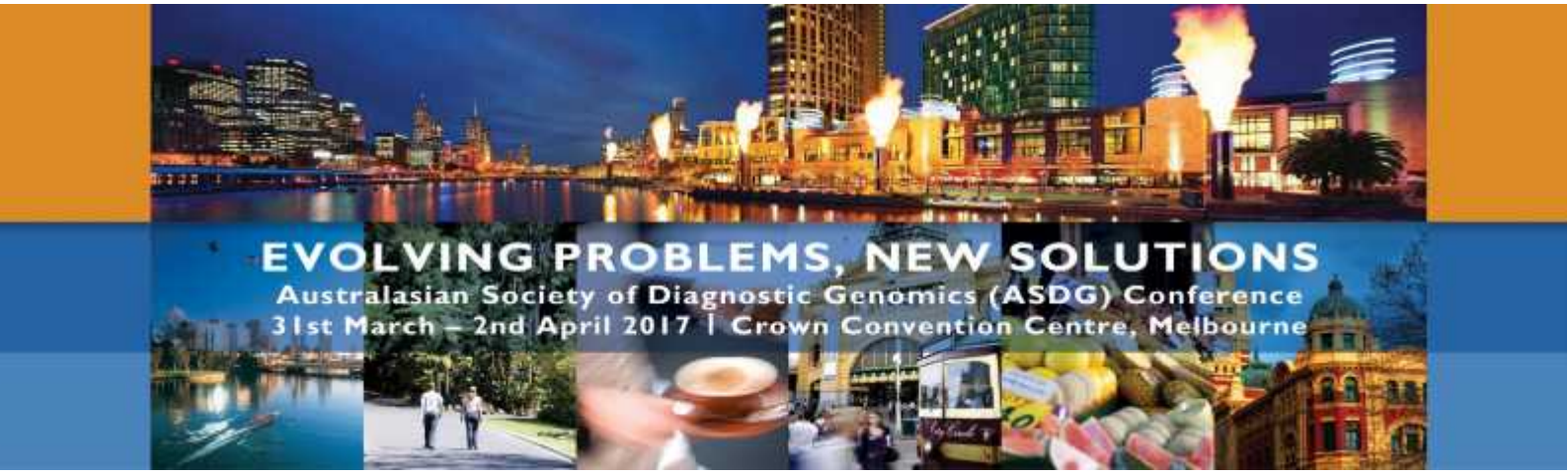
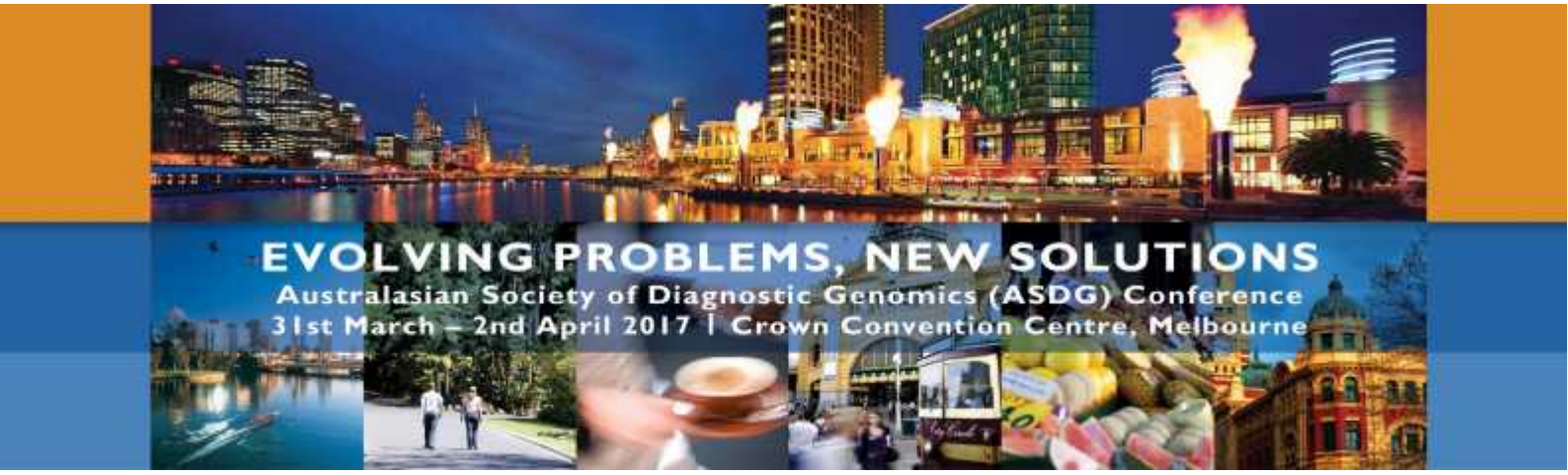


1330-1415 Friday 31st March 2017 - Invited Speaker: Professor David Amor

Genetic diagnosis of intellectual disability and autism: Past, present and future

Lorenzo and Pamela Galli Chair in Developmental Medicine, University of Melbourne



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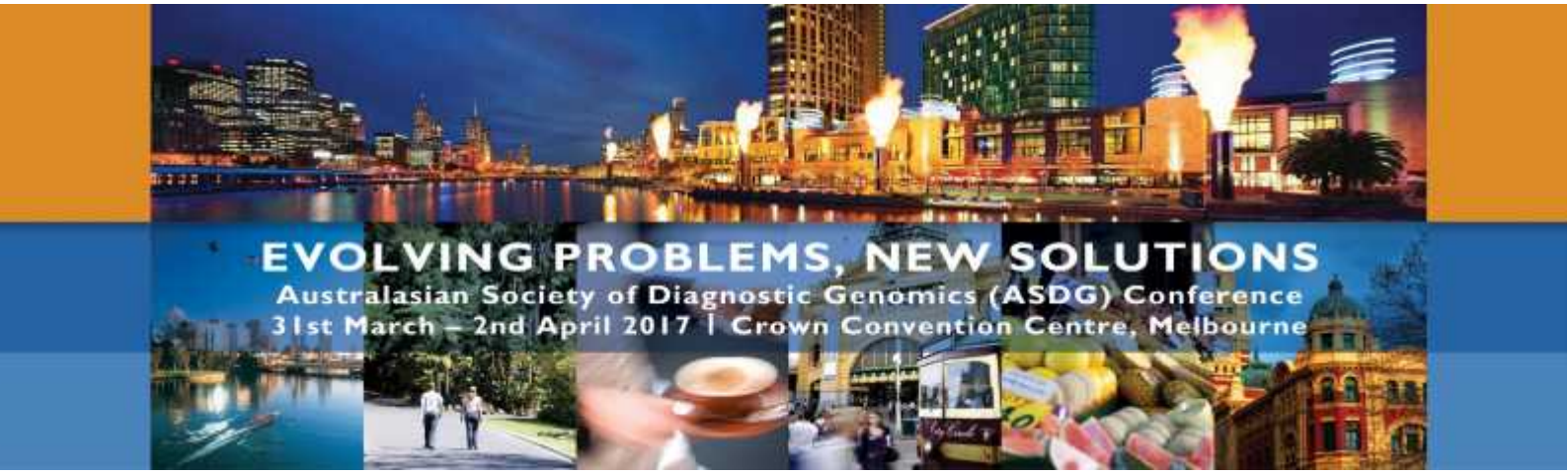

Ed Krumins award candidate

Four years of CMA: Ebbs and flows in prenatal cytogenetics

Lorna Williams[1], Paula Lall, Louise Hills, David Francis, Ralph Oertel, Amber Boys, Fiona Norris

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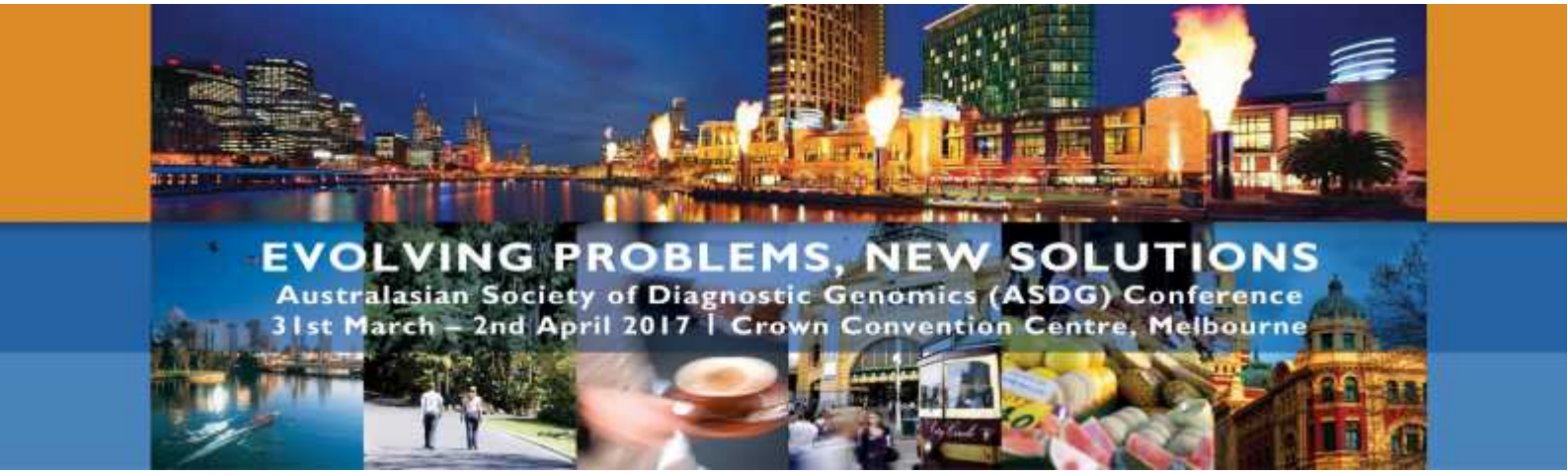
Chromosome microarray analysis (CMA), initially offered in the context of high risk pregnancies, is now commonly performed for a range of referral reasons. The clinical utility of CMA to detect pathogenic copy number changes is well established, however concerns of detecting variants of unknown significance or susceptibility loci for neurodevelopmental disorders are often raised as reasons for not offering CMA in pregnancies with normal ultrasound scans.

With this in mind, we review over 5,000 prenatal CMA results reported at VCGS Cytogenetics Laboratory between 2013-2016 – comparing outcomes from high and low risk referrals, examine the continued use of conventional chromosome analysis, and the impact non-invasive prenatal testing (NIPT) has made to referral numbers and indications over this time.

Biography

Lorna trained as a cytogeneticist at Oxford Cytogenetics Laboratory in the UK and has been working at the VCGS for the last 6 years as a medical scientist on the prenatal section.



Array CGH in prenatal diagnosis: a review of alternative approach?

Abhijit Kulkarni[1], Lucy Gugasyan[1], Paul Shekleton[2], Matthew Hunter[3]

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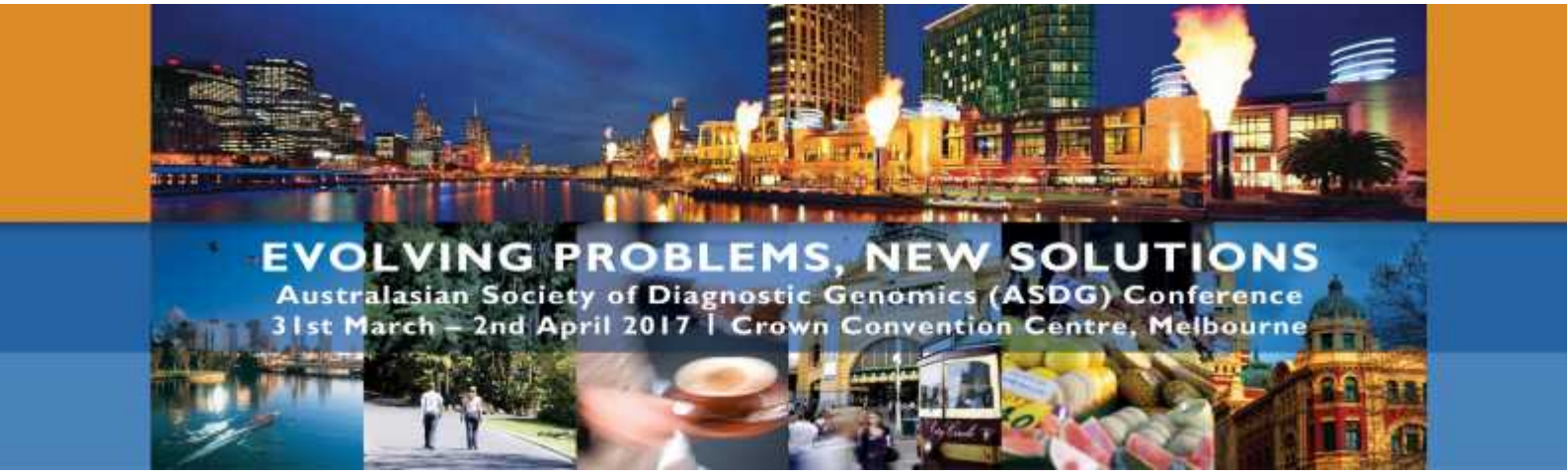
[3] Monash Genetics, Monash Medical Centre, Victoria, 3168

In Australia, Array CGH has replaced conventional cytogenetic analysis as the first line of investigation in prenatal diagnosis. One drawback is the detection of VoUS (Variations of Unknown Significance). There are now well established international guidelines for test indications, result interpretation and report writing for prenatal chromosomal analysis by Array CGH. Many laboratories take an approach to process all the prenatal samples by both FISH and Array CGH. We present data from the cytogenetics department at Monash Health, where array CGH was introduced in 2013 with a similar policy. There was a total of 850 prenatal specimens tested to date and 100 reports (11.7%) with VoUS issued, with parental studies completed in the majority of them. The internationally recommended approach of restricting array CGH testing to selected high risk cases with abnormal ultrasound scan and/or nuchal translucency of more than 3.5mm was implemented in September 2016 and 126 specimens are tested so far according to new protocol. We review and compare indications and fetal outcome for these cases. Interpretation criteria's for neurosusceptibilty loci in prenatal samples will be reviewed. The clinical and economic impact of the new approach with special emphasis in a public hospital setup will be summarized.

Biography

Dr Abhijit is Medical Scientist trained in India and UK, with special interest in Prenatal diagnosis. He was Head of Prenatal cytogenetics at St. Georges NHS hospital in London before moving to Australia.



Analysis of tissue from products of conception and perinatal losses using QF-PCR and microarray – introduction of an efficient two-step protocol

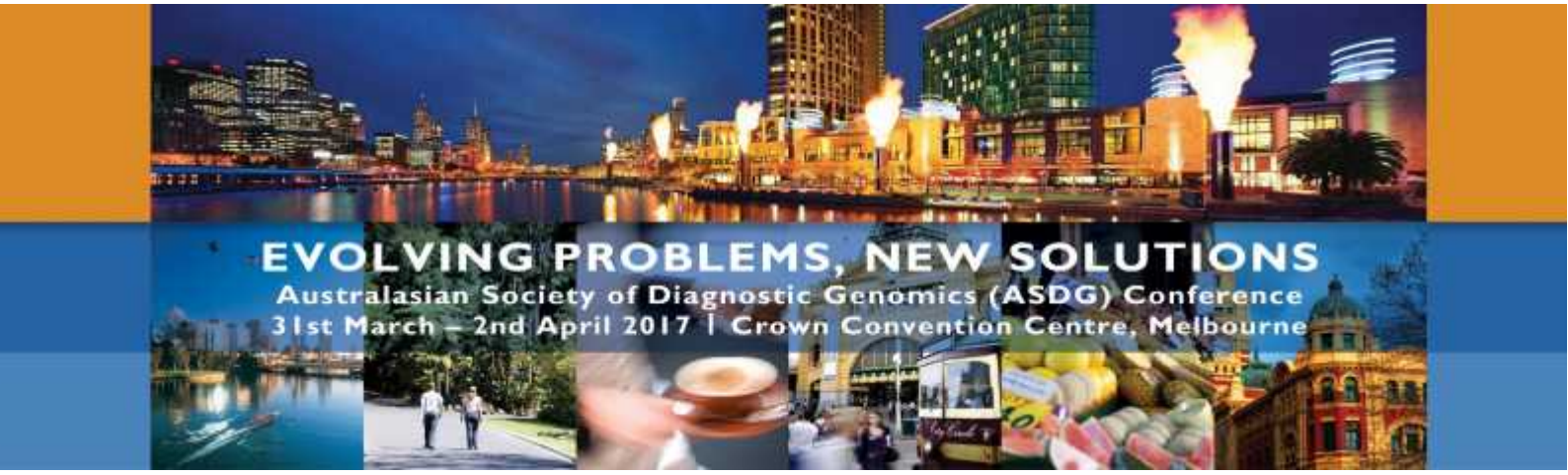
Paul De Fazio[1], Ling Sun[1], Matthew Hunter[2], Abhijit Kulkarni[1]

[1] Cytogenetics, Monash Health, Monash Medical Centre, Clayton, Victoria, 3168
[2] Monash Genetics, Monash Health, Monash Medical Centre, Clayton, Victoria, 3168

Approximately 15% of all clinically recognized pregnancies result in spontaneous miscarriage, of which about 50% are etiologically attributed to chromosome abnormalities. Of first trimester miscarriages with an identified genetic abnormality numerical chromosome abnormalities account for ~86% of cases, structural abnormalities for ~6% and single gene mutations or mosaicism the remaining ~8%. There is currently no international consensus on the criteria for recurrent miscarriage (RM) or on testing recommendations. Looking at retrospective data from 2015 in the Cytogenetics laboratory at Monash Medical Centre we evaluated the results of chromosome analysis on fetal tissues using microarray. 432 products of conception and fetal loss specimens were processed for microarray testing. Of these, 32% (n=104) showed a chromosomal aneuploidy, 3.5% (n=15) were triploid and an unbalanced chromosomal abnormality was identified in 2 cases. Presenting the validation data for QF-PCR to identify common aneuploidies, we propose a more efficient two-step protocol for cytogenetic testing of fetal loss tissues. The scientific, clinical and economic benefits of this protocol will be discussed.

Biography

Paul completed a Master of Science in Genetics at the University of Melbourne in 2013 before joining the Cytogenetics laboratory at Monash Health in 2014. His role at Monash is now focused around the development and implementation of new molecular test methods.



Assessing unknown sequence variations in thalassaemia diagnosis

Kerryn M Weekes[1], Wendy M Hutchison [1], Jeremy N Wells [1], Nicholas Clarke [1], Anastasia Adrahtas[1], Lily Li [1], Jesse Pinguinha [1], Asif Alam[1], Elizabeth Algar [2], Zane Kaplan.[3]

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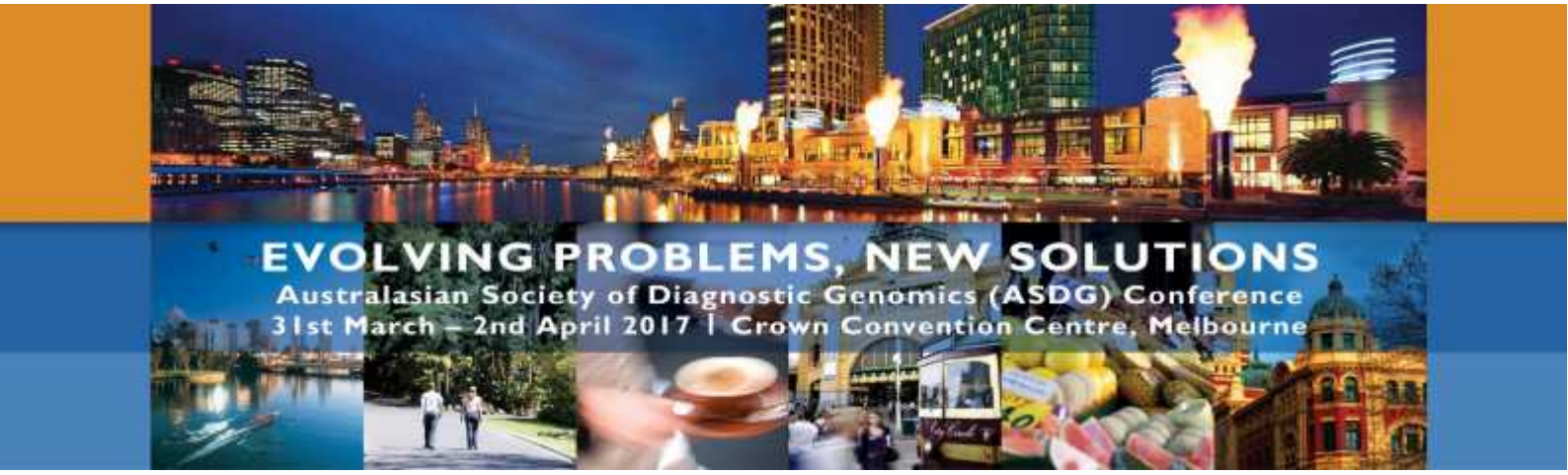
Thalassaemia and haemoglobinopathies are among the most common monogenic recessive disorders and are caused by mutations in both the alpha and beta globin gene complexes resulting in either decreased globin production or structural anomalies associated with distinct phenotypes. They are among only a few recessive disorders presenting with a mild phenotype in the carrier state that enable carriers to be detected during routine blood tests.

Recent advances in genetic testing for thalassemia have revealed increasing complexity with carriers described with mutations affecting more than one globin gene. Due to the increasing demand for thorough investigation of couples with mild phenotypic changes, many sequence variations in multiple genes are being discovered by our laboratory that are not reported in any of the databases or in scientific literature. The challenge is to evaluate the pathogenicity of these variations so that an accurate risk assessment for a couple can be reported.

We present a cohort of gene sequence variations and the difficulty in categorising them as pathogenic or benign using the current guidelines and standards.

Biography

Kerryn is the senior scientist in the Thalassaemia and Haemophilia Molecular Reference Laboratory. This laboratory is the Victorian reference laboratory and provides carrier, proband and prenatal testing for thalassaemia and haemophilia. Kerryn has been senior scientist for nearly 10 years and during this time the laboratory has grown 10-fold. She obtained her fellowship of the HGSA in 2016, one of the last candidates to receive a HGSA fellowship.



Mosaic RYR2 mutation identified in a childhood-onset cardiac disorder

Sarah Pantaleo[1], Belinda Chong[1], Daniel Flanagan[1], Ivan Macciocca [2], Jacob Mathew [3] & Desirée du Sart[1]

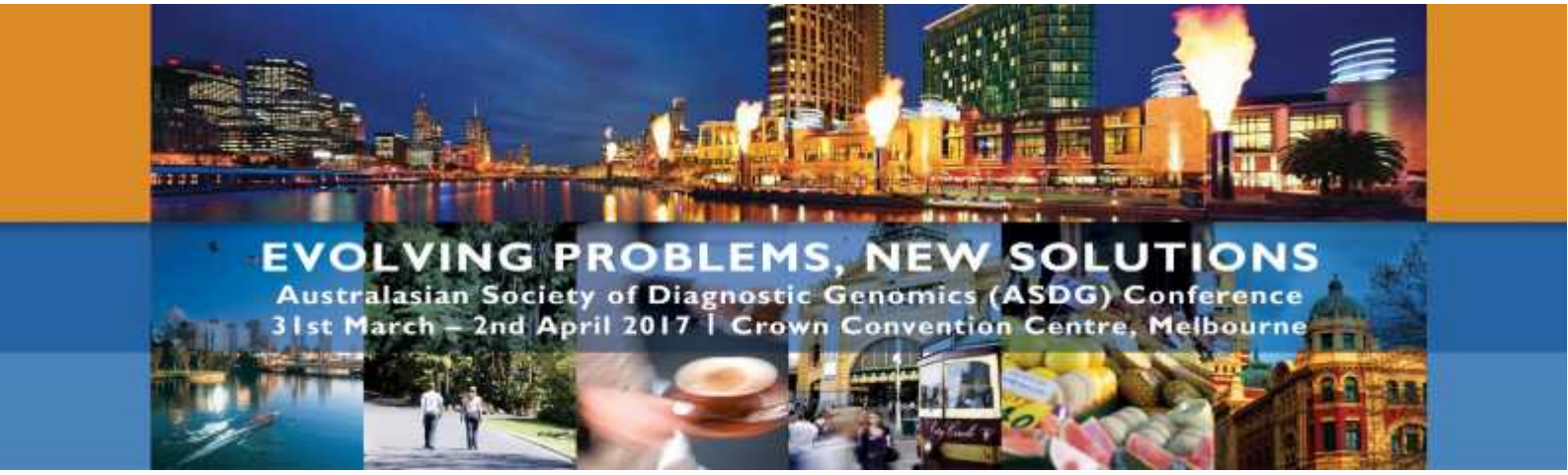
[1] Molecular Genetics Laboratory, Victorian Clinical Genetics Services, Murdoch Childrens Research Institute, Victoria, Australia
[2] Victorian Clinical Genetics Services, Murdoch Childrens Research Institute, Victoria, Australia
[3] Cardiology Department, Royal Children's Hospital, Victoria, Australia

We use a custom Next Generation Sequencing gene panel to screen patients with cardiomyopathies, arrhythmias, aortopathies and congenital heart disease. Data analysis occurs through a custom pipeline and the complete coding sequences of all genes are screened and all variants with population database frequency <1% are reported.

A 12 y.o. boy presented with dilated cardiomyopathy [DCM], multiple arrhythmias and cardiac remodelling. We analysed variants in genes associated with cardiomyopathies and arrhythmias in this patient and identified a novel, potentially disease-causing variant in the RYR2 gene. This variant was predicted to be deleterious by in silico software programs, was not present in a population database and was not reported previously in any cardiac disorder cases. It was classified as a variant of uncertain significance with high clinical significance. Upon analysing the NGS data, it was apparent that the variant was mosaic at a level of 22% (mutant allele present in 114/391 reads) and this was also evident on the Sanger sequencing confirmation performed on the blood DNA.

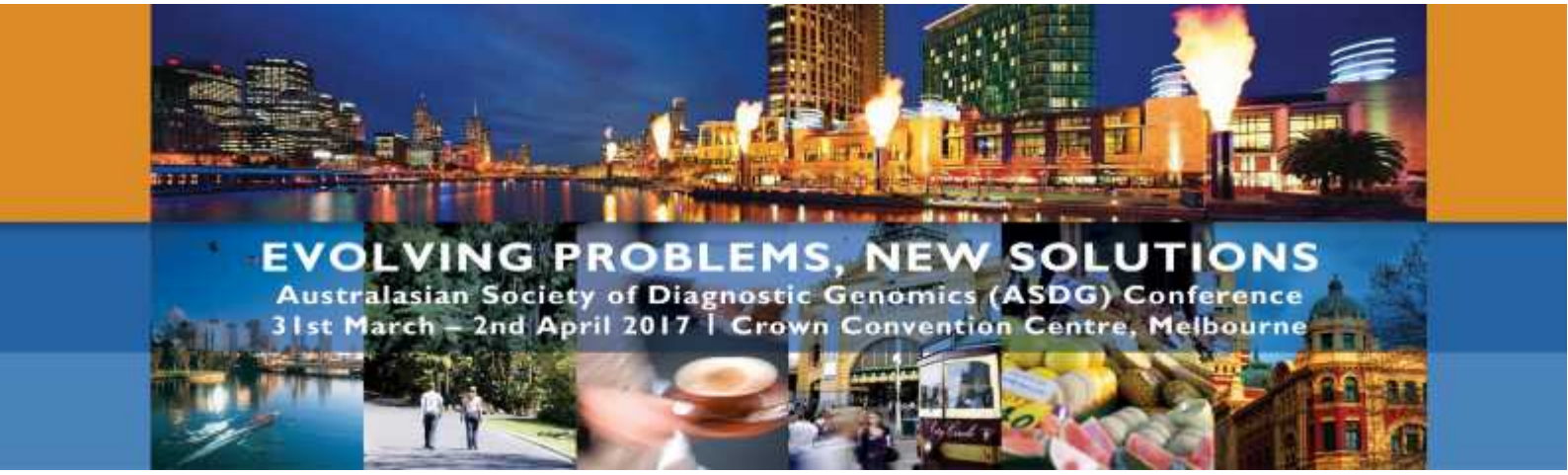
There are many genes associated with DCM, representing marked locus heterogeneity. The RYR2 gene is not reported to be associated with pure DCM however, it is reported to be associated with CPVT, a condition characterized by an abnormal heart rhythm and ARVD, a disorder of the muscular wall of the heart. The significance of this mosaic finding in blood DNA is uncertain. Data from further analyses will be presented to help clarify whether this variant is disease-causing, such as parental testing to confirm whether it is de novo and testing of other tissues from the patient, in particular cardiac muscle to detect the level of mosaicism present.

This case highlights the complexity of identifying a genetic cause in cardiac cases which have complex etiology.



Biography

Daniel Flanagan is a Medical Scientist at the Victorian Clinical Genetics Services (VCGS) with over 6 years of experience in molecular genetics. His main focus at the VCGS is the testing and classification of genetics variants associated with cardiac disorders, and the development of tests for rare disorders. He also has experience and a keen interest in developing automation protocols for molecular techniques.



Spinal muscular atrophy and next gen sequencing – can it really be that difficult?

Peter Field[1], Melinda Richter[1], Nicole Martin[1]

[1] Virtus Diagnostics – QFG Genetics, Level 1 Boundary Court, 55 Little Edward Street, Brisbane, QLD, 4000

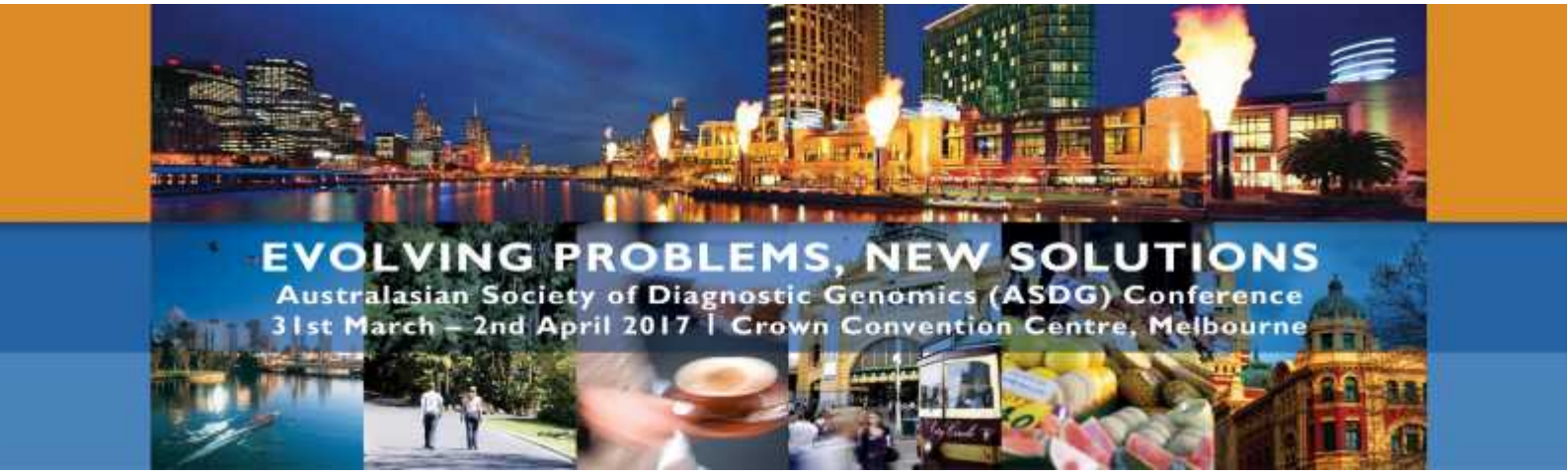
Spinal Muscular Atrophy (SMA) is a severe life limiting autosomal recessive condition with a carrier rate of approximately 1 in 40 to 1 in 60. Current testing for carrier and affected status relies on the few base pair differences between the SMN1 gene and the SMN2 pseudogene. These base pair differences allow for selective annealing of probes prior to MLPA or real time PCR for two successful methods of carrier screening.

Next Generation Sequencing (NGS) should be able to distinguish these base pair differences and allow the user to identify carrier from affected from normal samples, but this is not the case. The first problem is trying to sequence a deletion of an exon, the entire amplicon used in NGS is not there and no variant is reported. The sequence homology between the two genes is over 99.9%, so you rely on the software to capture those differences. The software preferentially analyses SMN2 prior to SMN1 leading to amplicons attributed to the incorrect location.

There has been a published method for identifying carriers with NGS but as we identified, this is not necessarily accurate and could lead to misdiagnosis for the unaware investigator.

Biography

Molecular Genetics Supervisor at QFG Genetics



Finding the lost CARRIERS of FRIEDREICH ATAXIA

Hazel E Phillimore[1], Rebecca Gould[1], Belinda Chong[1], Desirée Du Sart[1]

[1] Molecular Genetics Laboratory, Victorian Clinical Genetics Service, Murdoch Children's Research Institute/Royal Children's Hospital, 50 Flemington Road, Parkville, Victoria, Australia

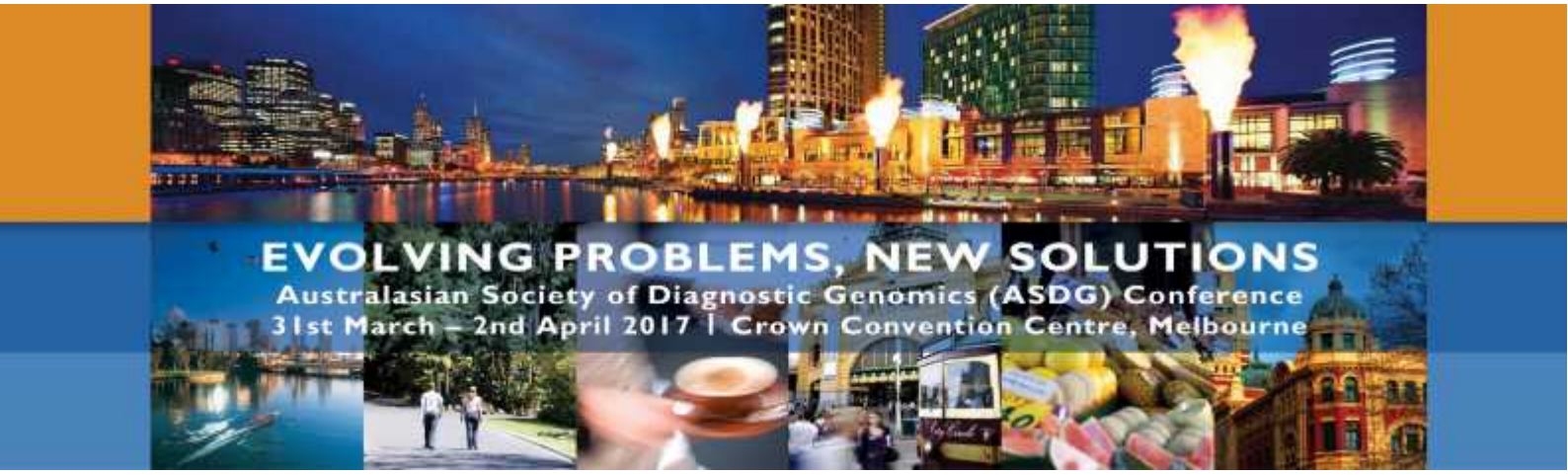
Friedreich ataxia (FRDA) is a common autosomal recessive ataxia that is mainly caused by a biallelic hyper-expansion of an intronic GAA trinucleotide repeat in the frataxin (FXN) gene. Most patients (>95%) have two expanded alleles in the affected range (66 -1700 repeats), while the remainder of patients have one expanded allele and an inactivating mutation on the other allele. Conventional PCR will reliably detect normal alleles and smaller expanded alleles. Detecting very large expansions can often prove difficult and carrier status could be missed due to non-amplification of an expansion, sometimes due to preferential amplification of the smaller allele or poor quality DNA.

The introduction of Triplet-primed PCR analysis (TP-PCR) into the analysis of several repeat disorders including FRDA has allowed the presence of an expanded allele to be robustly detected by PCR to confirm a diagnosis or determine carrier status. In particular, when samples appear homozygous with conventional PCR, TP-PCR can confirm the absence of an expansion, or detect the presence of an expanded allele not detected previously.

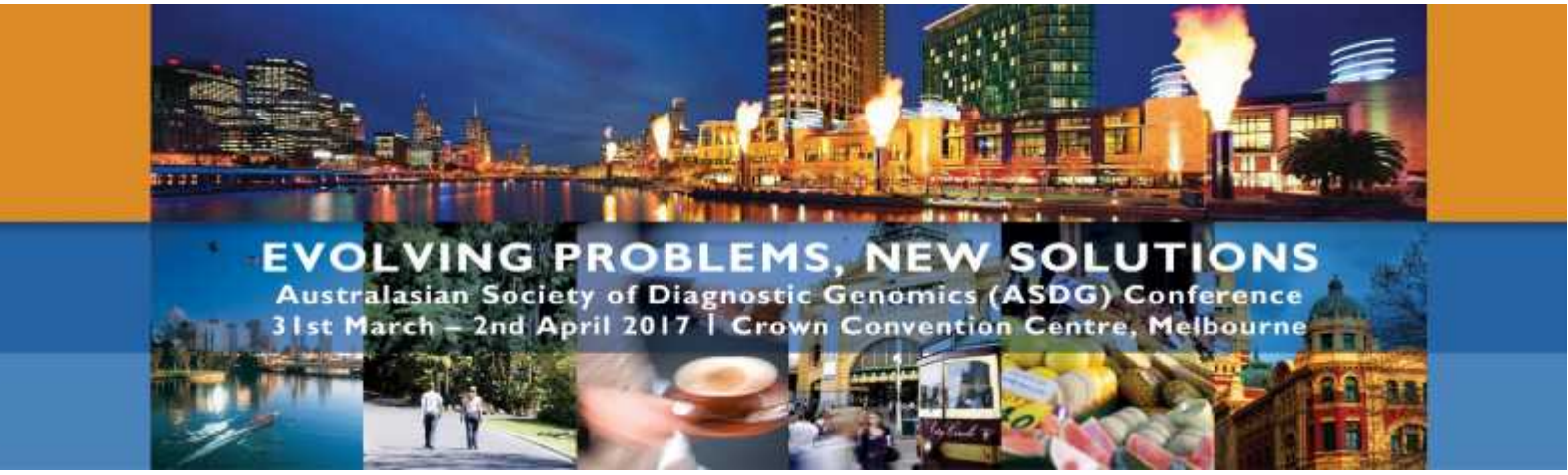
We present a case where an individual was tested in 2007 and reported not to be a carrier. Recent testing using TP-PCR shows the presence of an expanded allele in the patient, indicating carrier status for FRDA. Further analysis of other family members using conventional PCR has shown the presence of only one expanded allele in the affected family member, a confirmed carrier status in one parent and the absence of an expanded allele in the other parent. However, testing with TP-PCR shows the presence of an expanded allele in both parents as expected. In our presentation, we will present further investigations to determine the reason for the lack of amplification of the one expanded allele in this family.

Biography

Hazel Phillimore is a senior medical scientist in the Molecular Genetics Laboratory at VCGS (Victorian Clinical Genetics Service) at the MCRI (Murdoch Childrens Research Institute) within the Royal Children's Hospital, Melbourne. She has worked in molecular genetics in various roles since 1990 and mostly as a senior scientist in diagnostic genomics as part of a Regional Genetics Service in London, UK. Her skills and knowledge are in a wide range of inherited genetic disorders and different



technologies, as well as somatic cancer genetics (from working at the Peter MacCallum Cancer Centre, Melbourne) and in pharmacogenetics (from working at GenesFX, Melbourne).



Ed Krumins award candidate

Genomics delivering molecular diagnosis in the complex Inherited Retinal Dystrophies

Benjamin M Nash[1,2,3,4], Dale Wright[2,4], Bruce Bennetts[2,4], John Grigg[1,3,4], Robyn V Jamieson[1,3,4]

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[3] Save Sight Institute, Macquarie St, Sydney, NSW 2000 Australia
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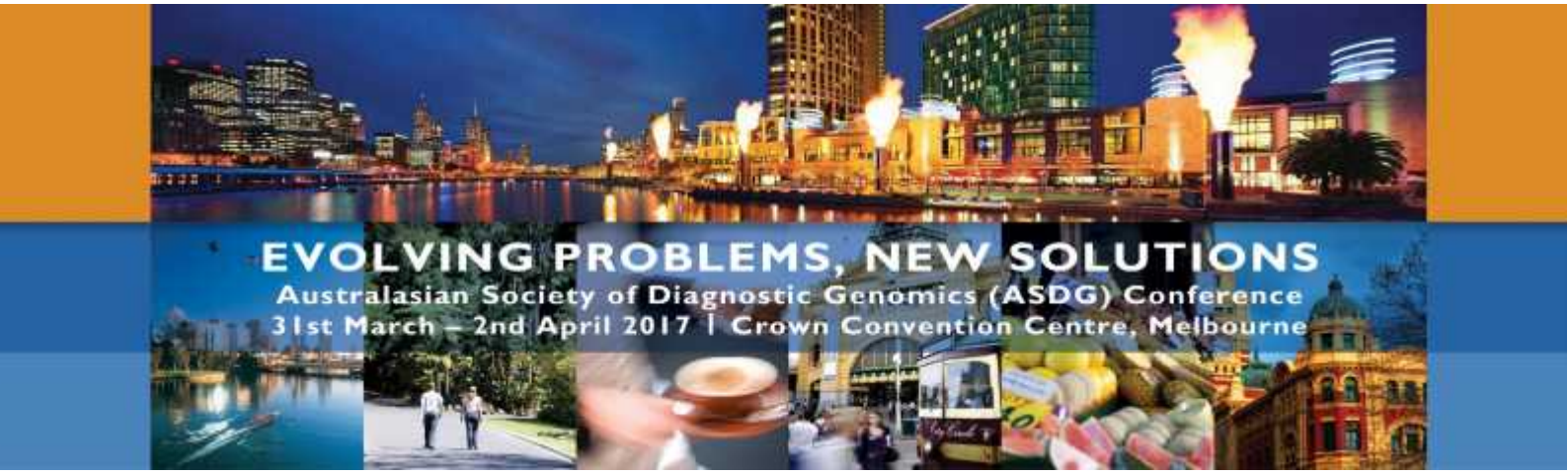
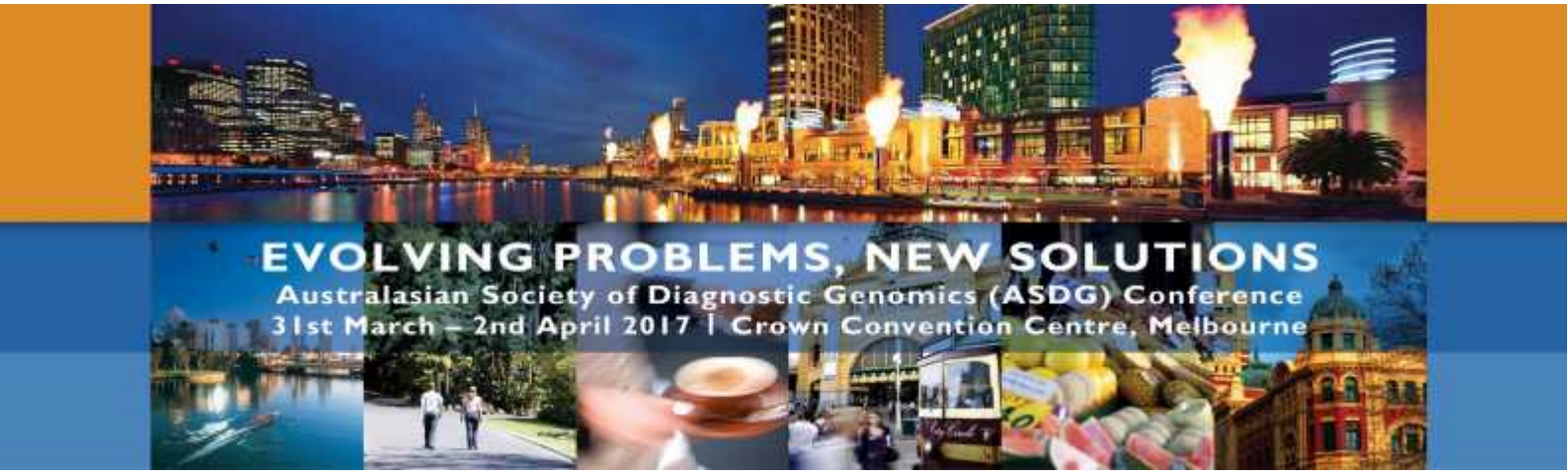
Genomic approaches to genetic diagnosis are proving to be of great value in conditions with high clinical and genetic heterogeneity. The inherited retinal dystrophies (IRD) affect approximately 1/3500 people worldwide and are degenerative disorders of the retina affecting both rod and cone photoreceptors. Prioritising the >250 known causative disease genes is challenging. Until recently, there was no clinical diagnostic testing available for IRD in Australasia allowing for the examination of all the known genes in a cost-effective and timely manner. We are using a combination of next-generation sequencing (NGS) strategies in IRD patients to determine their relative clinical value. In a cohort of 50 patients with familial or sporadic IRD, we have utilised the Illumina TruSight One clinical exome panel. Libraries generated were subsequently sequenced on the NextSeq 550. Variants detected in the 217 RD genes of interest were filtered and prioritised on in silico allele frequencies, conservation and pathogenicity prediction scores, with final candidate variants categorised using ACMG guidelines. Novel and previously reported frameshift, missense and premature stop mutations were identified in several genes including the syndromic genes BBS1, USH2A and IFT140. Molecular diagnosis was achieved in 38/50 (76%) families allowing for improved patient management and recurrence risk information. Our panel-based testing has identified novel genotype-phenotype correlations for the gene NMNAT1, while in other cases has facilitated a change in initial clinical diagnosis to a syndromic form or other type of IRD. The application of our NGS strategy has been successful in identifying pathogenic variants in the heterogeneous IRDs, highlighting the high clinical value of genomic technologies in highly heterogeneous disease. The successful integration with existing NGS testing processes has resulted in our panel-based approach now being provided as a clinical service.



Biography

Ben has been working in the field of diagnostic genomics for 10 years, having gained experience across various aspects of cytogenetics and molecular genetics. He is currently in his final year of a part-time Masters by research with the University of Sydney where he is applying next generation sequencing technologies to the blinding retinal dystrophies.



Inversions within the MSH2 gene

Anna C Ritchie[1], Shannon Cowie[1], Desirée du Sart[1].

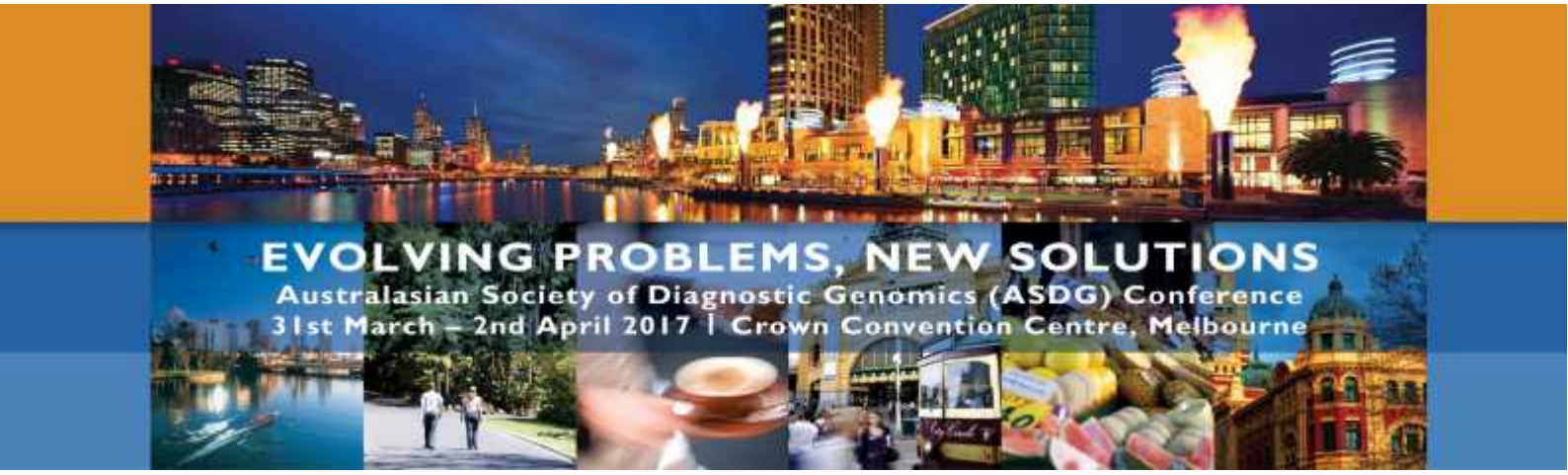
[1]Molecular Genetics Laboratory, VCGS Pathology, Murdoch Childrens Research Institute, Flemington Rd, Parkville, Victoria 3052.

Lynch syndrome is caused by a germline mutation in a mismatch repair gene (MLH1, MSH2, MSH6, PMS2 and EPCAM) resulting in a predisposition to colorectal and other cancers. Testing of these MMR genes by Next Generation sequencing and MLPA analysis will identify point mutations, small deletions and insertions, splice site mutations as well as intragenic and whole gene deletions and duplications. However, gene rearrangements, such as inversions and chromosome translocations, will not be detected.

A 10Mb inversion within the MSH2 gene was initially identified by Wagner et al. 2002 and a further study by Rhees et al. 2014 found that six out ten previously unexplained MSH2-type Lynch syndrome families had this inversion. To assist in identifying these mutations, recently two new probes have been introduced into the MCR-Holland P003-D1 MLPA kit to detect this recurrent pathogenic inversion. The assay focuses on the breakpoint within intron 7 of the MSH2 gene which will bind and produce a peak at 265 and 317nt when the inversion is present. We have confirmed the same 10Mb inversion by PCR amplification and gel electrophoresis in a family where this inversion was previously identified. We have also identified another inversion of exons 2 to 6 within the MSH2 gene in a different family with a history of Lynch syndrome, which will not be detected by the MLPA assay. It is currently unclear how common inversions within the MSH2 gene are and further testing of intronic regions within this gene would be required to gain a better understanding. We will present our data of screening for the 10Mb inversion and the exon 2 to 6 inversion in mutation-negative Lynch syndrome patients to determine whether these are common inversions and whether a more universal screening method should be developed to identify other inversions within the MSH2 gene.

Biography

Anna Ritchie is a medical scientist in the Molecular Genetics laboratory within VCGS pathology in Melbourne. She is a Grade 2 scientist, obtaining her HGSA membership in 2011, and has been part of the Molecular Genetics team for over 12 years. Currently, her main role involves the management of the Next Generation Sequencing (NGS) service for Cancer patients, which includes the testing, analysis, curation and reporting of cancer diagnostic patients. Previously she has been involved with the testing and reporting for Cystic Fibrosis, Mitochondrial disorders, Duchenne/Becker Muscular Dystrophy and predictive testing for various cardiac conditions and cancers



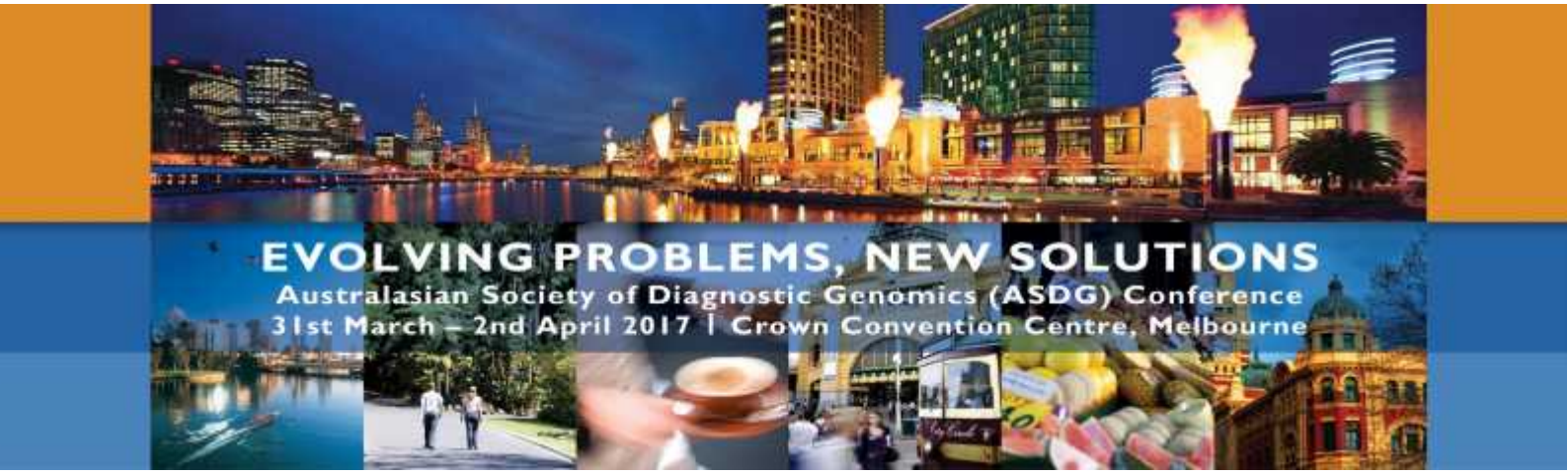
0830-0915 Saturday 1st April 2017 - Invited Speaker: Dominic J. McMullan BSc FRCPath

Clinical Genomics in the UK; more seismic changes ahead?

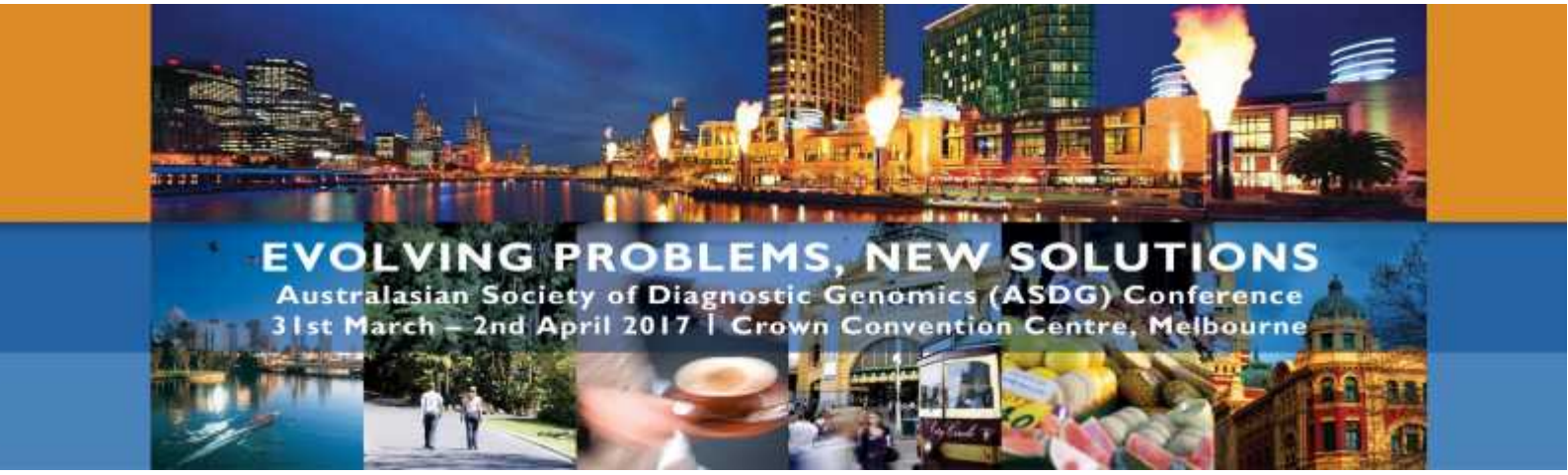
This talk will give an overview of the many overlapping challenges and initiatives faced by the UK NHS Clinical Genomics community as we enter the era when WGS potentially becomes a one-stop shop for many diagnostic pathways and personalised medicine becomes a reality, following investment of over £500 million in the launch of 100,000 Genomes project and the establishment of NHS Genomic Medicine Centres. The Association for Clinical Genomic Science (in many ways a "first cousin "organisation to ASDG) formed in 2012 from a merger of the Association for Clinical Cytogenetics (ACC) and the CMGS (Clinical Molecular Genetics Society), reflecting a coalescence of technology, analysis and interpretation. ACGS plays a pivotal role in guiding and inputting into key areas of service and professional development around Quality, Training as well as developments in Science and Technology and is heavily involved, as part of a constituent body of the British Society for Genomic Medicine, in initiatives and various national agendas in UK Clinical Genomics. In England, 2017 will see start of procurement of a new genomic laboratory infrastructure, with networked Regional Genomic Central Laboratory Hubs providing routine diagnostic clinical sequencing and complex WGS analysis, the latter likely provided centrally by a national provider. A National Coordinating Centre will be established within an agreed governance and operational framework that will oversee the test repertoire and support labs to work together. This is the vision. What will it take to make it happen and how will it really work?

Biography

Dom McMullan is a Consultant Registered Clinical Scientist at West Midlands Regional Genetics Laboratories, Birmingham, United Kingdom, with 25 years' experience in all aspects of diagnostic / clinical laboratory genetics. He graduated from the University of Sheffield in Genetics and is a Fellow of the Royal College of Pathologists (Genetics). He leads the Germline Programme of the laboratory service, which encapsulates all rare disease and reproductive genetic testing serving a patient population of ~5.5 million. He is current Chair of the Scientific Subcommittee of the Association of Clinical Genetic Science (ACGS) and Chair of the Scientific Programme Committee for the British Society of Genetic Medicine (BSGM) annual conference. His main interests lie broadly in application of genomic technologies in detection and interpretation of structural and sequence variation; in particular in patients with developmental disorders/congenital anomalies both in the postnatal and prenatal settings and he is co-applicant/collaborator and WMRGL lead on the UK National Health Innovation Challenge Fund (HICF) Prenatal Assessment of Genomes and Exomes (PAGE) project. A



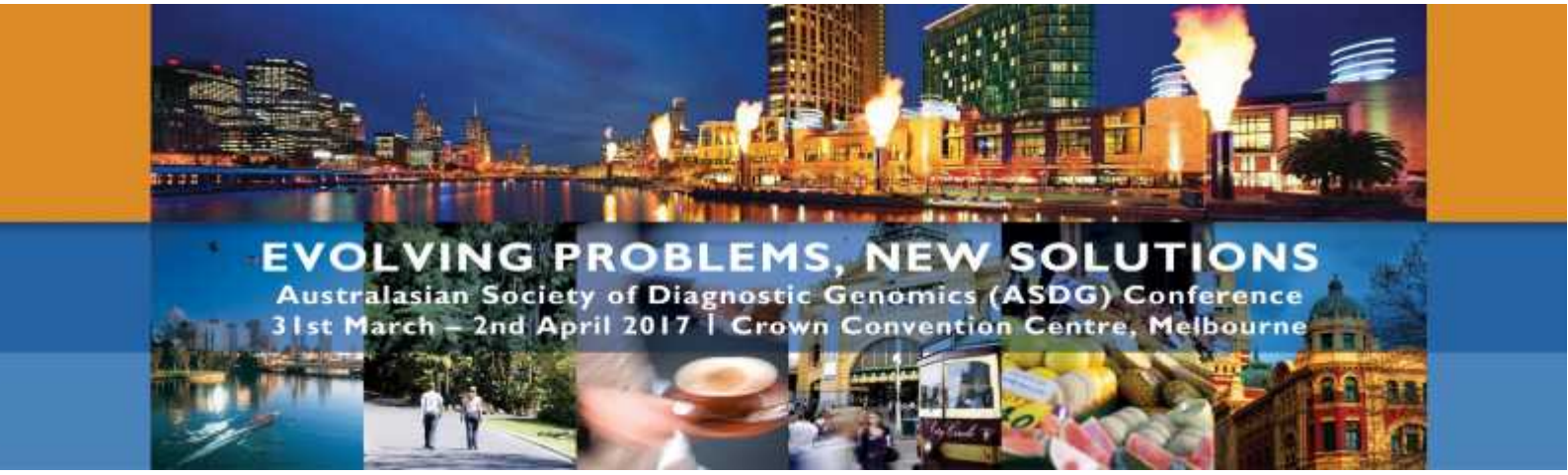
strong advocate of the need for improved data-sharing between UK-NHS diagnostic laboratories (and further) he is involved in several initiatives around this with both DECIPHER and the PHG Foundation. He has been involved internationally with the ClinGen (formerly ISCA) consortium as a member of the Gene Dosage Curation working group and as an assessor on multiple UK National External Quality Assessment Schemes (NEQAS) in genetic testing.



Oral Presentations

0915 – 1200 - Saturday 1st April 2017

0915-0930	Cryptic end-to-end chromosome joining in the dic(20;22) points to telomere fusion as a significant mechanism for dicentric chromosome formation in myeloid malignancy
0930-0945	Improved detection of cytogenomic prognostic markers by chromosome microarray in a group of clinically heterogeneous neuroblastoma patients
0945-1000	Molecular subtyping of medulloblastoma
1030-1045	The lumpiness of the “CNVome” ! Why is it so? …and what does it tell us?
1045-1100	Fragile X syndrome FMR1 CGG retractions; Not so rare?
1100-1115	PGD for reciprocal translocations using next-generation sequencing
1115-1130	PGD for reciprocal translocation and CNVs using Karyomapping
1130-1145	PGD for HLA matching and mutation detection by Karyomapping
1145-1200	Trisomy 2 mosaicism with high trisomic fraction identified by cell-free DNA screening is associated with an increased risk for adverse feto-placental outcomes



Cryptic end-to-end chromosome joining in the dic(20;22) points to telomere fusion as a significant mechanism for dicentric chromosome formation in myeloid malignancy

Ruth N MacKinnon[1,2], Hendrika M Duivenvoorden[3], Lynda J Campbell[1,2] Meaghan Wall[1,2,4]

[1] Victorian Cancer Cytogenetics Service, PO Box 2900, Fitzroy, Vic 3065
[2] Department of Medicine (St Vincent's), University of Mebourne, Fitzroy, Vic 3065
[3] Department of Biochemistry and Genetics, La Trobe Institute for Molecular Science, La Trobe University, Bundoora, Vic 3086
[4] St Vincent's Institute of Medical Research, Princess St, Fitzroy ,Vic 3065

Complex karyotypes in acute myeloid leukaemia (AML) and myelodysplastic syndromes (MDS) are associated with a poor clinical outcome, and often have dicentric chromosomes. These malignancies, particularly with a complex karyotype, can be caused by chemotherapy or radiotherapy for a different cancer.

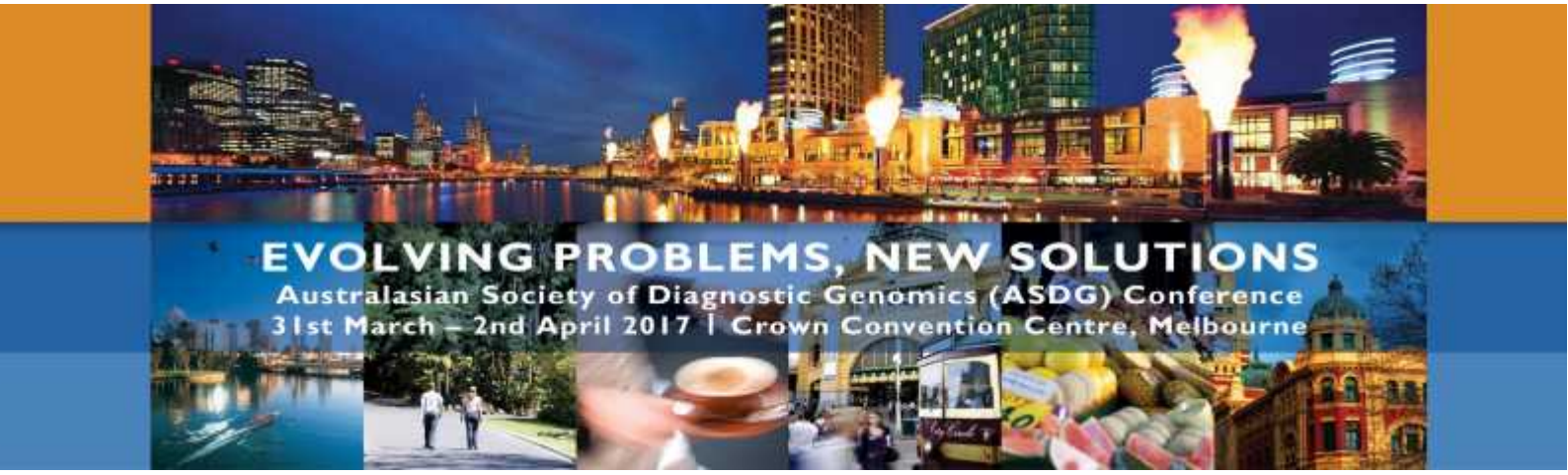
We describe four examples of the rare recurrent dicentric (20;22) in AML or MDS. These abnormal chromosomes had strikingly similar structural features. Combining cytogenetic and molecular genetic technologies has given us insight into how they arose.

All four retained the 20q subtelomere despite 20q12 deletion, and notably telomere sequence was also detected at the junction of chromosomes 20 and 22 in three of the four examples. As telomeres normally occur at the ends of chromosomes, this suggests that the dicentric chromosome arose by end-to-end fusion of 22p and 20q.

Other characteristics in common were instability, deletion of the common deleted region at 20q12, presence of the nucleolar organiser region at 22p near the breakpoint, and gain of the recurrently amplified region at 20q11.21.

We propose the following steps in the evolution of the dic(20;22). End-to-end joining of chromosomes 20q and 22p produces an unstable dicentric chromosome. This instability allows the chromosome to evolve rapidly, selecting for loss of a tumour suppressor gene at 20q12 and amplification of 20q11.21.

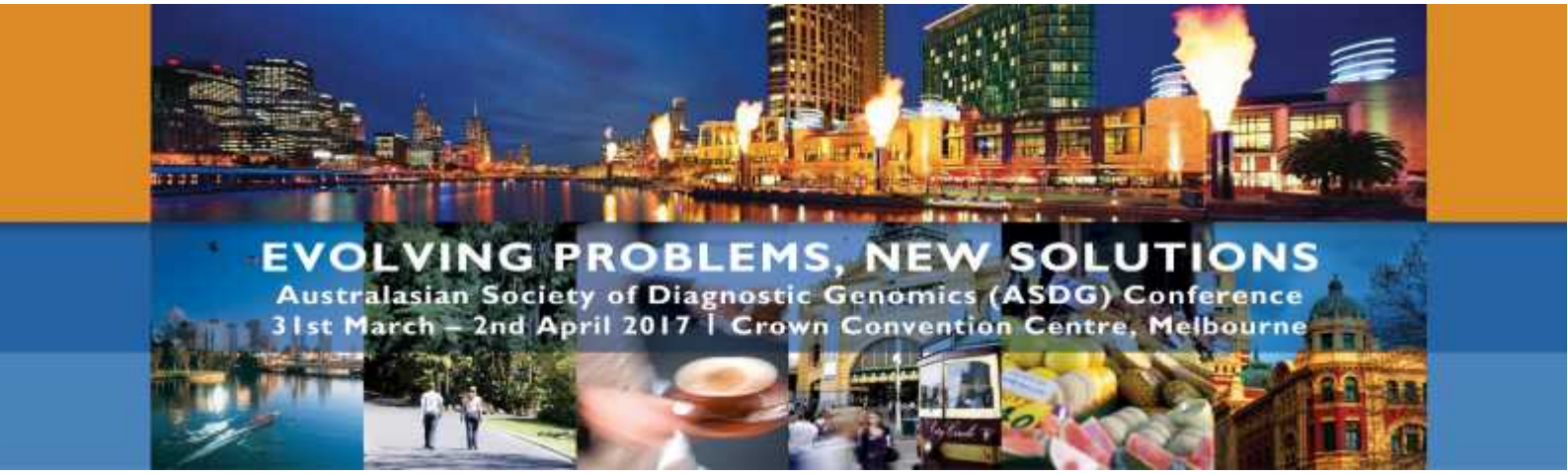
A high incidence of 20q subtelomere retention in dicentrics involving chromosome 20 has been reported. These abnormal chromosomes are usually not recognised as possible telomere fusions because subsequent rearrangements have made the breakpoints appear closer to the centromeres. Our results show that there is enough residual internal telomere sequence for detection by FISH in at



least some instances of telomere fusion involving 20q. Testing of other dicentrics may show that telomere

Biography

Dr MacKinnon has investigated dicentric chromosome abnormalities in AML and MDS during her time at the Victorian Cancer Cytogenetics Service. Previously she has worked on fragile sites at the Adelaide Children's Hospital, the Fragile X at the Molecular Institue of Medicine, Oxford, and cattle genomics at CSIRO.



Improved detection of cytogenomic prognostic markers by chromosome microarray in a group of clinically heterogeneous neuroblastoma patients

Dale C Wright[1], Luke St Heaps[1], Geoff McCowage[2], Nicole Graf[3].

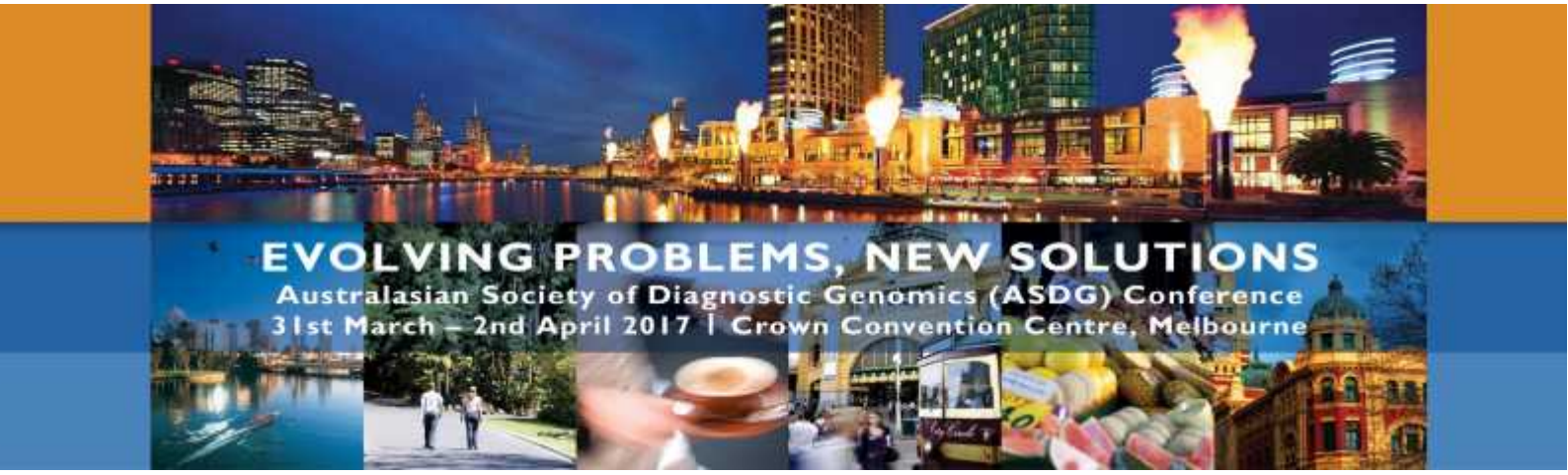
[1]The Children's Hospital at Westmead, Sydney Genome Diagnostics, Cytogenetics, Westmead
[2]The Children's Hospital at Westmead, Oncology, Westmead
[3]The Children's Hospital at Westmead, Anatomical Pathology, Westmead

BACKGOUND: Neuroblastomas show genetic and clinical heterogeneity. They can occur in infants with subsequent spontaneous regression, be localised with favourable outcome, or become refractory to treatment. Prognostic markers include age, histology and tumour stage, and genetic/genomic alterations. The latter includes DNA-ploidy, MYCN amplification (MYCNA), loss of heterozygosity (LOH) of 1p/11q and other segmental chromosome abnormalities (SCA); e.g. loss 17p, gain 1q/17q, among others. LOH/ SCA detection can be performed by FISH and/or microsatellite STR markers but compared to chromosome microarray (CMA) can be laborious. This study aimed to improve prognostic cytogenomic marker detection in neuroblastoma.

METHOD: Thirteen neuroblastoma patients [five retrospective, eight prospective] were investigated with median age at diagnosis 6 months [range: 2 – 72] and varying tumour stage: poorly differentiated, III, IV and IV-S. Fresh/frozen tissue was analysed using a customised 8x60K CGH+SNP cancer microarray [5Mb resolution] (Agilent Technologies). FISH was performed on touch-imprints using MYCN and chromosome 1p [TP73] probes on 12/13 and 2/13 patients, respectively. Karyotyping was attempted on three tumours.

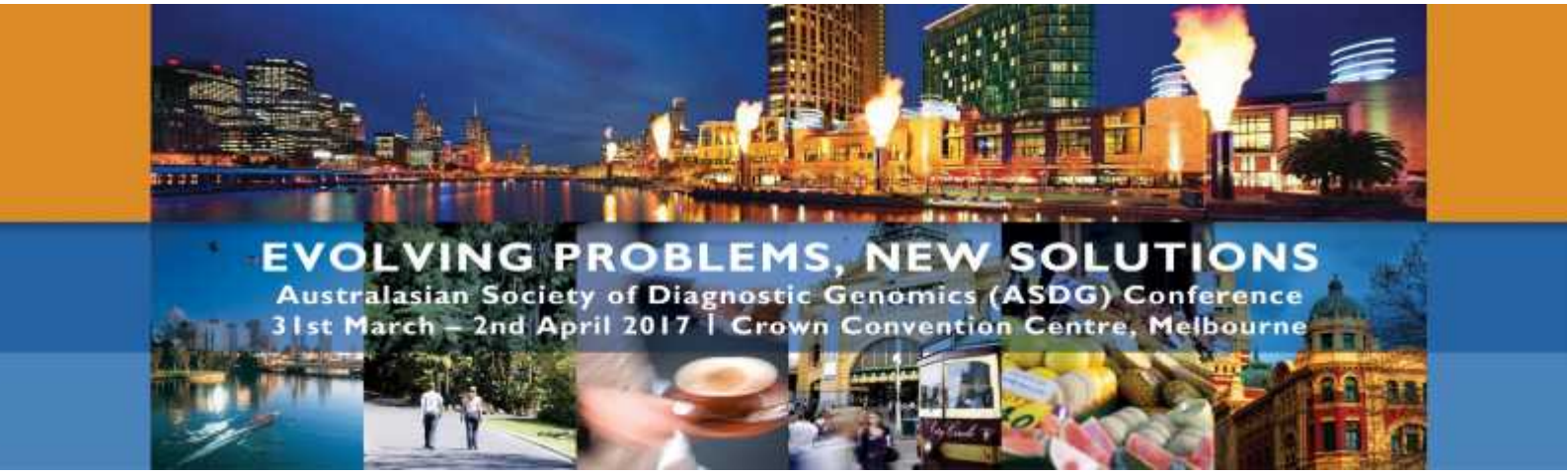
RESULTS: CMA identified ploidy and MCYN status, and other SCAs in 11/13 tumours. One showed no abnormality and one failed. A single MYCNA tumour was diploid with LOH 1p and 12 SCAs. The remaining showed hyperdiploidy only (n=4), hyperdiploidy with SCA (n=5) [four with LOH 11q], hypodiploidy LOH 1p with three SCA (n=1), and diploidy with LOH 1p (n=1). These findings confirmed MYCN FISH, where one showed MYCNA and 9/11 tumours showed increased MYCN copy number (3-6) but NOT amplification. Two showed three 1p copies. Tumour karyotypes showed no abnormality (n=2) or failed (n=1).

CONCLUSION: CMA overcomes the challenges of karyotyping and targeted FISH, providing improved detection of ploidy and cytogenomic markers. However, rapid MYCN FISH remains important. Along with age, tumour stage and MYCN status, CMA can identify ploidy and LOH/SCA that refines patient risk-stratification.



Biography

Dale is a Principal Hospital Scientist and Head of Cytogenetics for Sydney Genome Diagnostics at The Children's Hospital at Westmead, Sydney. He has wide experience in Clinical Cytogenetics, mostly involving infertility, prenatal and preimplantation genetic diagnosis, but more recently has been working with microarrays in multiple myeloma and paediatric solid tumours.



Molecular subtyping of medulloblastoma

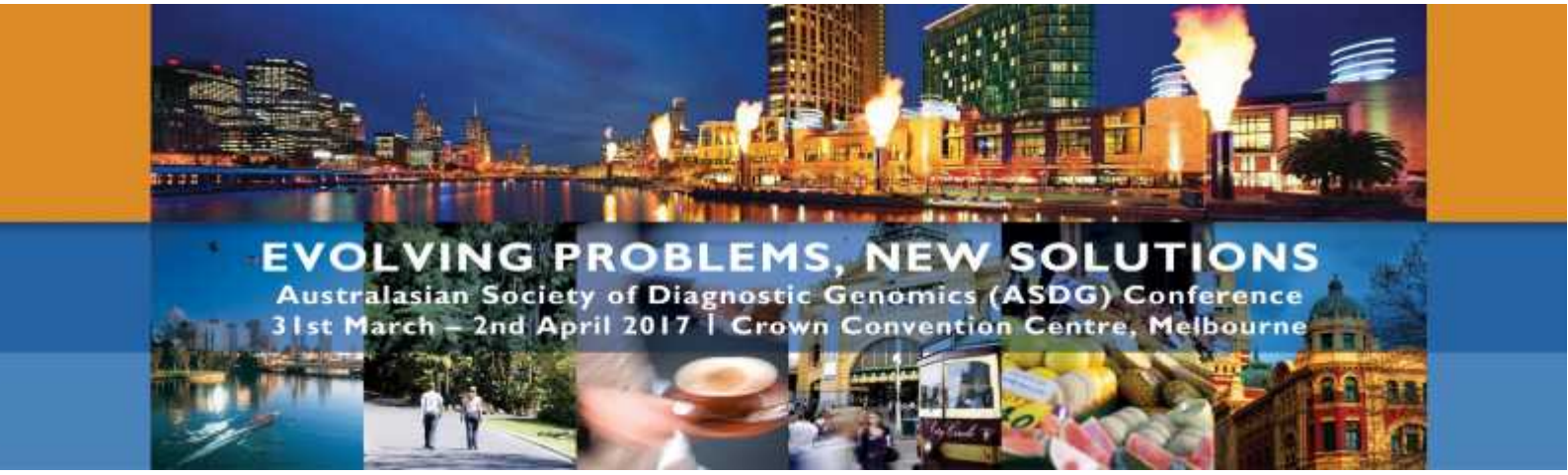
R. Fraser[1], C.C. Young[1], M. Nicola[1], J. Suttle[1], R. Kenyon [2], N. Manton[3], S. Moore[1]

[1] SA Cancer Cytogenetics Unit, Genetics and Molecular Pathology Directorate, SA Pathology, Adelaide, South Australia
[2] ACRF Cancer Genome Facility, Adelaide, South Australia
[3] Anatomical Pathology Directorate, Women's and Children's Hospital, Adelaide, South Australia

Medulloblastoma is a highly malignant embryonal tumour of the cerebellum, and is the most common form of malignant paediatric brain tumour. Treatment involves surgical resection, and in some cases radiation therapy and chemotherapy. Current recurrence free survival is approximately 50-70%. Traditional clinical prognostication and stratification incorporates clinical factors (age, presence of metastases, extent of resection), histological/immunohistochemical subgrouping, and tumour cytogenetics. More recently, molecular profiling of medulloblastoma cases has suggested the existence of distinct subgroups that differ in their demographics, transcriptomes, somatic genetic events, and clinical outcomes. Consensus was reached recently for four main molecular subgroups of medulloblastomoa (ie Wnt, Shh, Group 3, and Group 4) and there is evidence to suggest that some arise from different cellular origins. The demanding nature of tumour culturing and karyotyping has led us to investigate the use of SNP-array analysis to provide critical somatic genetic information to help stratify patients into one of these subgroups. We now report the results of a small pilot study of local medulloblastoma patients for whom we have performed SNP-array and karyotyping and compared our data with the Children's Oncology Group findings. SNP-array results were easier to interpret than karyotyping, could be performed in a shorter time frame, since there is no need for culture of FISH analysis, and resulted in correct molecular classification of medulloblastoma.

Biography

Rachel works as a medical scientist in the cancer cytogenetics laboratory in Adelaide.



The lumpiness of the "CNVome" ! Why is it so? …and what does it tell us?

Greg B Peters[1], Con Ngo, & Dale Wright.

[1] Sydney Genome Diagnostics, Children's Hospital Westmead, Hawkesbury Road & Hainsworth Street, Westmead, NSW 2145, Australia

Microarray technology has been in routine diagnostic use for more than a decade, and much data has been accumulated, concerning the size and distribution of those mutations classed as copy number variants [CNVs], across the human genome. Elaborate maps of these distributions are now available, both in the large publicly-available databases, and in the many smaller databases accumulated in-house, by diagnostic laboratories like our own. From the total information embodied within these mappings, a clear understanding of CNV distribution should emerge. It is a distribution that is strikingly non-random, heterogeneous, and peculiar. And it is this entity we refer to here as the "CNVome".

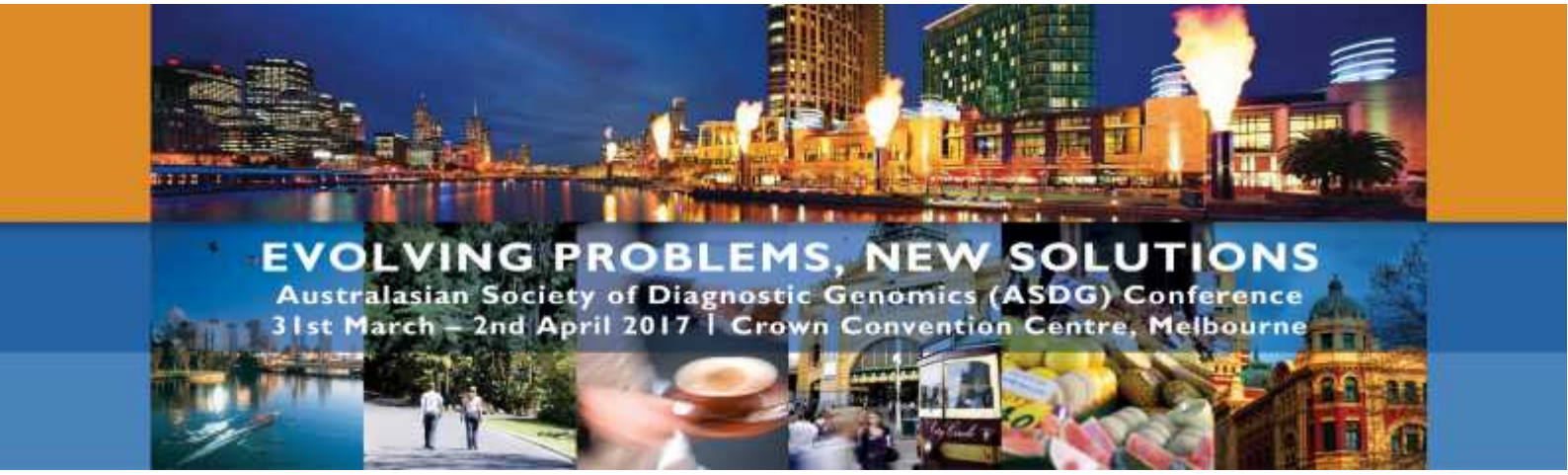
The CNVome in many places exhibits extreme clustering of its elements, some of this clustering associated with CNV length. The larger variants, for example, are often concentrated in analogous regions of each chromosome, e.g. the pericentric or sub-telomeric regions. To borrow a term from statistics and cosmology: we might characterise the CNV distribution data as "lumpy" in its nature. And we might, on that basis, use that lumpiness to explore the origins [and fates] of the elements in question, to arrive at some model explaining their origin, incidence, and evolutionary persistence [not to mention their effects on their hosts: i.e. all of us]. Such a model is attempted here.

We further suggest that this lumpiness of the CNV data, and its potential explanatory power, has not yet received anything like the attention it deserves – possibly because:

in our "post-genome" world, the dominant paradigm of DNA point mutation does not readily lend itself to an understanding of CNVs' effects on fitness, and
copy number mutation was traditionally the fiefdom of the cytogeneticists: an out-group considered extinct, from around the end of the Mesozoic.

Biography

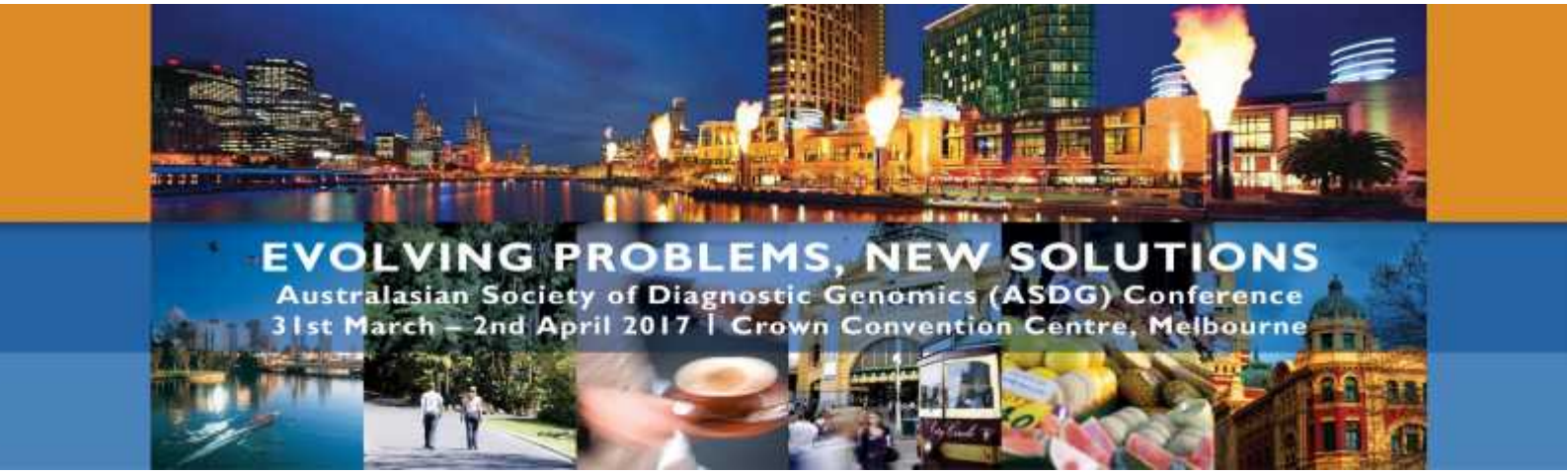
Greg Peters, PhD in the field of insect cytogenetics and population biology, Australian National University (Canberra),1978, FHGSA [Cytogenetics] 1991, FFSc(RCPA) 2010, HGSA State Secretary (South Australian Branch), 1986-8, HGSA: Federal Treasurer, 1988-91, Member of the assessment board for the ASOC* Cytogenetics QAP program, 1994-8, Member of the assessment board for the



ASOC/HGSA Microarray quality assessment program, 2009-2015, Head of Cytogenetics, RNSH 1995-2000, Head of Cytogenetics, CHW 2000-2010, Introduced routine array testing from 2006.
Current: Head of Microarray Testing, Sydney Genome Diagnostics, Children's Hospital at Westmead;

other appointment:

Conjoint Senior Lecturer, Discipline of Paediatrics and Child Health, Faculty of Medicine, University of Sydney, NSW, Australia.



Fragile X syndrome FMR1 CGG retractions; Not so rare?

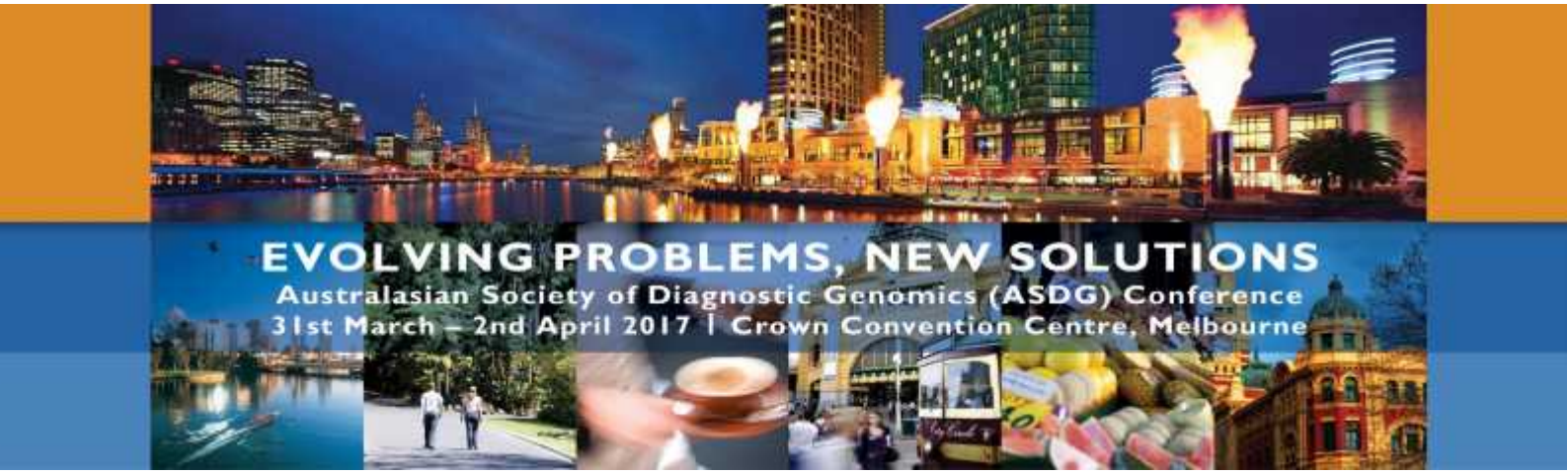
David I Francis[1], Matthew Hunter[2], Yael Prawer[2], Zornitza Stark[1], Robin Forbes[1], David Amor [1],Mike Field[3], Carolyn Rogers[3], Ralph Oertel[1], Sara Cronin[1], Amber Boys[1], Olivia Giouzeppos[1], Essra Bartlett[1], David Godler[4]

[1] Victorian Clinical Genetics Service, Murdoch Childrens Research Institute, Flemington Road, Parkville, VIC, 3052.
[2] Genetics Dept., Monash Health, Monash Medical Centre, 246 Clayton Rd, Clayton VIC 3168.
[3] GOLD Service, PO Box 84, Waratah NSW 2298
[4] Murdoch Childrens Research Institute, Flemington Road, Parkville, VIC, 3052.

FMR1 premutation (PM: 55-199 CCGs) alleles are highly unstable upon maternal transmission expanding at high frequency into the full mutation (FM: = or >200 CGGs) range. However there is increasing evidence that FM's are highly unstable postzygotically, retracting into smaller size alleles, including the intermediate (45-54 CGGs) and normal (<45 CGGs) range. This has important implications for counselling, as mosaic individuals are less severely affected due to expression of FMR1; thought to be silent in non-mosaic fully methylated FM alleles. I present conclusive evidence in monozygous Fragile X twins of postzygotic retraction as well as three other FXS cases demonstrating complete retraction into the normal range. Further evidence of instability is confirmed by analysis of all VCGS male Southern Blot detected positive cases showing a high incidence of PM/FM mosaics of 25%, comparable to the literature which is variable (average of 26%). This is likely to be an under representation of mosaicism as Southern blot cannot detect mosaic alleles if present in less than 20% of cells (Aliaga et al 2016 Clin Chem). Further studies of 100 males with typical FXS (manuscript in preparation) showed a significantly higher proportion of mosaic FMR1 alleles was detected in FM males using a more sensitive test, termed MS-QMA, than by Southern blot. Together, this suggests that mosaicism is currently under diagnosed by standard testing and retraction from FM to smaller size alleles is not as uncommon as previously thought.

Biography

Over 20 years of experience in the Cytogenetics/Molecular diagnostic field. I have published widely in the cyto/molecular area and currently involved in Fragile X syndrome and Prader Willi syndrome research projects. Recently appointed as the Head of the Postnatal Cytogenetics Laboratory at VCGS and was the past/last President of ASoC.



PGD for reciprocal translocations using next-generation sequencing

Mirjana Martic[1], Sophie Falle[1], Katerina Mitsiou[1], Maria Kemeridis[1], Sharyn Stock-Myer[1]

[1] Virtus Diagnostics, Melbourne IVF, 344 Victoria Parade, East Melbourne 3002

The 24sure+ BAC array Comparative Genomic Hybridisation (CGH) system has been the first commonly available technology for many years used to detect unbalanced segregants in the embryos of reciprocal translocation carriers in Preimplantation Genetic Diagnosis (PGD) programs. Next generation sequencing (NGS) based testing has recently been introduced and widely accepted for aneuploidy testing. Here we present the application and limitation of a NGS based chromosome testing system, VeriSeq (Illumina, USA) on single cells and trophectoderm (TE) samples for reciprocal translocation carriers.

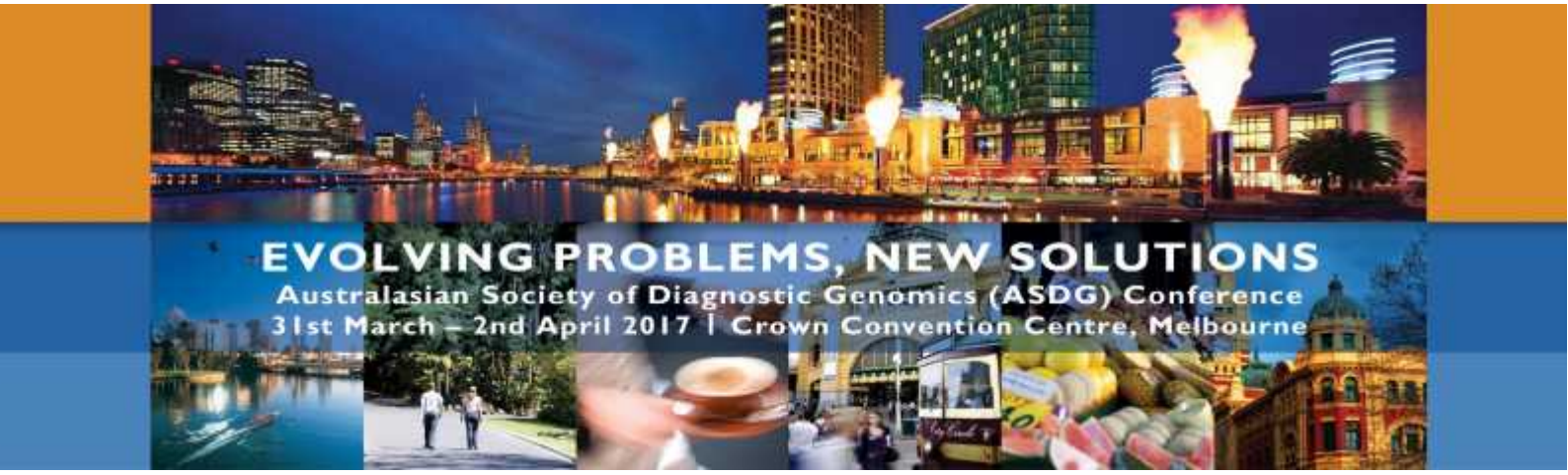
Aliquots of whole genome amplified DNA (Sureplex, Illumina, USA) from either single cells or TE samples of embryos diagnosed as unbalanced using arrayCGH, were subjected to NGS. Amplified samples were from carriers of 15 different reciprocal translocations with varied sizes of the unbalanced segments. The chromosome status of these samples was analysed and concordance determined.

Thirteen single blastomeres and 27 TE samples were amplified with 100% efficiency and results were obtained on 100% of amplified samples. NGS confirmed clinical diagnosis predicted by arrayCGH in all samples. Although individual segmental imbalances were detected in all samples, two unbalanced segments smaller than 6 Mb were not as apparent in the NGS profile as they were in the arrayCGH. Additionally, the NGS system was able to detect full aneuploidy and mosaicism of other chromosomes not involved in the translocation.

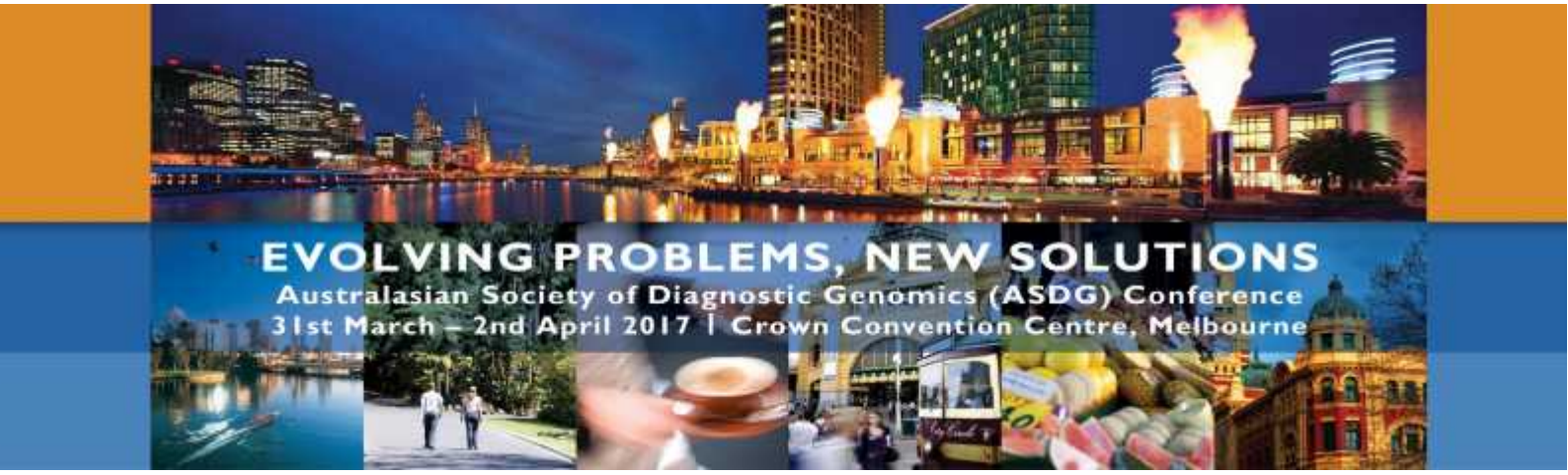
The NGS system is a reliable alternative to array CGH to detect large unbalanced chromosome segments as well as full aneuploidy and mosaicism of any other chromosome in single blastomeres and TE samples. In reciprocal translocation carriers in which unbalanced segments are smaller than 6 Mb, trophectoderm biopsy has to be requested and the confirmation of results by array CGH is strongly recommended.

Biography

Mirjana is a Preimplantation Genetics Laboratory manager at Virtus Diagnostics. She completed her Medical degree at the University of Zagreb, Croatia and her PhD at the University of Melbourne.



Initially, she worked as an embryologist at Melbourne IVF and for the last 13 years she has been working in Preimplantation Genetics.



PGD for reciprocal translocation and CNVs using Karyomapping

Sharyn Stock-Myer[1], Andrea Twomey, Paisu Tang, Anke Kohfahl, Mirjana Martic

[1] Virtus Diagnostics, Melbourne IVF, 344 Victoria Parade, East Melbourne 3002, Sharyn.stockmyer@virtusdiagnostics.com.au

Pre-implantation Genetic Diagnosis (PGD) allows the diagnosis of known gene disorders from pre-implantation embryos significantly reducing the risk of ongoing affected pregnancy in a couple at known risk for a particular disorder. PGD for reciprocal translocations typically utilises either array CGH or Next Generation Sequencing to detect unbalanced segregants and allows embryos to be transferred that have normal copy number DNA. However, using these technologies it is impossible to distinguish embryos that are balanced and have the derivative chromosomes from those that have inherited normal chromosomes. Additionally, these technologies are unable to reliably detect pathogenic CNVs (below about 5 Mb in size) that may be inherited by embryos from known carrier parents.

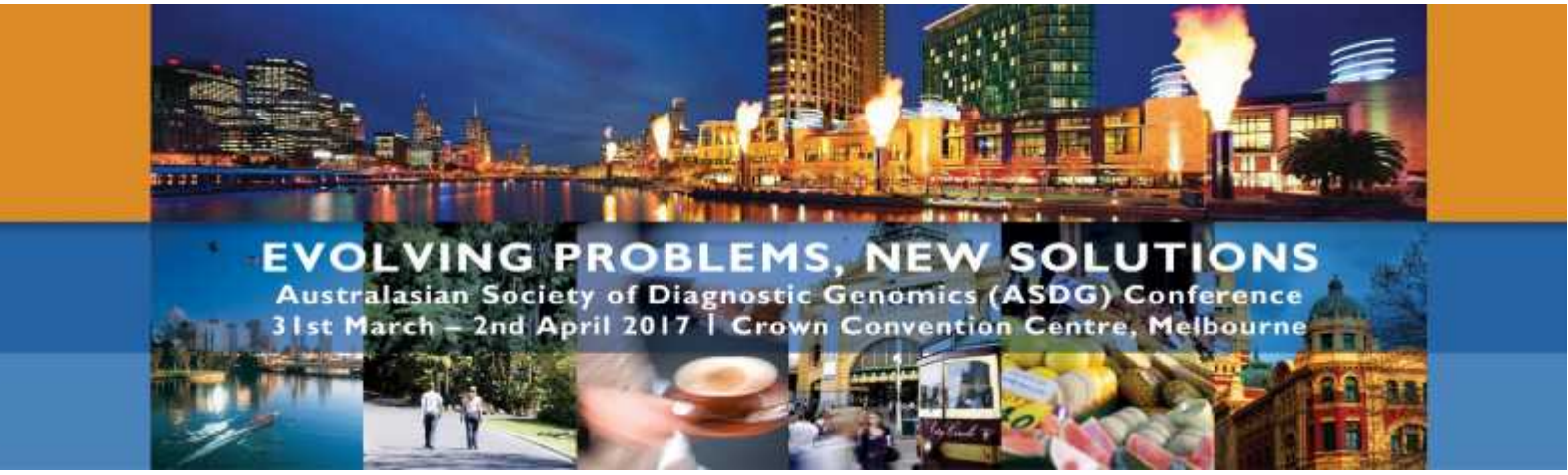
Karyomapping, a recently developed PGD technology that utilises a SNP array, was developed as a universal tool for diagnosing single gene disorders by linkage analysis. Our aim was to attempt to use this method to distinguish embryos that are balanced from those that have inherited normal chromosomes, and also to diagnose very small CNVs by linkage (and in the case of deletions, also by direct detection).

To date, we have successfully used Karyomapping to perform PGD for duplications and deletions ranging from 0.2 – 2.5 Mb in size in 13 carrier couples and also for one translocation case. In this translocation case we were clearly able to see unbalanced segregants, as well distinguish embryos that had inherited balanced segregants with derivative chromosomes from those that had inherited normal chromosomes only.

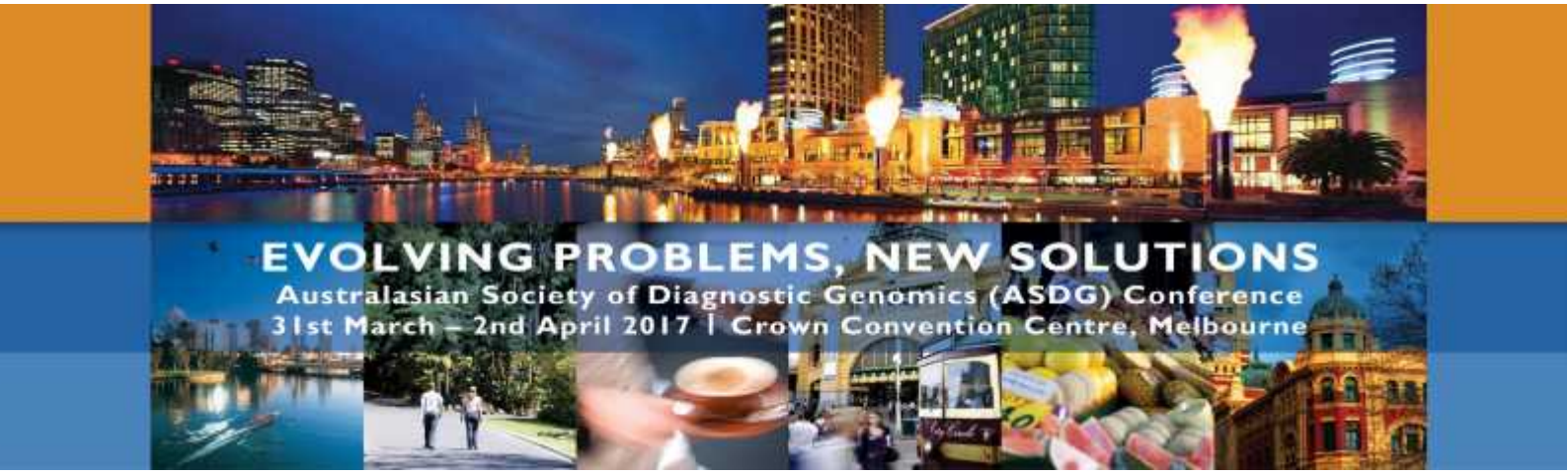
Karyomapping is a reliable method for performing PGD for CNVs below the level of detection of other technologies. This method has also been used successfully to perform PGD for a translocation case and can enable the preferential transfer of embryos with normal chromosomes if available and clinically indicated.

Biography

Sharyn has been working for Melbourne IVF since 2002 when she was employed to establish PGD services for monogenic patients. She has continued running this program since that time, and in 2015



took over role of Scientific Director for Pre-implantation Genetics. She is honoured to be able to help couples in their dream to have a healthy child.



PGD for HLA matching and mutation detection by Karyomapping

Paisu Tang[1], Andrea P. Twomey, Anke E. Kohfahl, Sharyn E. Stock-Myer

[1] Virtus Diagnostics, Melbourne IVF, 344 Victoria Parade, Victoria, 3002

The most effective treatment option for many acquired and inherited paediatric haematological disorders is Haematopoietic stem cell transplantation (HSCT). Preimplantation genetic diagnosis (PGD) for HLA typing is an established procedure for assisting a couple to have a healthy sibling who can donate cord blood or haematopoietic stem cells to an ill child. PGD-HLA in Australia is performed under guidelines provided by the NHMRC.

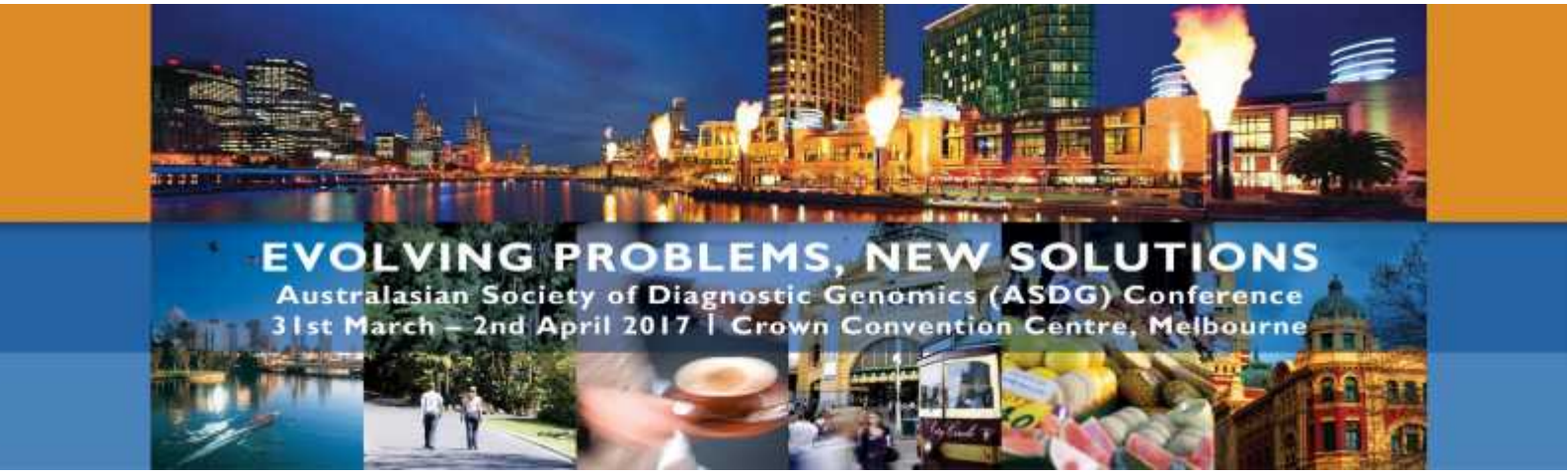
Traditional PGD for HLA typing involves the search for informative STR markers and the establishment of a family-specific multiplex PCR test. While effective, this method typically requires a significant investment of time which is often precious in the case of acute haematological failure such as leukaemia and aplastic anaemia.

The recent availability of Karyomapping, a high resolution SNP array system, has dramatically reduced the test development time in PGD for HLA typing and single gene disorders. Karyomapping eliminates the need for patient-specific tests and allows for the simultaneous analysis of multiple loci and chromosome copy number for all 24 chromosomes in the human genome. Thus it is possible to diagnose the HLA compatibility, mutation status and aneuploidy status of an embryo within the one test.

We report on the application of Karyomapping for beta thalassaemia and HLA typing in 3 families. Each couple had one child affected with beta thalassaemia and their eligibility for PGD-HLA was assessed by our Reproductive Services Clinical Review Committee according to NHMRC guidelines. Overall, a total of 17 embryos were tested with a diagnostic efficiency of 100%. One family delivered a healthy HLA-matched child, one family has an ongoing pregnancy and the third family is yet to produce a genetically suitable embryo. We discuss the benefits and limitations of Karyomapping for PGD-HLA.

Biography

PhD in Genetics, have been working as a PGD scientist at Virtus Diagnostics-Melbourne IVF for 8 years.



Trisomy 2 mosaicism with high trisomic fraction identified by cell-free DNA screening is associated with an increased risk for adverse feto-placental outcomes

Mark D Pertile[1,2], Nicola Flowers[1], Grace Shi[1], Olivia Giouzeppos[1], Shelley Baeffel[1], Ian Burns[1], Tom Harrington[1], Rebecca Manser[1], Absera Tsegay[1], Ralph Oertel[1], Fiona Norris[1].

[1] Victorian Clinical Genetics Services, Murdoch Childrens Research Institute, Royal Children's Hospital, Flemington Road, Parkville, VIC, 3052
[2] Department of Paediatrics, University of Melbourne, Parkville, VIC, 3010.

Whole genome sequencing (WGS) of maternal plasma cell-free DNA (cfDNA) can potentially evaluate all 24 chromosomes to identify abnormalities of the placenta or fetus. We have systematically analysed WGS data from all chromosomes to identify rare autosomal trisomies (RATs) to improve our understanding of discordant findings and feto-placental biology. Here, we describe our experience with prenatally ascertained trisomy 2 mosaicism.

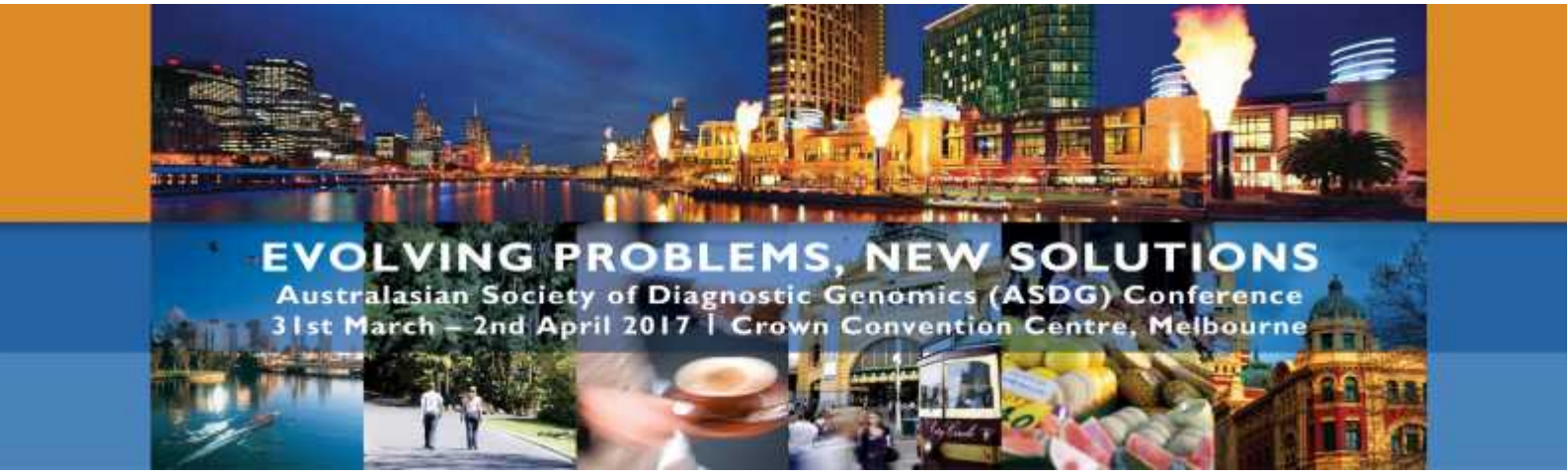
Trisomy 2 usually presents as a benign mosaic finding at CVS, commonly confined to the chorionic mesenchyme and rarely involving the cytotrophoblast. Involvement of the cytotrophoblast increases the likelihood that the conception is trisomic, with subsequent increased risk for true fetal mosaicism (TFM) and uniparental disomy (UPD) following trisomy rescue.

We have identified six cases of trisomy 2 mosaicism ascertained by cfDNA screening. In five samples, the mean ratio of the trisomic fraction (TF) to fetal fraction (FF) approached 1.0 (TF:FF = 0.83 ± SD 0.09), consistent with very high levels of trisomy 2 cells in placental cytotrophoblast. These pregnancies were associated with TFM, UPD, intrauterine growth restriction (IUGR) and/or intrauterine fetal demise (IUFD), in keeping with a meiotic origin of the trisomy. In the sixth , the mean ratio of the trisomic fraction to fetal fraction was low (TF:FF = 0.25). This pregnancy had normal prenatal investigations and continued to an uncomplicated term delivery. Examination of chorionic villi from the term placenta indicated the trisomy 2 mosaicism was most likely of mitotic (post zygotic) origin.

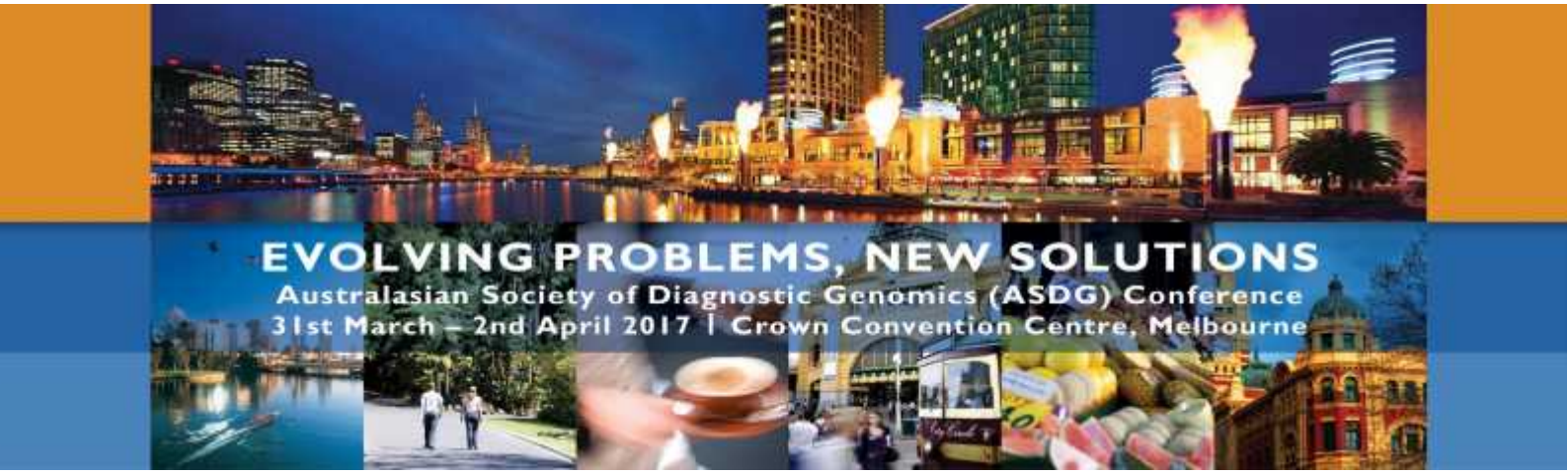
This data, together with our experience involving other RATs, suggests cfDNA screening can potentially identify those pregnancies at highest risk for relevant fetal-placental complications.

Biography

Dr. Mark Pertile is a senior medical scientist who specialises in reproductive cytogenetics and genomics. He is currently the Deputy Director of Laboratories at VCGS, Heads the Division of



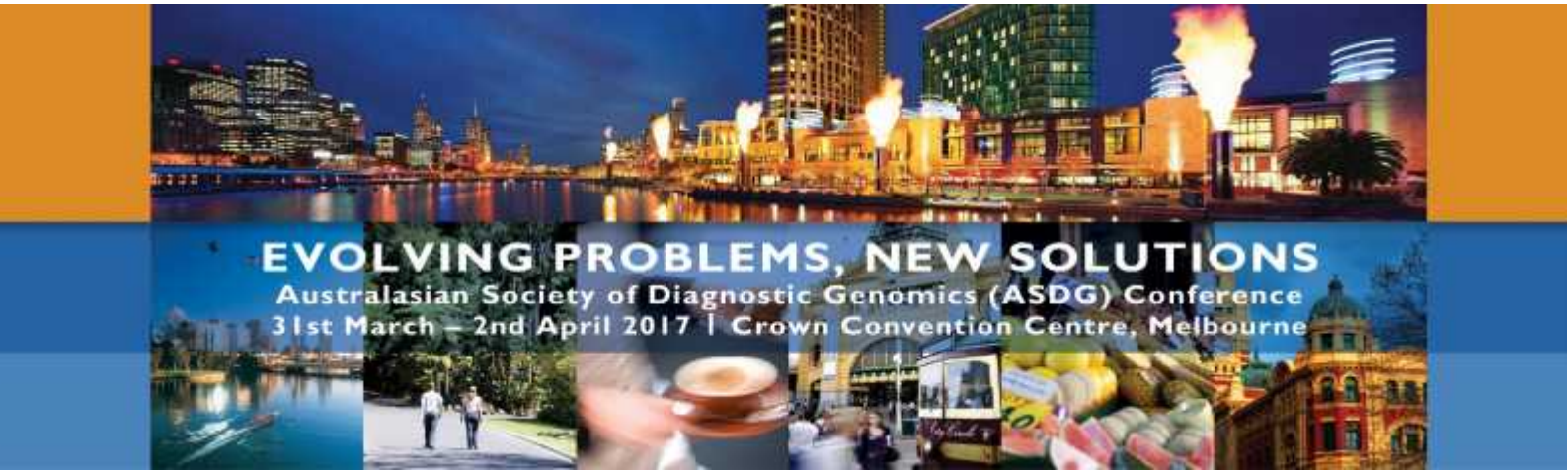
Reproductive Genetics and is also Head of the NIPT Laboratory. Mark has a long standing interest in early human embryology and development. He works with a team that applies molecular cytogenetics and genomics technologies to help identify the causes and origins of genomic conditions early in pregnancy.



1600-1700 Saturday 1st April 2017 - Invited Speaker: Professor Ingrid Winship

Great testing, better care

Chair of Adult Clinical Genetics, University of Melbourne; Executive Director of Research, Melbourne Health.



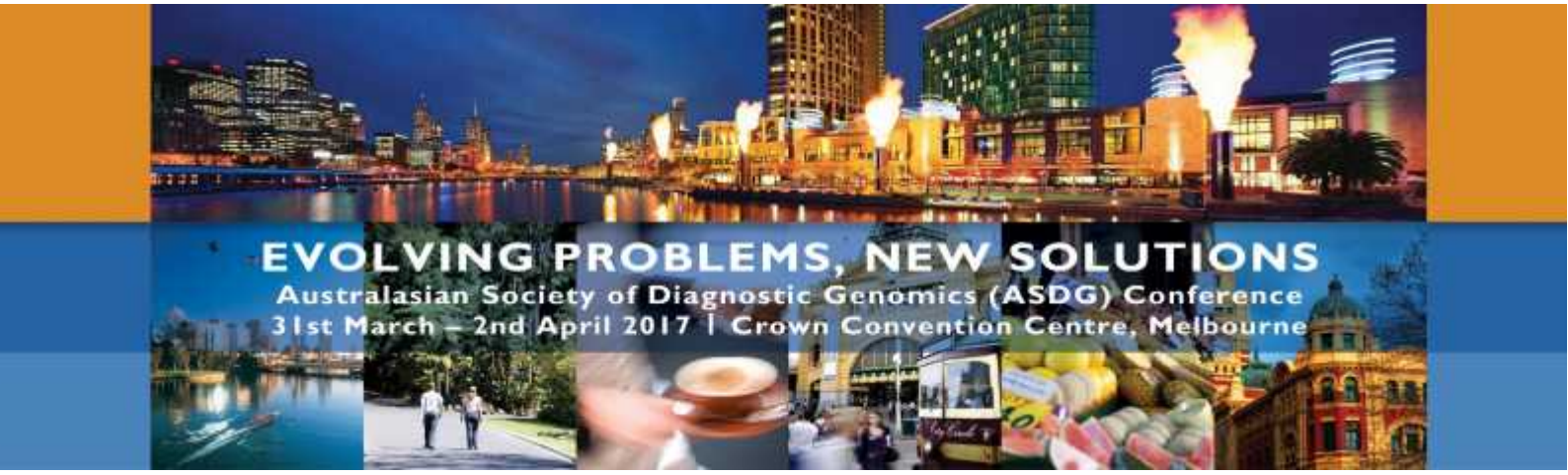
0930-1030 Sunday 2nd April 2017 - Invited Speaker: Associate Professor Elizabeth Algar

Validation studies on a gene panel interrogating paediatric growth disorders and tumour predisposition.

Associate Professor Elizabeth Algar BSc Hons M.Phil. PhD FFSc RCPA [1]

[1] Principal Scientist, Genetics & Molecular Pathology, Monash Health

The Genetics and Molecular Pathology laboratory at Monash Health is the predominant Australian testing laboratory for paediatric overgrowth disorders associated with increased cancer risk in childhood, including Beckwith Wiedemann syndrome (BWS) and Hemihypertrophy (HH). Cascade testing typically involves SNP microarray, methylation analysis of imprinting centres on 11p15.5 and CDKN1C (P57) mutation screening. Rare point mutations in NSD1, NLRP2, DNMT1 and ZFP57 have been described in BWS and like disorders as well as deletions and insertions within the 11p15.5 imprinting centres IC1 (H19/IGF2) and IC2 (KCNQ1OT1/CDKN1C). Tumour risk is increased in most genetic and epigenetic subtypes of BWS and HH however degree of risk and tumour type varies between groups. Parents of affected children are often understandably anxious to know the recurrence risk for these conditions and as the number of childhood cancer survivors' increases, the possibility for transmission of a causative mutation is becoming an increasingly important issue. To improve our capacity to detect predisposing mutations in BWS, HH and in the paediatric tumours that have been described in these conditions, we have designed a gene panel comprising 37 genes as well as intergenic regions spanning imprinting centres on 11p15.5 and 11p13. We have used the Haloplex target enrichment system with sequences run on an Illumina MiSeq. We have performed pilot testing to show that the panel has clinical utility and demonstrates excellent sequence coverage of the 11p imprinting centres. Analysis of results to date has revealed novel mutations including OCT-4 binding site disruption in IC1 and subregions of homozygosity.



1300-1345 Sunday 2nd April 2017 - Invited Speaker: Dominic J. McMullan BSc FRCPath

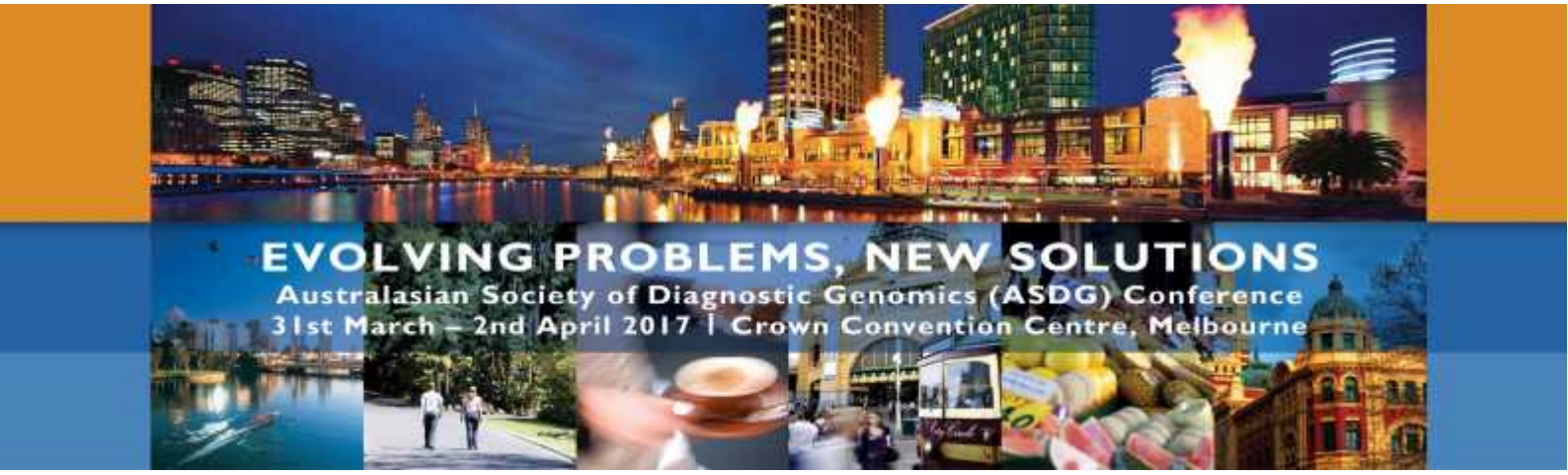
Exome sequencing of 406 parental/fetal trios with structural abnormalities revealed by ultrasound in the UK Prenatal Assessment of Genomes and Exomes (PAGE) project

D. J. McMullan[1], J. Lord[2], R. Eberhardt[2], G. Rinck[2], S. Hamilton[1], R. Keelagher[1], L. Jenkins[3], E. Quinlan-Jones[4], D. Williams[5], R. Scott[6], M. Kilby[4,7], L. Chitty[6], E. Maher[8], M. Hurles[2];

[1]West Midlands Regional Genetics Laboratory, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, United Kingdom,
[2]The Wellcome Trust Sanger Institute, Wellcome Genome Campus, Hinxton, Cambridge, United Kingdom,
[3]NE Thames Regional Genetics Service, Great Ormond Street Hospital for Children, London, United Kingdom,
[4]Department of Fetal Medicine, Birmingham Women's and Children's Hospital, Birmingham, United Kingdom,
[5]West Midlands Clinical Genetics Service, Birmingham Women's and Children's NHS Foundation Trust, Birmingham, United Kingdom,
[6]Genetics and Genomic Medicine, UCL Institute of Child Health and Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom,
[7]Centre for Women's and New-born Health, IMSR, University of Birmingham, Birmingham, United Kingdom,
[8]Department of Medical Genetics, University of Cambridge and Cambridge NIHR Biomedical Research Centre, Cambridge, United Kingdom.

PAGE aims to apply whole exome sequencing (WES) to 1000 trios recruited in the UK-NHS over 3 years to identify pathogenic variation underlying heterogeneous fetal structural abnormalities detected by ultrasound scan (USS).

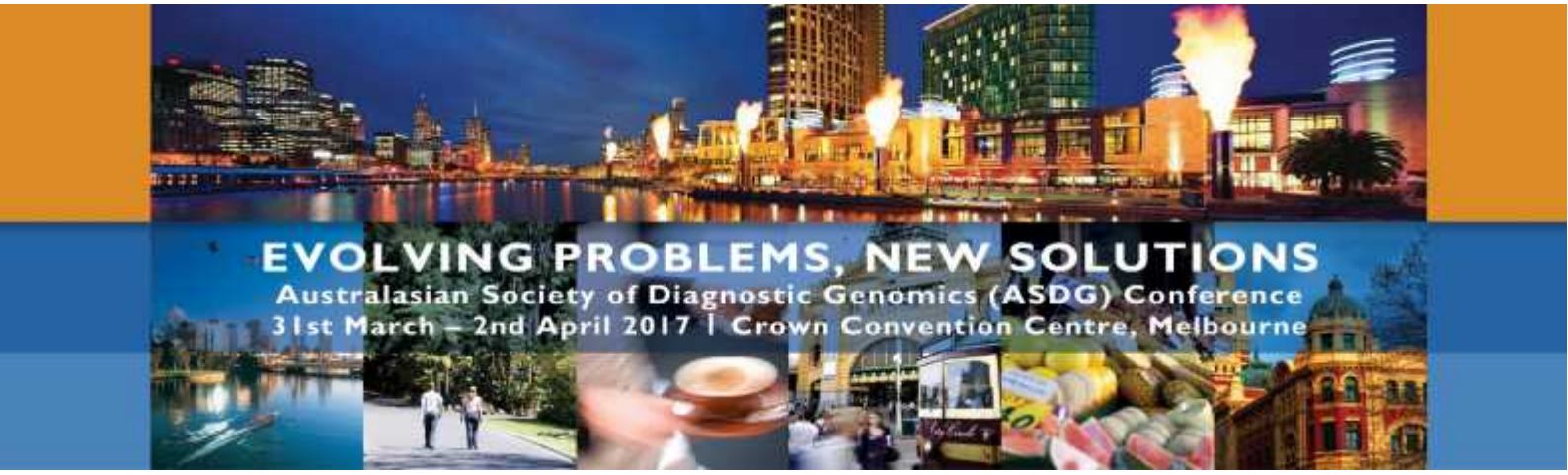
Trio WES is conducted only after resolution of pregnancy if conventional testing (QF-PCR, chromosomal microarray or targeted single/panel gene testing) fails to establish a definitive diagnosis. Genetic variants are triaged via a stringent filtering pipeline established for the UK Deciphering Developmental Disorders (DDD) project and potentially pathogenic variants are assessed and classified by a UK-wide multidisciplinary clinical review panel (CRP), technically validated in NHS accredited labs and reported back to Clinical Genetics units and families where appropriate. Thus far from 259 trios reviewed by the CRP, 16 likely diagnoses have been revealed, giving a diagnostic yield of ~6%.



Diagnostic yield varies by phenotypic class, with multisystem phenotypes showing the highest (~16%). The majority of variants are SNVs/indels which would escape targeted detection by conventional testing. When compared to a null model based on triplet mutation rate, an excess of de novo mutation is observed, more pronounced in known dominant genes (such as KMT2D). Further analysis is predicted to identify new gene and mechanistic associations underlying observed phenotypes as more samples are processed. PAGE aims to catalyse responsible adoption of WES and potentially WGS in routine diagnostics in the prenatal setting and this talk will outline all aspects of this multidisciplinary and multifaceted project.

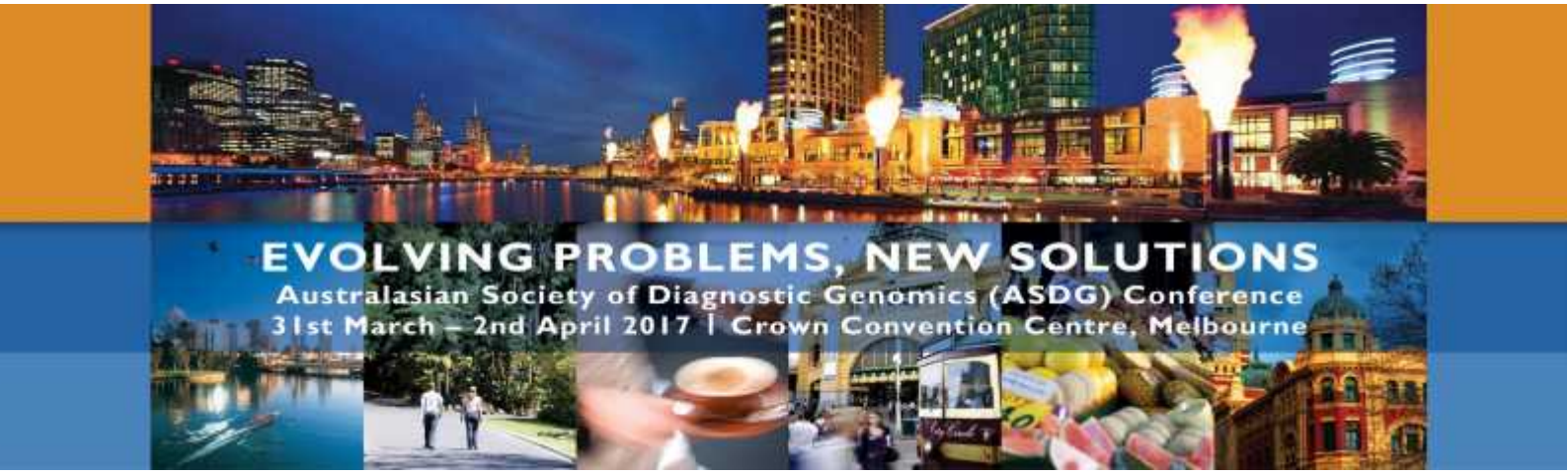
Biography

Dom McMullan is a Consultant Registered Clinical Scientist at West Midlands Regional Genetics Laboratories, Birmingham, United Kingdom, with 25 years' experience in all aspects of diagnostic / clinical laboratory genetics. He graduated from the University of Sheffield in Genetics and is a Fellow of the Royal College of Pathologists (Genetics). He leads the Germline Programme of the laboratory service, which encapsulates all rare disease and reproductive genetic testing serving a patient population of ~5.5 million. He is current Chair of the Scientific Subcommittee of the Association of Clinical Genetic Science (ACGS) and Chair of the Scientific Programme Committee for the British Society of Genetic Medicine (BSGM) annual conference. His main interests lie broadly in application of genomic technologies in detection and interpretation of structural and sequence variation; in particular in patients with developmental disorders/congenital anomalies both in the postnatal and prenatal settings and he is co-applicant/collaborator and WMRGL lead on the UK National Health Innovation Challenge Fund (HICF) Prenatal Assessment of Genomes and Exomes (PAGE) project. A strong advocate of the need for improved data-sharing between UK-NHS diagnostic laboratories (and further) he is involved in several initiatives around this with both DECIPHER and the PHG Foundation. He has been involved internationally with the ClinGen (formerly ISCA) consortium as a member of the Gene Dosage Curation working group and as an assessor on multiple UK National External Quality Assessment Schemes (NEQAS) in genetic testing.



Posters

01. Therapy-related myeloid leukaemia in patients treated for breast cancer
02. Manual vs automated plasma cell (CD138+) enrichment: A validation study
03. Inverted duplicated deleted 8p: How microarray presents a prettier picture.
04. Targeted molecular testing for cancer therapy
05. Undetectable levels of UNCONJUGATED ESTRIOL in maternal serum have led to a diagnosis of X-LINKED ICHTHYOSIS in a male fetus
06. Phenotype risk assessment in a couple with multiple alpha and beta-globin variants.
07. Two cases of the rare but emerging syndrome associated with the recurrent “3q13.2q13.31 Microdeletion”.
08. Detection of parental mosaicism following non-mosaic findings in their offspring on array
09. Limitation of molecular karyotyping: Discordance between molecular vs. conventional cytogenetics
10. A very complex and rare cytogenetic finding of a patient with two balanced chromosomal rearrangements involving one chromosome 1, one chromosome 6 and one chromosome 4.
11. A family with a 22q11.2 distal deletion
12. Fusion of two transferred embryos following IVF delivers monochorionic diamniotic ‘chimeric’ twins with sex discordance.
13. What is lurking in the Karyotype? A review of aUPD in haematological malignancy.
14. Cystic fibrosis mutations and infertility – using Next Gen Sequencing to identify infertility related variants
15. A deletion in CFTR causes double trouble
16. Alport syndrome testing – 18 months experience with NGS
17. Molecular testing for imprinting disorders at Monash Health
18. Seeing the whole picture – integrated view of CNVs, AOH, and sequence variants for Improved results
19. Diagnosing two syndromes with one test
20. Maternal Y chromosome derived copy number variant causes false positive klinefelter syndrome (XXY) sex chromosome results during noninvasive prenatal testing
21. Familial alzheimers disease exclusion testing and an incidental finding: A PGD case.
22. Two rare pathogenic copy number gains on chromosome 10
23. Severe haemophilia A caused by a duplication in the factor VIII gene covering exons 7 to 9
24. An unbalanced mosaic structural chromosome abnormality: A case study
25. Immunohistochemistry as a screening tool for FISH testing in the diagnosis of double hit lymphoma



01. Therapy-related myeloid leukaemia in patients treated for breast cancer

Siobhan Battersby, Praveen Sharma, Dorothy Hung, Luke St Heaps, Dale Wright

[1]Sydney Genome Diagnostics, Children's Hospital at Westmead, NSW, Australia

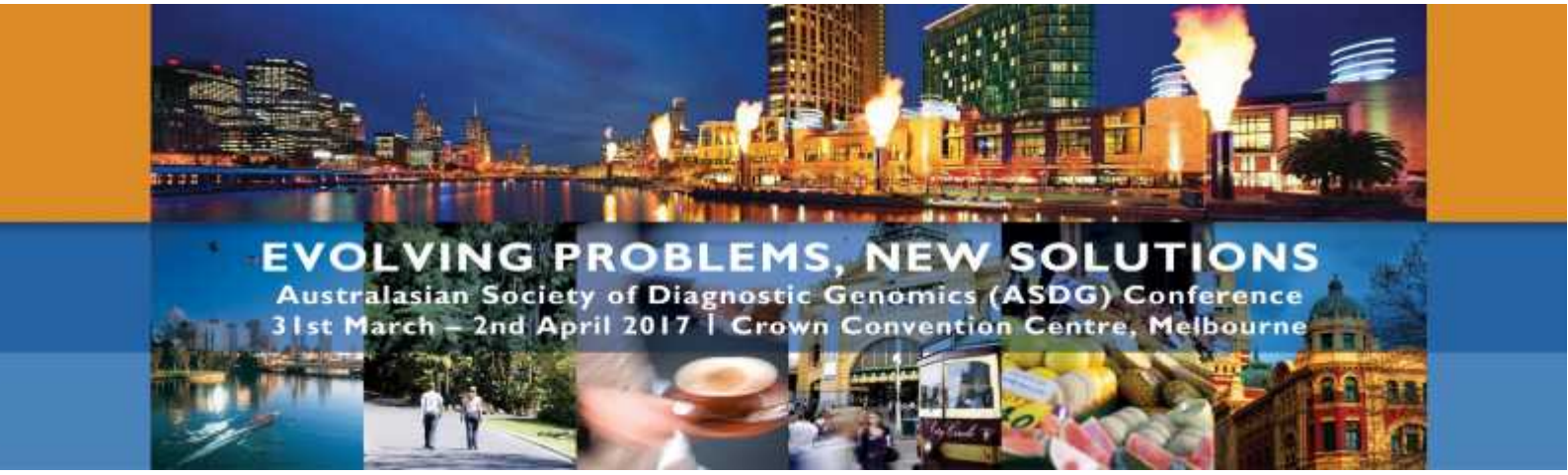
Background:
The recurrent t(8;21) abnormality found in primary acute myeloid leukaemia (AML) is associated with a favourable prognosis. In therapy-related myeloid leukaemia (t-AML), previous exposure to topoisomerase-II inhibitors tends to be associated with secondary abnormalities involving balanced rearrangements at 11q23 (KMT2A) and 21q22 (RUNX1). Breast cancer is often treated with topoisomerase-II inhibitors and t-AML can be associated with secondary acquired abnormalities.

Aim:
We present two cases identified with t(8;21) following cytotoxic therapy for breast cancer.

Method:
Case 1: 51yo female with pancytopenia and blasts on peripheral blood. The patient was 2 years post chemotherapy for breast cancer.
Case 2: 61yo female with blasts on peripheral blood and previously diagnosed with breast cancer.
These patients were investigated by karyotyping of 24hr and 48hr synchronised cultures, initiated and harvested according to standard laboratory protocols. Twenty G-band cells were analysed. FISH was performed using the t(8;21) probe for RUNX1/RUNX1T1 (VYSIS).

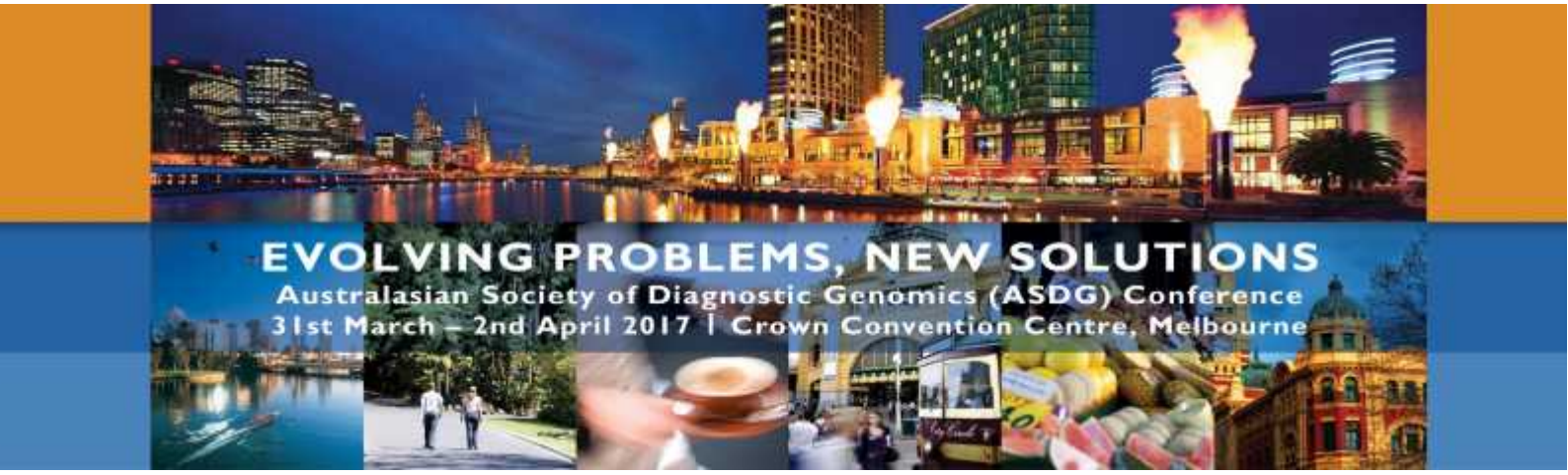
Results:
Case 1 showed a karyotype involving 45,X,-X,t(8;21)(q22;q22,del(9)(q22q32)[15]/46,XX[5]. FISH results failed. Case 2 showed a more complex karyotype involving 46,XX,t(8;17;21)(q22;q23;q22),t(10;20)(p15;p11.2)[14]/46,XX[6]. FISH results showed gene fusion of RUNX1/RUNX1T1 probe.

Conclusion:
The finding of the t(8;21) and variant t(8;17;21) with RUNX1/RUNX1T1 gene fusion is consistent with a secondary abnormality associated with t-AML following breast cancer treatment. Although the t(8;21) has a favourable prognosis in primary AML, when found as a secondary abnormality it portends to a more unfavourable outcome.



Biography

Hospital Scientist (8th year) currently working in cytogenetics at The Children's Hospital at Westmead. Completed a Bachelor of Science in 2008 and will be sitting the MHGSA exam in March this year.



02. Manual vs automated plasma cell (CD138+) enrichment: A validation study

El-Hajj Racha, St. Heaps Luke, Clark Alissa and Wright Dale.
Sydney Genome Diagnostics, Cytogenetic Department, The Children's Hospital at Westmead, NSW, Australia.

Background
Multiple myeloma (MM) is a plasma cell (PC) neoplasm in which the surface antigen CD138 (syndecan-1) is highly expressed. We have previously shown that FISH gives higher abnormalities rates on uncultured CD138+ enriched cells compared to routine cultured bone marrow cells (50.8% vs 7.4%, P<0.001). In our laboratory, CD138+ cell enrichment has subsequently become standard practice for FISH and chromosome microarray testing for MM patients.

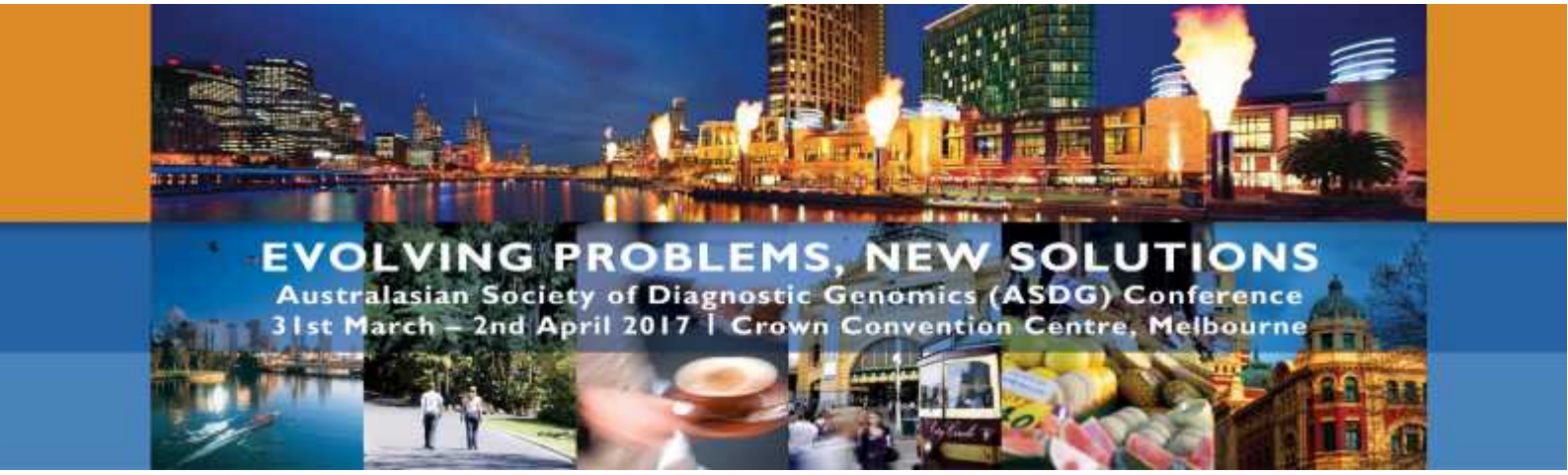
Aim
To validate and implement the AutoMACS Pro Separator for automated enrichment of CD138+ PCs.

Method
To date, eleven bone marrow samples have been enriched using the MACS whole Blood CD138 MicroBeads human kit (Miltenyi Biotec), which was performed in parallel with manual vs. autoMACS Pro Separator (Miltenyi Biotec) protocols, according to the manufacturer's instructions. FISH was performed using the probes IGH/CCND1, IGH/FGFR3, IGH/MAF, IGH break-apart, TP53/D17Z1 and/or CKS1B/CDKN2C (Carl Zeiss). The proportion of FISH abnormal cells between the two methods was compared using the paired-means t-test with a significance level α=0.05. Hands-in processing time was also evaluated.

Results
The mean proportion of abnormal cells by FISH for each method was 77.7% vs 86.4% for the manual vs. automated method, respectively. The increased yield (8.8%) was marginally significant (t=2.3, df=10, P=0.0442). Hands-on time taken to perform the manual vs. automated method was 140min vs. 55min, respectively.

Conclusion
Although there was a marginally increased yield of abnormal CD138+ cells (8.8%) using the autoMACS Pro, we considered there to be no real practical difference given the small sample size of the study. More importantly, when processing time was considered, the autoMACS Pro reduced processing by ~45 minutes. Furthermore, up to six samples can be batch processed. Although sample recruitment is ongoing, the results to date indicate the benefits of automation for CD138+ cell enrichment in a busy laboratory.

Program Sponsor:
igenz



03. Inverted duplicated deleted 8p: How microarray presents a prettier picture.

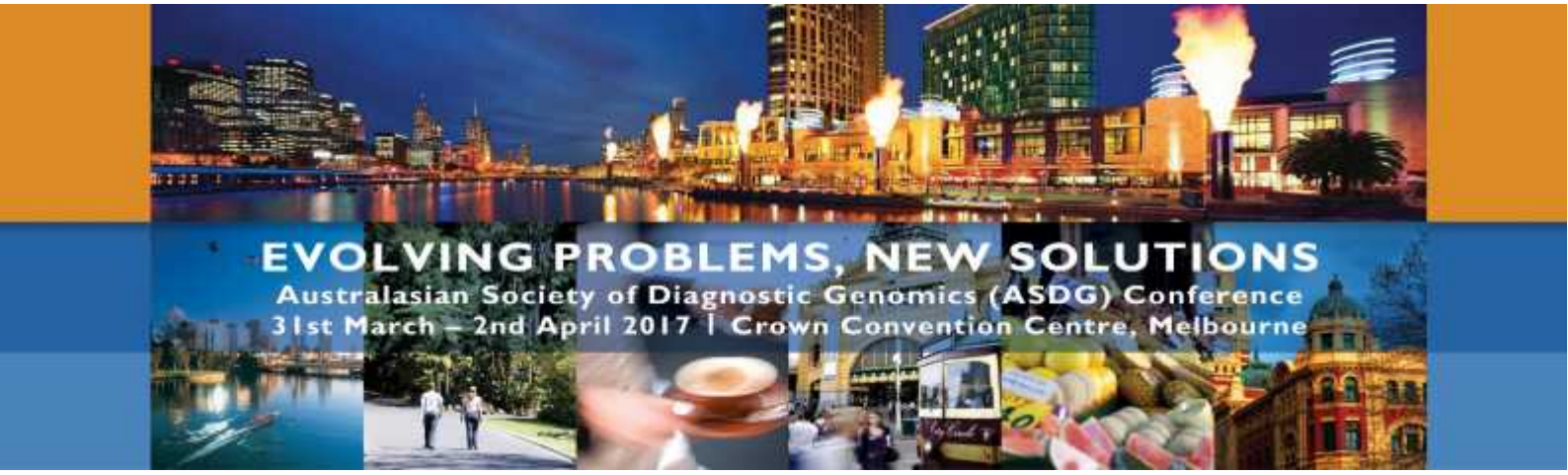
Mahony Fenn[1], Ryan Hedley[1], Dr. Melody Caramins[2], Dr. Nicole Chia[3]

[1] Western Diagnostic Pathology, 74 McCoy St, Myaree, WA, 6154, Mahony.Fenn@wdp.com.au
[2] Genomic Diagnostics, 60 Waterloo Road, Macquarie Park, NSW, 2113
[3] Queensland Medical Laboraory, Metroplex on Gateway, 11 Riverview Pl, Murarrie, QLD, 4172

The distal short arm of chromosome 8 is a well described hotspot for chromosomal rearrangement resulting in inversion, duplication and deletion. Until recently these have been detected by conventional chromosome analysis with subjective interpretation of chromosomal bands. The implementation of molecular karyotyping by chromosome microarray has elucidated these rearrangements with respect to the genomic location of the duplicated and deleted segments. Several mechanisms have been described which hypothesise the derivation of these rearrangements. In general these stem from the formation of a dicentric chromosome with a subsequent breakage leading to the classical invdupdel(8p). Parental paracentric inversions within 8p23 and Olfactory receptor (OR) gene clusters (including low copy repeat regions REPP and REPD) have been highlighted as the major triggers involved in the generation of the dicentric chromosome.
The subsequent breakage of the dicentric chromosome will often leave this derivative without a telomere resulting in chromosome instability. Stability is regained by restoration of the telomere. This can be done through telomere healing with the addition of telomeric sequences or by telomere capture whereby telomeres are sourced from another chromosome.
Here we describe 5 case studies of invdupdel(8p) and demonstrate the presence of the dicentric chromosome consistent with the early hypothesis and 2 cases showing telomere capture as the mechanism of telomere repair. This study highlights the value of the information provided by molecular karyotyping for the detection of chromosomal anomalies and additional insight of the mode of derivation.

Biography

I am one of the senior scientists at WDP and the 2IC of the Cytogenetics dept at WDP. I have worked in the field of cytogenetics for just over 15 years. Our main areas of interest currently at WDP are fertility, prenatal and paediatrics. We use conventional cytogenetics, FISH, QFPCR and microarray as our main techniques of analysis.



04. Targeted molecular testing for cancer therapy

Shravan K Yellenki, **Mioara Gavrila**, Elizabeth M Algar

Genetics and Molecular Pathology, Monash Health, 246 Clayton Rd, Clayton, VICTORIA

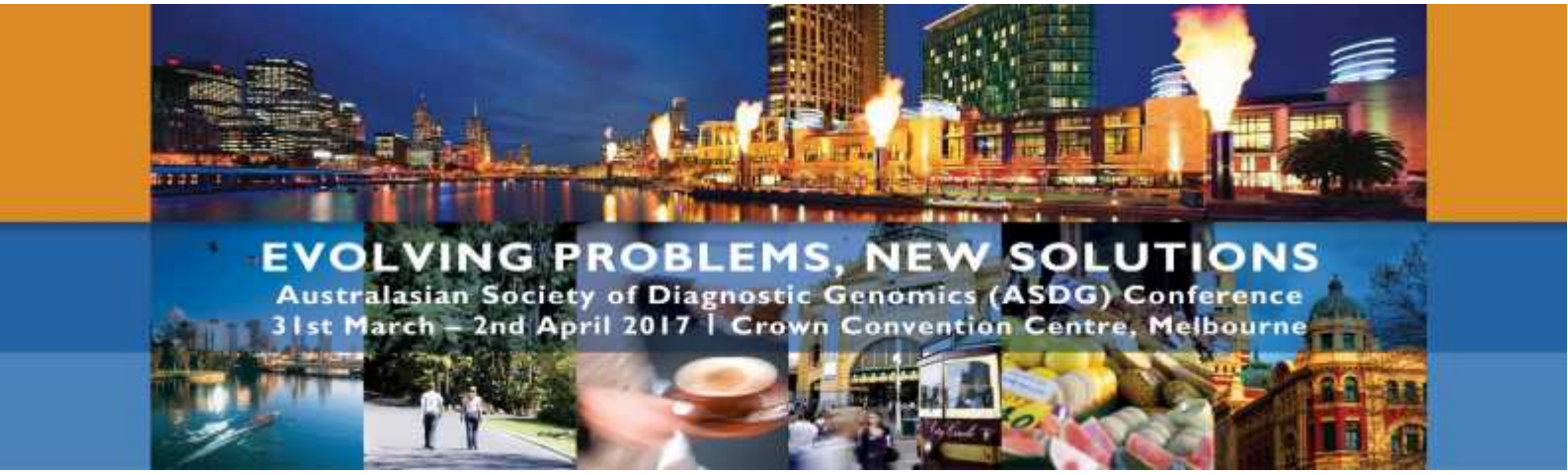
1 in 3 Australian men and 1 in 4 Australian women will be diagnosed with cancer before the age of 75. Cancer treatment has changed significantly over the past 10 years with the introduction of targeted therapies that result in less severe adverse effects compared to traditional chemotherapy. The ascertainment of genetic alterations in cancer is of increasing importance for informing the choice of targeted therapies.

Targeted molecular testing in adult cancer was implemented in the Genetics and Molecular Pathology laboratory at Monash Health at the end of 2014. In two years, 800 molecular tests have been performed on 600 tumour specimens from lung, colorectal, melanoma, thyroid and brain cancer. On average, 45% of mutation screening requests have been for EGFR in lung cancer, 22% for KRAS in colorectal cancer,10% for NRAS in colorectal cancer, melanoma or thyroid cancer, and 24% for BRAF in melanoma, thyroid or brain cancer.

Our method of choice for mutation screening has been the CE IVD Vienna Labs Strip Assay. These are mutant-enriched PCR-based assays that employ reverse hybridisation to detect clinically actionable mutations in EGFR (exons 18-21), KRAS (exon 2,3,4), NRAS (exon 2,3,4) and BRAF (exon 15). The assay utilizes 1-10ng of DNA and reliably detects to a sensitivity of 5% allowing testing of very small biopsy and cytology samples with low tumour content. A minimal equipment outlay is all that is required for set-up. Between 96-99% of clinically relevant mutations are covered by the assays. In our experience, the Strip Assay offers a flexible, rapid and sensitive test platform that although widely used in Europe has not been widely adopted in Australia yet for clinical testing.

Biography

Mioara is a senior scientist in the Genetics and Molecular Pathology laboratory at Monash Health. Previously she was in charge of Molecular Genetics Department at Australian Clinical Labs. She has 18 year experience in public and private NATA accredited molecular pathology services.



05. Undetectable levels of UNCONJUGATED ESTRIOL in maternal serum have led to a diagnosis of X-LINKED ICHTHYOSIS in a male fetus

Dannielle Ghezzi[1], Khoa Lam[1], Wendy Waters[2], Sarah Smith[2], Enzo Ranieri[1], Dr Michael Metz[1], Dr Janice Fletcher[1], Peter Sharp[3]

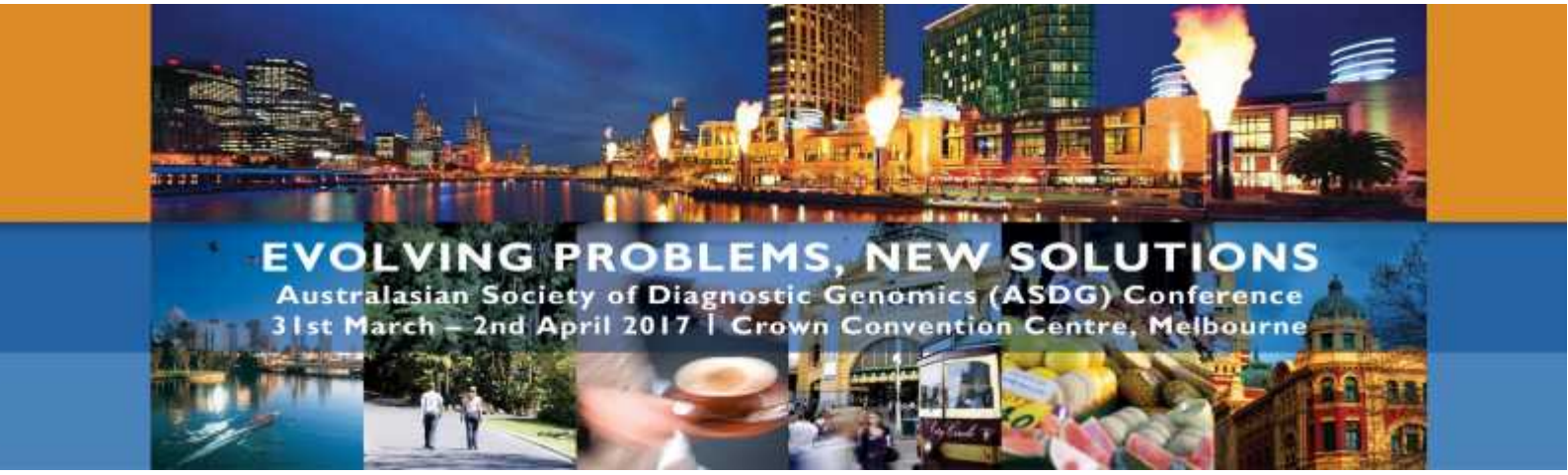
1 *Antenatal Screening Laboratory , Department of Biochemical Genetics, Directorate of Genetics & Molecular Pathology, SA Pathology, Women's and Children's Hospital, Adelaide, South Australia 5006, Australia*
2 *Department of Cytogenetics, Directorate of Genetics & Molecular Pathology, SA Pathology, Women's and Children's Hospital, Adelaide, South Australia 5006, Australia*
3 Metabolic Laboratory, Department of Biochemical Genetics, Directorate of Genetics & Molecular Pathology, SA Pathology, Women's and Children's Hospital, Adelaide, South Australia 5006, Australia

The South Australian Maternal Serum Antenatal Screening (SAMSAS) laboratory provides antenatal screening to the women of South Australia, Tasmania and Northern Territory. In combination with the Nuchal Translucency (NT) scan provided between 11 weeks + 2 days (11w2d) to 14 weeks, SAMSAS tests maternal serum for biochemical markers and generates a risk of aneuploidy and/or open neural tube defects using a SAMSAS developed 'triple test' algorithm.

Non-invasive Prenatal testing (NIPT) is becoming the preferred screening test for common aneuploidies in place of the biochemical 'triple test' screen. We present a case of a microdeletion that was identified through the biochemical testing method, which currently is undetectable by commercial aneuploidy NIPT.

Unconjugated Estriol (uE3) is a marker used in the second trimester biochemical screen. A patient aged 19 years (G1P0), showed undetectable serum levels of uE3 at 14w1d, 15w2d and 17w0d of gestation. The levels of uE3 were persistently undetectable by the Siemens Immulite2000 Immunoassay platform (LLD< 0.24nmol/L). The requested repeat analysis confirmed the low uE3 levels where metabolic studies for the exclusion of Smith-Lemli-Opitz (SLO) Syndrome were performed. SLO was exclude by testing on amniotic fluid revealing low levels of the 7-dehydrocholesterol, the precursor of cholesterol in the steroid biosynthesis pathway.

The patient was also referred for cytogenetic testing by prenatal microarray with particular concern for X-linked Ichthyosis. The microarray that was performed on amniocytes identified a male fetus with a 1.6Mb interstitial microdeletion at Xp22.31. This involved the STS gene which codes for the Steroid Sulfatase enzyme (EC 3.1.6.2); an important step in the biosynthesis of UE3 and a diagnosis of X-linked

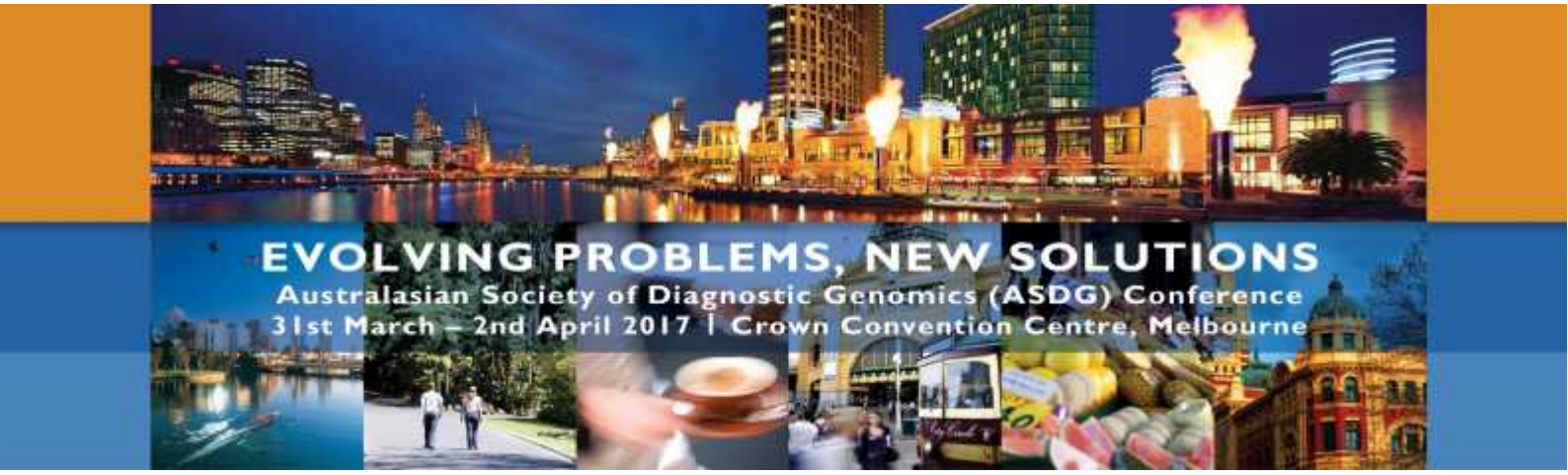


Ichthyosis was made. The mother was referred for FISH testing and was found to be a carrier of this deletion which could potentially affect future pregnancies.

This highlights the importance of a biochemical screen of maternal serum and the collaboration between testing laboratories to provide additional clinical information on a pregnancy.

Biography

The South Australian Maternal Serum Antenatal Screening (SAMSAS) laboratory provides antenatal screening to the women of South Australia, Tasmania and Northern Territory. In combination with the Nuchal Translucency (NT) scan provided between 11 weeks + 2 days (11w2d) to 14 weeks, SAMSAS tests maternal serum for biochemical markers and generates a risk of aneuploidy and/or open neural tube defects using a SAMSAS developed 'triple test' algorithm.



06. Phenotype risk assessment in a couple with multiple alpha and beta-globin variants.

Wendy M Hutchison[1], Kerryn M Weekes[1], Jeremy N Wells[1], Ruoxin Li[1], Nicholas Clark[1,] Anita Feigin[2,3], Asif Alam[1], Elizabeth Algar[4,] Zane Kaplan[2]

[1] Thalassaemia & Haemophilia Molecular Reference Laboratory, Level 3 Monash Medical Centre 246 Clayton Road, CLAYTON, VIC, 3168, wendy.hutchison@monashhealth.org
[2] Medical Therapy Unit, Level 2 Monash Medical Centre 246 Clayton Road, CLAYTON, VIC, 3168
[3] Genetics Services, Monash Medical Centre 246 Clayton Road, CLAYTON, VIC, 3168
[4] Genetics and Molecular Pathology, Level 3 Monash Medical Centre 246 Clayton Road, CLAYTON, VIC, 3168

Copy number variations in the α-globin genes are the result of unequal crossover between homologous segments in the α-globin gene cluster that misalign during meiosis. The reduction or increase in α-globin gene copy number leads to an imbalance of α and β-globin chains in the haemoglobin tetramer and consequently ameliorates or exacerbates

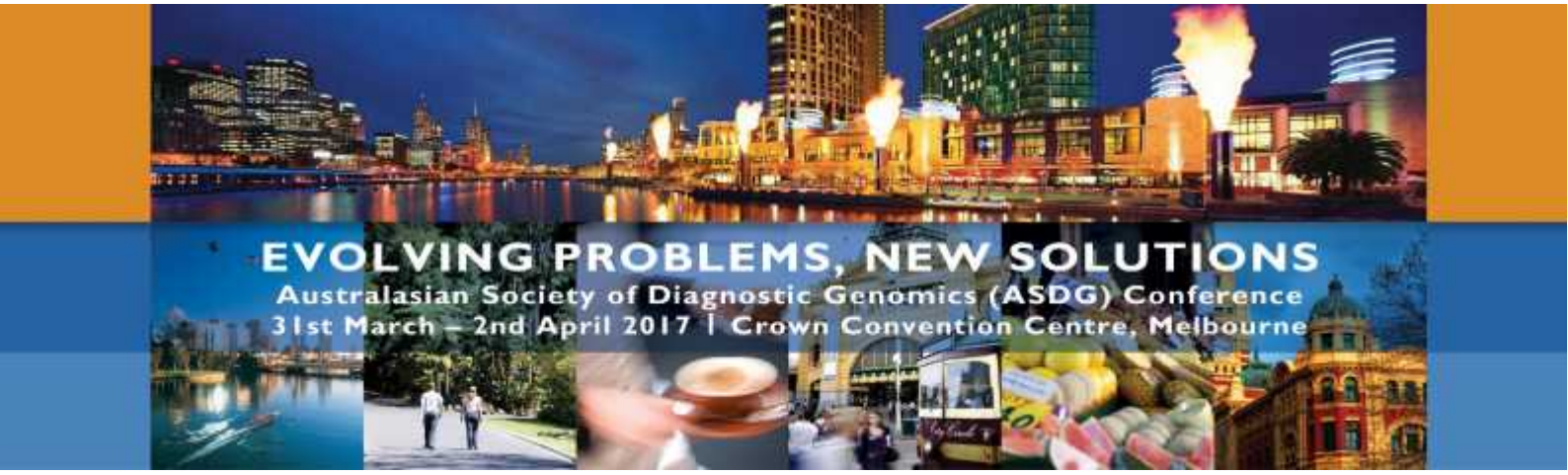
β thalassaemia clinical symptoms.

We describe a couple with one partner, with transfusion-dependent β thalassaemia major, who is a compound heterozygote for two beta-globin splice site mutations and heterozygous for both the anti3.7 alpha-globin gene triplication and the alpha-globin -3.7 single gene deletion mutation. The second partner is heterozygous for the anti3.7 alpha-globin gene triplication.

Possible genotype combinations and clinical phenotypic risks are discussed.

Biography

After many years working in Molecular Genetics Research Wendy moved to the Thalassaemia and Haemophilia Molecular Reference laboratory at Monash Health in 2013.



07. Two cases of the rare but emerging syndrome associated with the recurrent "3q13.2q13.31 Microdeletion".

Sharanbeer Kaur, Gregory Peters, Dale Wright

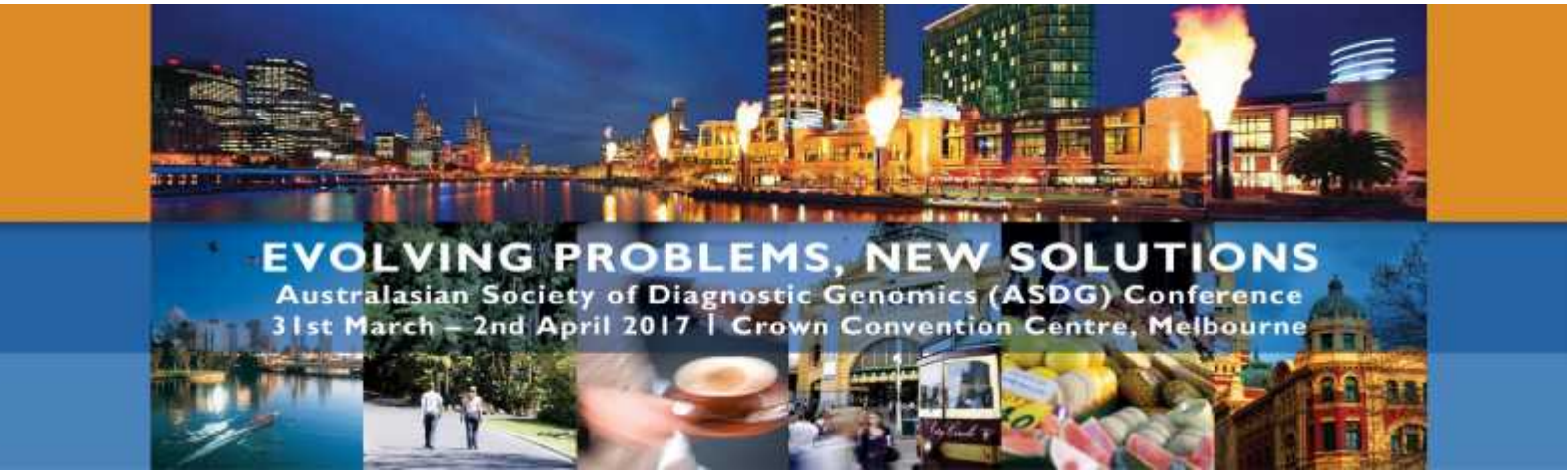
Sydney Genome Diagnostics, The Children's Hospital Westmead, NSW, 2145

Introduction:
The recurrent 3q13.2q31.31 microdeletion has been associated with a rare but emerging syndrome with clinical features overlapping Primrose syndrome. Herein, two cases are described.

Method:
Case 1: 9 year old female with moderate global delay. Case 2: 4 year old female with global development delay (motor and language), macrocephaly and 'distinctive appearance'. CGH microarray was performed using an 8x60K ISCA design (Agilent Technologies), and data analysed using the ADM-2 algorithm with copy number abnormalities (CNA) calls based on five consecutive probes (Cytogenomics v2.9.2.4). UCSC genome browser [hg19] was used to evaluate CNA pathogenicity and segmental duplications >1000bp. Parental follow-up studies were requested to investigate inheritance.

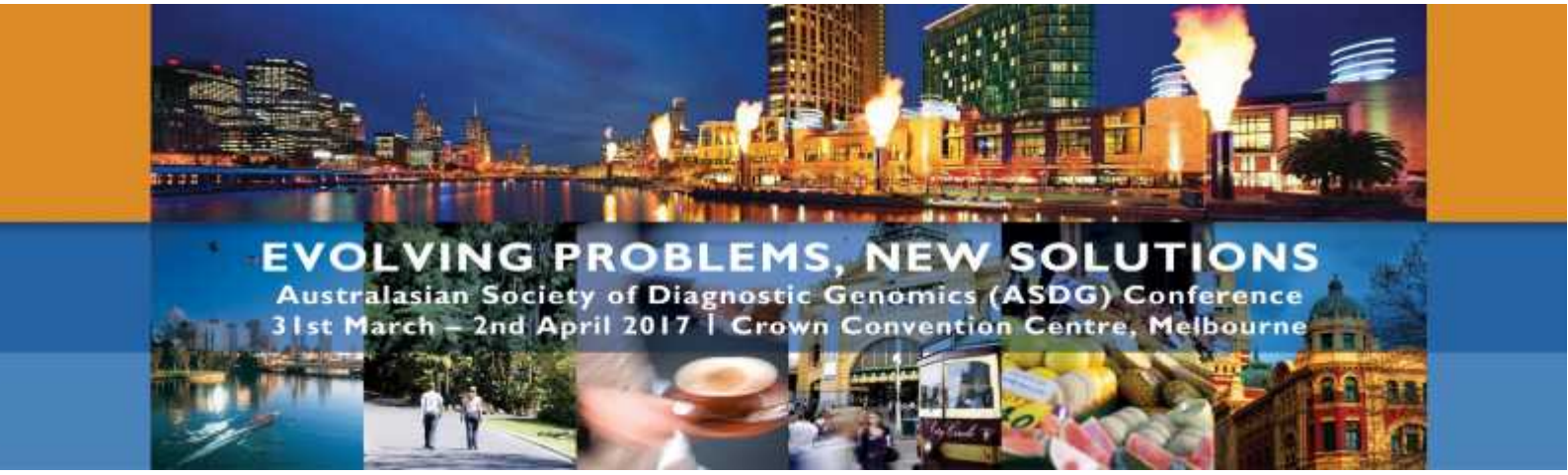
Results:
Case 1 and 2 both showed heterozygous deletions [~3.31Mb] within chromosome band 3q13.2q13.31, extending from coordinates 112.18Mb to 115.49Mb. This included 29 genes, from *BTLA* to *GAP43*. Two of the 29 genes are associated with OMIM-listed disease; *DRD3* and *ZBTB20*. No flanking segmental duplications were identified. Parental studies for Case 2 were negative, indicating a de novo mutation. Parental samples for Case 1 have not been received.

Conclusion:
The recurrent 3q13.2q13.31 deletion was identified in two cases. Case 2 was de novo and Case 1 of unknown inheritance. Clinical features of the emerging syndrome include development delay, hypotonia, high-arched palate, increased occipitofrontal circumference and distinctive facial features; short philtrum and protruding lips. A smallest region of overlap has been defined as ~0.6Mb, which includes five genes: *DRD3, ZNF80, TIGIT, MIR568* and *ZBTB20*. Primrose syndrome is caused by heterozygous mutations in *ZBTB20*. *DRD3* is associated with schizophrenia. Both are considered candidate genes with respect to development delay, psychiatric features, and associated structural brain malformations. Recurrent deletions typically arise via non-homologous allelic recombination facilitated by flanking segmental duplications, however none were identified >1000bp. This may suggest involvement of smaller duplicated segments, or an alternative mechanism.



Biography

I am a Trainee Hospital Scientist at the Children's Hospital Westmead under the Sydney Genome Diagnostics Program.



08. Detection of parental mosaicism following non-mosaic findings in their offspring on array

Louise Korte[1], Sarah Higgins[1], Jillian Nicholl[1], Alison Attwood[1], Ryan Storer[1], Sarah Smith[1], Yvonne Hull[1], Sue Brown[1], Rhonda Hutchinson[1], Christopher Barnett[2], Jan Liebelt[2]

[1]SA Pathology, Cytogenetics Unit, Department of Genetic Medicine, WCH, 72 King William Road, North Adelaide, SA, 5006
[2]SA Clinical Genetics Services, WCH, 72 King William Road, North Adelaide, SA, 5006

Microarray technology is now widely used to diagnose pathogenic copy number variants (CNVs) in neurological disorders (Intellectual disability, autism, schizophrenia etc.). We routinely ask for parental follow up to determine if changes are inherited or de novo and to clarify the clinical significance of the majority of CNVs we detect. We will present four cases where SNP array has identified a CNV in the proband and parental follow up has shown mosaicism. This significantly increases the possibility of recurrence of another similarly affected child. Three of these inherited changes were not detectable by routine cytogenetic analysis. This illustrates the value of FISH investigation for parental follow up.

Case 1: An additional supernumerary bisatellited chromosome 22 marker was detected, consistent with a diagnosis of Cat Eye Syndrome. Family studies showed the marker chromosome 22 was maternally inherited, present in 67% of metaphases examined.

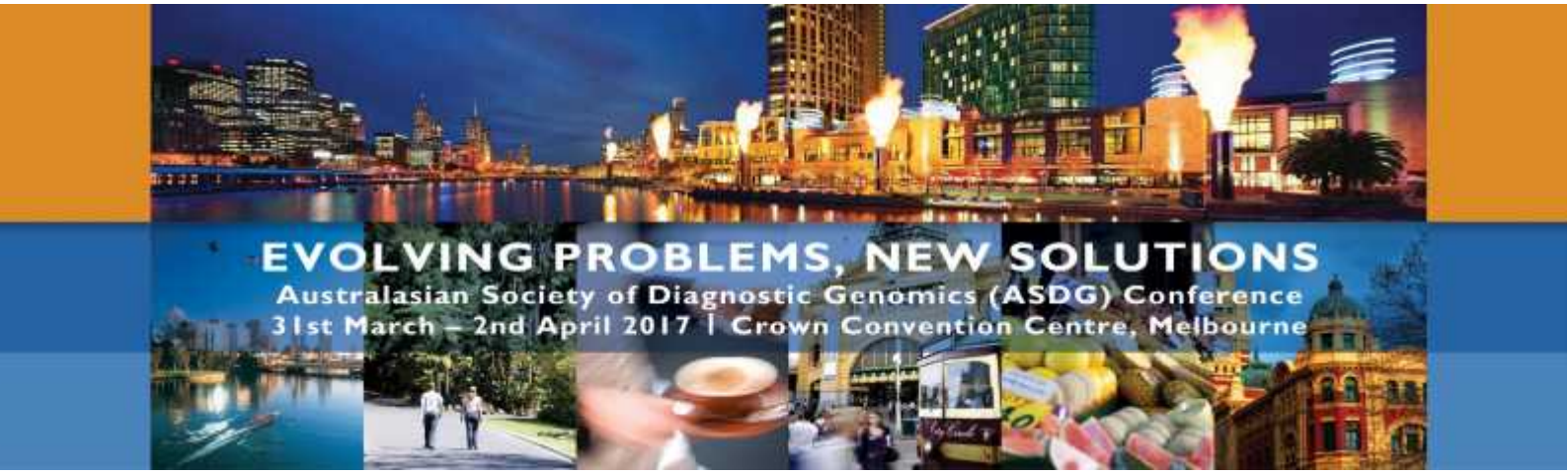
Case 2: A 2Mb deletion of chromosome 17p11.2 involving the RAI1 gene was detected, consistent with a diagnosis of Smith-Magenis syndrome. The deletion was maternally inherited, present in 64% of cells examined.

Case 3: 4.2Mb duplication at chromosome 1q43-q44 involving the AKT3 gene was detected. A low level of mosaicism was detected in the mother, however FISH results fell outside the reporting guidelines. A Masked array showed a slight divergence of the B allele frequency, which supports this FISH result.

Case 4: A 560kb deletion of chromosome 2p16.3, involving the NRNX1 gene was detected. The deletion was maternally inherited, present in approximately 30% of cells examined.

Biography

Cytogenetics laboratory at the women's and children's hospital



09. Limitation of molecular karyotyping: Discordance between molecular vs. conventional cytogenetics

Shea Ming Lim, Toni Saville, Pauline Dalzell, Christopher Lucas, Joan Junio, Krystle Standen, Genevieve Temple, Louise Carey

[1]Molecular and Cytogenetics Unit, SEALS Pathology, Prince of Wales Hospital, Randwick

Introduction: Most laboratories are moving towards molecular based cytogenetics such as QF-PCR, CGH microarray, and MLPA as their first line of prenatal testing, therefore conventional cytogenetics is not routinely performed, and is often supplementary to molecular karyotyping.

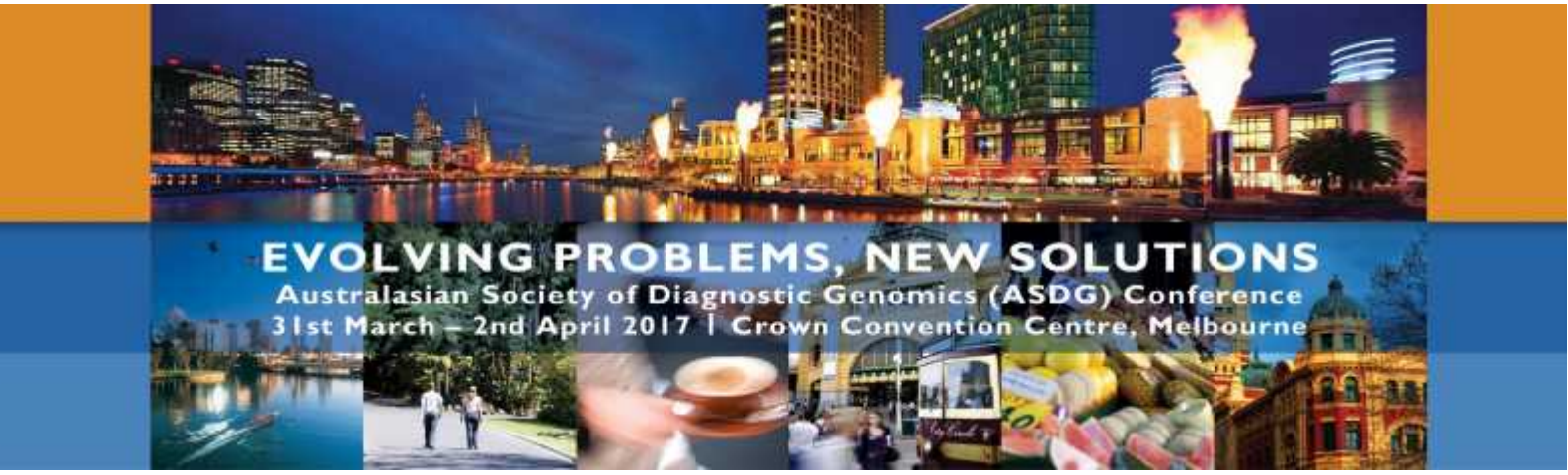
Methods: We performed a retrospective audit of 648 fetoplacental referrals (322 prenatal chorionic villus samples and 326 product of conceptions) received in 2016 to identify cases in which cytogenetic discordance between molecular and conventional cytogenetic testing were reported. All prenatal CVS referrals received standard QF-PCR and CGH microarray testing, while the majority of POC referrals received QF-PCR and subtelomere MLPA testing. Conventional karyotype was only performed in a small number of these cases. The main indication for conventional karyotyping is to rule out Robertsonian translocation following a trisomy 13 or 21 result, or as a confirmatory test for any CNVs reported. POC referrals with 3 or more miscarriages also received a conventional karyotype in addition to a molecular karyotype.

Results: We identified 9 cases (9/648; 1.38%) where a discordance between molecular and conventional karyotype was observed. The findings of these cases are presented in this study, with a discussion of the limitations of molecular testing over conventional cytogenetics.

Conclusion: Conventional cytogenetics is still a useful tool in the diagnosis of prenatal cytogenetic abnormalities. However, consideration needs to be given to the resources available in each laboratory.

Biography

Graduated from Charles Sturt University, Wagga Wagga, Australia with Bachelor of Medical and Applied Biotechnology in 2007 and Bachelor of Medical Science (Pathology) in 2008. Started working for SEALS Pathology, Prince of Wales Hospital in 2009 and has been in the Molecular and Cytogenetics Unit since 2011.



Poster Prize Candidate

10. A very complex and rare cytogenetic finding of a patient with two balanced chromosomal rearrangements involving one chromosome 1, one chromosome 6 and one chromosome 4.

Vanessa McLaughlin[1], Paula Lall[1], Louise Hills[1], Sorour Voghoei[1], Dao Nguyen[1], Michael Cronin[1], Amber Boys[1], Fiona Norris[1], David Francis[1], Martin Delatycki[1]

[1]VCGS, Level 4 MCRI Building, Royal Children's Hospital, Flemington Rd, Parkville, 3052

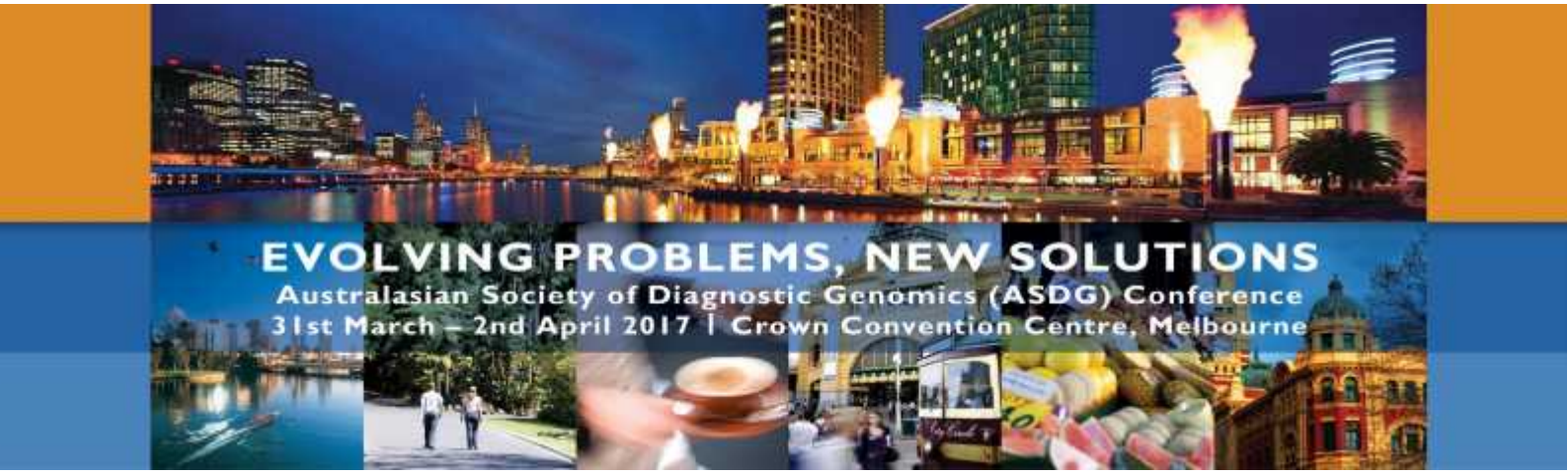
Microarray analysis and FISH testing were requested on an amniotic fluid sample with clinical indications of 1:7 risk of T21 on combined serum testing (CST), NF 4.0mm and low risk NIPT. The X, Y, 18, 13, 21 aneuploid FISH panel showed a normal male signal pattern. The SNP microarray analysis showed a male molecular karyotype with an interstitial deletion of approximately 6.9 megabases from chromosome region 1q42.13q42.3 and an interstitial duplication of approximately 4.7 megabases from chromosome region 4q28.3. Parental blood samples were requested for both microarray and conventional chromosome analysis to determine the origin and significance of this finding.

Microarray analysis of both the maternal and paternal blood samples were normal, with no evidence of the deletion or duplication found in the amniotic fluid sample. However, a complex rearrangement between chromosomes 1, 4 and 6 was identified by conventional chromosome analysis in the father. This complex rearrangement involved a balanced reciprocal translocation between the short arm of one chromosome 1 and the long arm of one chromosome 6, and a balanced interstitial exchange of material between the long arm of the derivative chromosome 1 and the long arm of one chromosome 4. Metaphase FISH analysis was performed using BAC probes to confirm this finding.

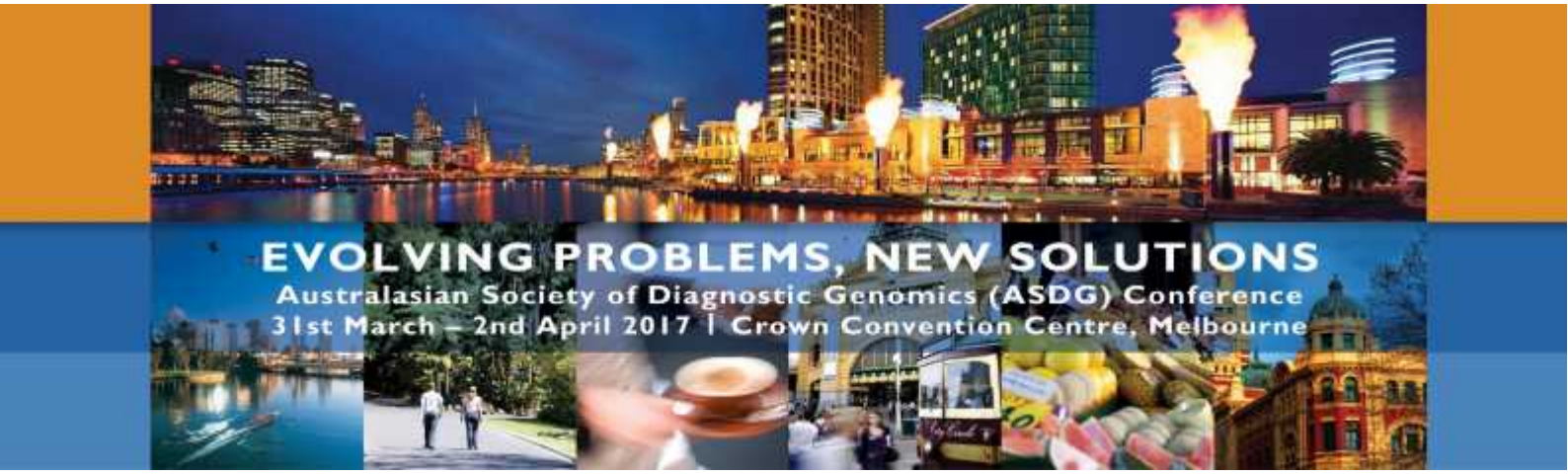
This patient therefore carries two balanced chromosomal rearrangements, which is a very rare cytogenetic finding.

Upon learning of this finding, this couple requested cytogenetic testing for their 2 year old son with developmental delay. Microarray analysis showed the same unbalanced pattern of inheritance found in the couple's original prenatal sample.

Biography



Vanessa McLaughlin has been working in the Cytogenetics department at VCGS since 2008 and is currently a Team Leader in the Prenatal and FISH sections. Vanessa has extensive experience in conventional chromosome analysis and FISH analysis.



11. A family with a 22q11.2 distal deletion

Holly Napret, Dean Grimmond, Artur Darmanian and Dale Wright

[1]Sydney Genome Diagnostics, The Children's Hospital at Westmead, Hawkesbury Rd, Westmead NSW 2145

Background: The 22q11.2 region is complex with well-defined segmental duplications, or low copy repeats (LCR), which predispose to genomic instability. Eight LCRs (A-H) can be found in the region. Heterogeneous copy number abnormalities (CNA) and structural rearrangements arise typically via non-homologous allelic recombination (NHAR). Four centromeric LCRs (A-D) are associated with a proximal deletion and Velocardiofacial/Di George syndrome (VCFS/DGS), whereas telomeric LCRs (D-H) are associated with various distal microdeletions and reciprocal microduplications. We describe a family with a distal 22q11.2 deletion.

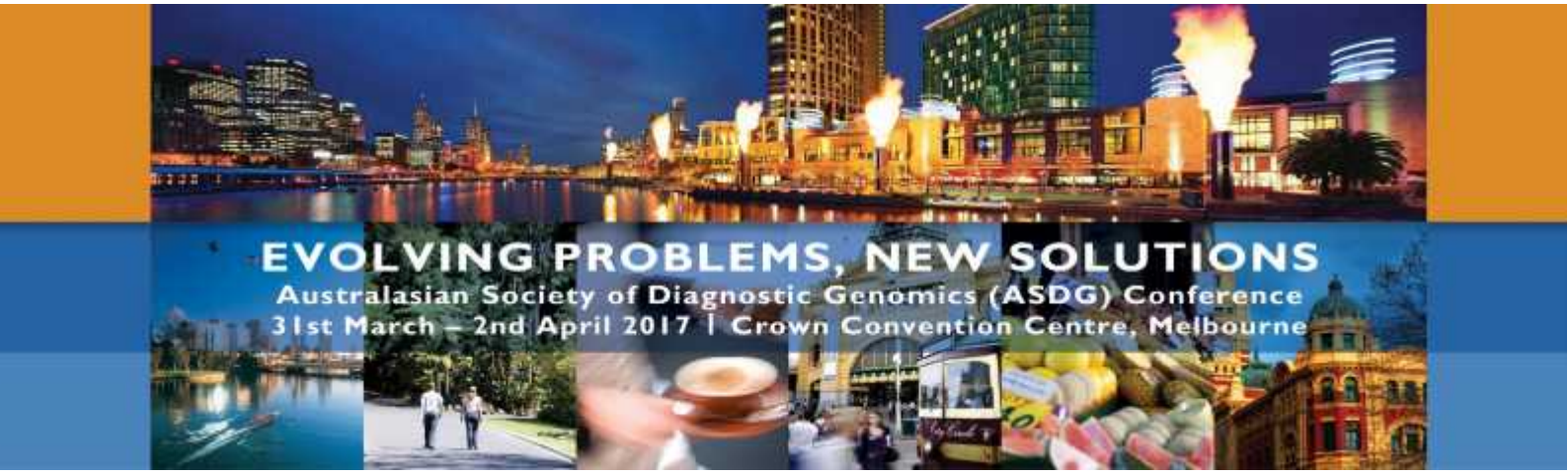
Methodology: A male presented with preauricular skin tags, short stature and abnormal behaviour. The sister was overweight with ADHD. His uncle had moderate development delay. The mother and grandmother appeared phenotypically normal. All had an 8x60K ISCA microarray (Agilent Technologies), analysed using the ADM-2 algorithm with CNA called based on 5 consecutive probes (Cytogenomics v2.9.2.4). UCSC genome browser [hg19] was used to evaluate Development Delay CNAs and segmental duplications >1kb.

Results: All individuals showed a heterozygous deletion [~0.59Mb] within chromosome 22 bands q11.22q11.23, extending from coordinates 23.01 to 2365Mb. This included five genes, from *MIR650* to part of *BCR*, of which only *BCR* is OMIM-disease listed. However, the uncle showed an additional deletion within [2.85Mb] chromosome 14 band q24.2. Chromosome 22 LCRs flanked the deletion.

Conclusion: The inherited 22q11.2 deletion here is rare but found enriched in Development Delay cases vs. controls. It is flanked by LCRs with 90-98% sequence homology, suggesting a mechanism of NHAR. The function of genes involved is poorly understood. Clinical features of 22q11.2 distal deletion described include development delay, microcephaly, low birthweight, short stature; including preaurical skin tags. The deletion may contribute to the uncle's phenotype but more likely explained by the 14q24.2 deletion. The different clinical features and asymptomatic carriers in this family are consistent with a variably expressed and penetrant phenotype.

Biography

Holly Napret is a trainee Hospital Scientist who is currently learning chromosome microarray



12. Fusion of two transferred embryos following IVF delivers monochorionic diamniotic 'chimeric' twins with sex discordance.

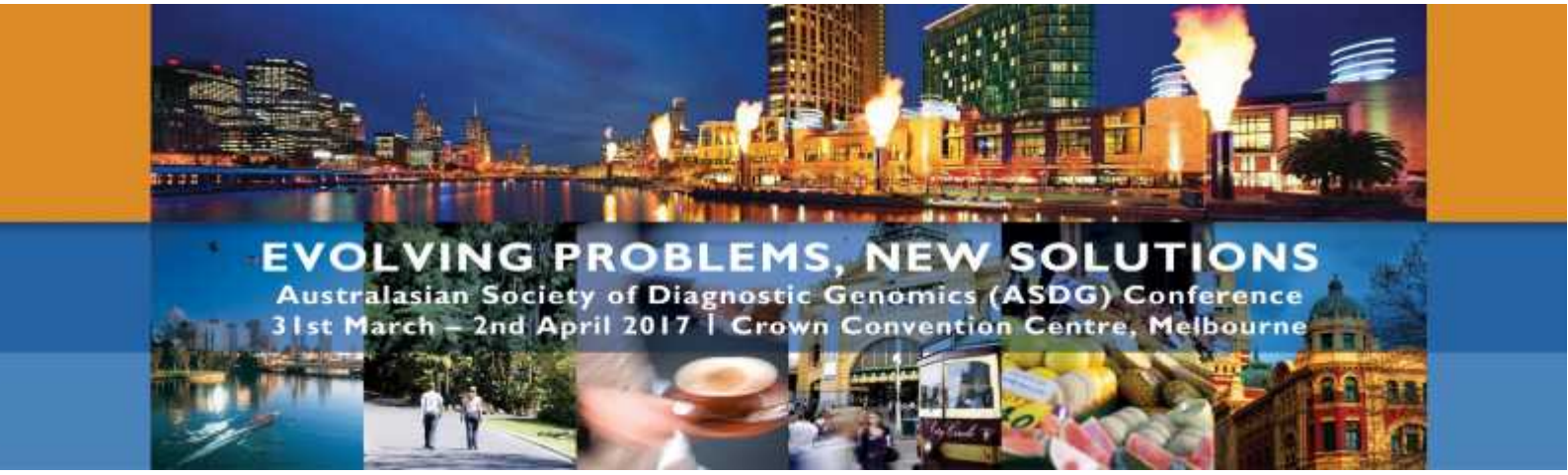
Jennifer Ong[1], Con Ngo[1], Shubha Srinivasan[2], Komal Vora[2], Meredith Wilson[3], Dale Wright[1]

[1] Department of Cytogenetics, The Children's Hospital at Westmead, Corner Hawkesbury Road Hainsworth Street, Westmead, NSW, 2145.
[2] Department of Endocrinology and Diabetes, The Children's Hospital at Westmead, Corner Hawkesbury Road Hainsworth Street, Westmead, NSW, 2145.
[3] Department of Clinical Genetics, The Children's Hospital at Westmead, Corner Hawkesbury Road Hainsworth Street, Westmead, NSW, 2145.

Background: In vitro fertilisation (IVF) is an assisted reproductive technology where gametes are fertilized in-vitro with uterine transfer. Although single embryo transfer is recommended practice, occasionally two or more embryos may be transferred. IVF is also associated with increased identical and non-identical twinning. Furthermore, twins may rarely arise from embryo-fusion resulting in a tetragametic chimera. We describe monochorionic diamniotic (MCDA) 'chimeric' twins with discordant sex following IVF.

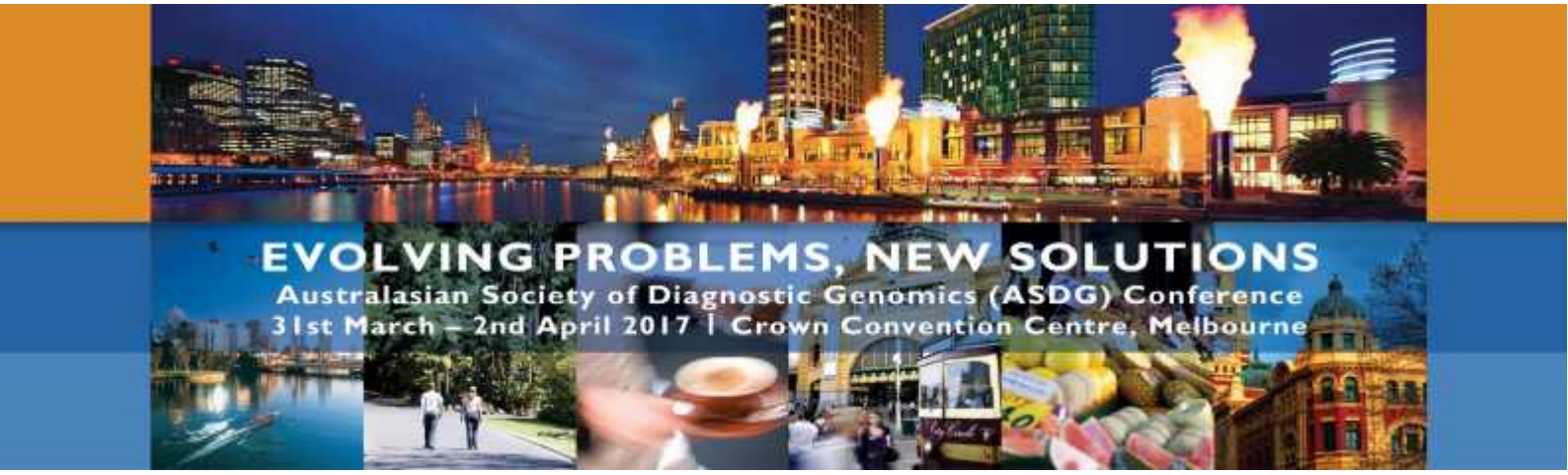
Methodology and Results: Phenotypic male and female twins were born after IVF with two embryo transfer. A single placenta was noted. Neonatal blood cytogenetic investigation by FISH, QF-PCR, karyotype and genome-wide SNP microarray was performed. Both twins showed 46,XX and 46,XY cell lines in approximately equal proportions. The QF-PCR profiles were identical for both twins but the STR marker D18S386 showed four alleles, suggestive of tetragametic chimerism. SNP microarray confirmed this finding. Subsequent FISH analysis of urine sediment and buccal cells showed predominantly XX cells in the female whilst the male showed predominantly XY cells. Ovaries could not be identified on ultrasound in the female but the male had bilateral descended testes. The female showed high follicle-stimulating hormone (FSH) levels (17.7 IU/L; normal range: 0.1-8.7 IU/L).

Conclusion: The distribution of XX and XY cell lines among tissues of different embryonic origin is consistent with chimeric MCDA twins that arose from fusion of two embryos [male and female], which also excludes twin-twin transfusion syndrome. We propose that embryo fusion likely occurred at the late-morula or blastocyst stages of development to account for wide-spread tissue distribution of XX and XY cells. The sex discordance likely reflects the higher proportion of XX and XY cell lines within gonadal tissues for the female and male twin, respectively. The elevated FSH levels in the female may indicate gonadal dysgenesis with a risk of gonadoblastoma, thereby necessitating ongoing assessment.



Biography

My name is Jennifer Ong. I am currently studying a Bachelor of Biomedical Science at the University of Technology Sydney and employed as a Trainee Hospital Scientist in the Cytogenetics Department at The Children's Hospital in Westmead for over 2 and a half years. I am interested in cytogenomics.



13. What is lurking in the Karyotype? A review of aUPD in haematological malignancy.

Rebecca Reid[1], Jodie Fitness [1], Emmie Pushkareff [1], Redmond Orth [1], Aynsley Bryce [1], Nick Hovey [1], Dr Melody Caramins [2], Dr Nicole Chia[1]

[1] Queensland Medical Laboraory, Metroplex on Gateway, 11 Riverview Pl, Murarrie, QLD, 4172
[2] Genomic Diagnostics, 60 Waterloo Road, Macquarie Park, NSW, 2113

Conventional karyotyping and targeted fluorescence in-situ hybridisation (FISH) analysis have long been the gold standard of cytogenetic investigation for haematological malignancies. The detection of non-random balanced rearrangements and duplication and deletion that is associated with gene deregulation, formation of chimeric protein or unmasking of tumour suppressor gene mutations, is the primary objective of these investigations.

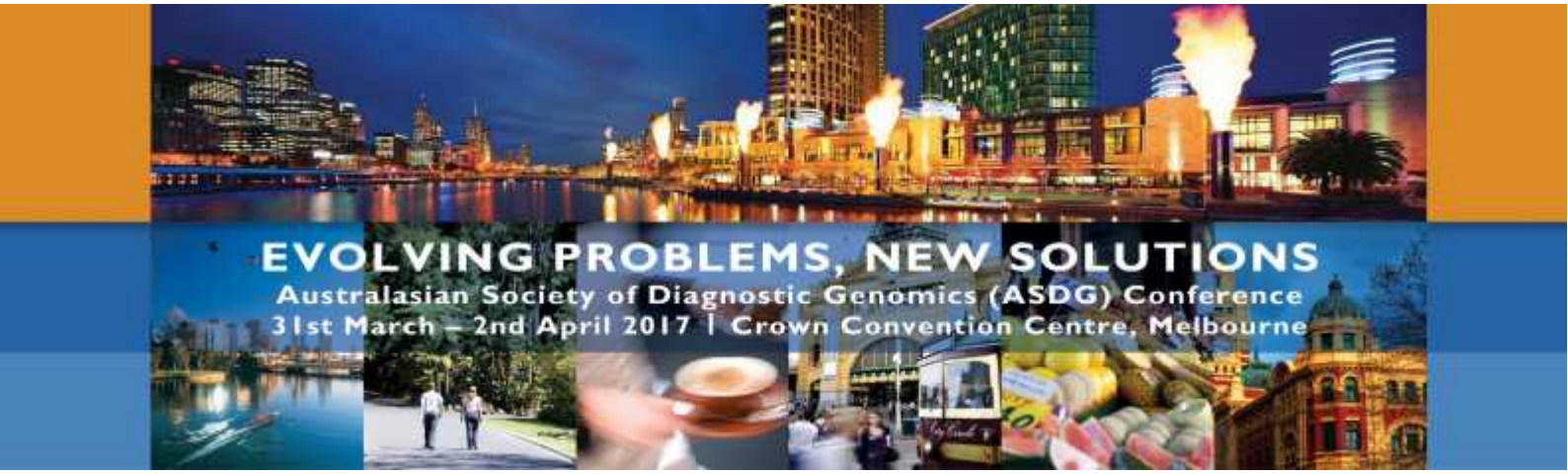
The higher level of resolution afforded by molecular karyotyping by microarray has characterised some of the well described duplications and deletions with respect to genomic location and gene involvement. Copy number changes, and where SNP microarray platforms are applied, non-random events of acquired uniparental disomy (aUPD) that are beyond the scope of conventional analysis have been detected.

Here we review the conventional and molecular karyotypes of haematological malignancies (CLL and myeloid malignancies) referred to a diagnostic service. The objective of this study is to investigate events of aUPD, identify the putative candidate genes within these regions and evaluate the impact to the prognostic significance when compared to the conventional cytogenetic results. Preliminary findings reveal an incidence of 12.6% of non-random events of aUPD involving primarily chromosomes 1, 9, 13, 17 and 20, some of which, such as aUPD 17p, alter the prognostic significance from the low risk to high risk clinical category. Comparison of genomic locations of aUPD demonstrated a correlation with the type of haematological malignancy.

This study illustrates the benefits of SNP based microarray investigation as an adjunct to conventional methods for the comprehensive investigation of haematological malignancies and progression towards precision medicine.

Biography

Since graduating from Massey University in New Zealand at the end of 2015, Rebecca has been employed in the Genetics Department at QML Pathology, primarily working in haem-oncology.



14. Cystic fibrosis mutations and infertility – using Next Gen Sequencing to identify infertility related variants

Melinda Richter[1], Nicole Martin[1], Peter Field[1]

[1] Virtus Diagnostics – QFG Genetics, Level 1 Boundary Court, 55 Little Edward Street, Brisbane, QLD, 4000

Cystic Fibrosis is the most common severe autosomal recessive disease in those individuals with Northern European ancestry. Cystic Fibrosis is known to be linked with male infertility, with over 95% of CF affected males having Congenital Bilateral absence of the vas deferens (CBAVD).

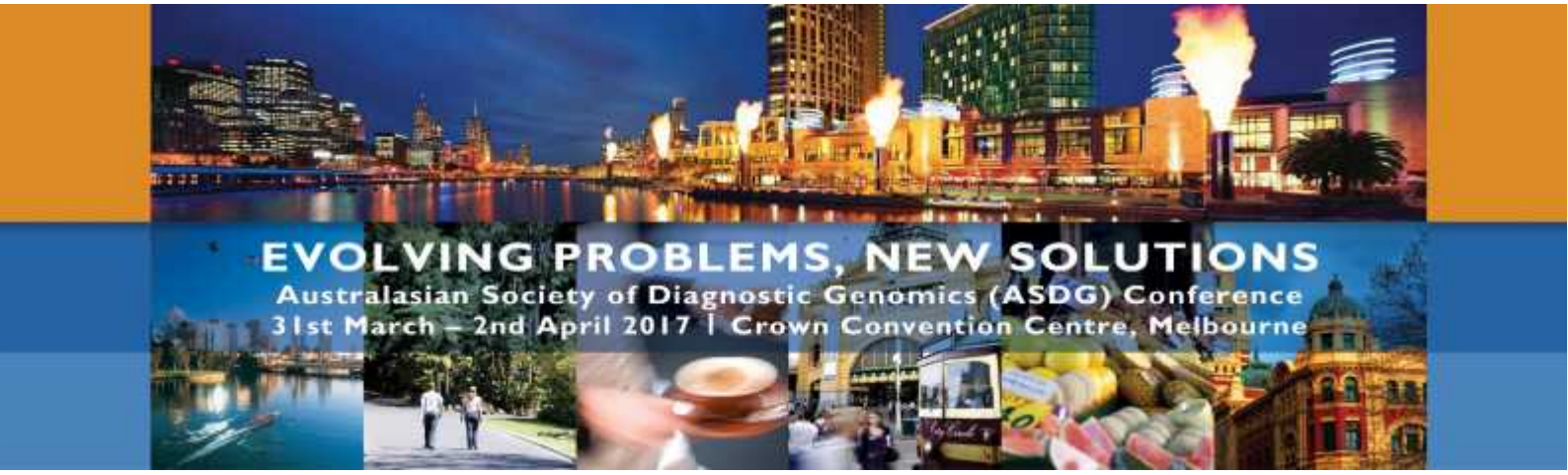
Using a targeted Next Generation Sequencing (NGS) panel we can detect base changes in codons that are not commonly represented in the traditional genotyping kits and thus give more information to patients seeking infertility treatment.

Mutations such as R117H have been shown to have varying clinical consequence but not classical Cystic Fibrosis in clinical presentation. However, R117C (caused by a single base change in the same codon as R117H) is a CF mutation that does occur in classic Cystic Fibrosis. Both of these variants have the potential to be involved in CBAVD.

By utilising NGS we are able to detect more base change variants associated with different ethnic ancestry as well as varying clinical consequence, leading to better treatment pathways for infertility patients.

Biography

Molecular Genetics Scientist at QFG Genetics



Poster Prize Candidate

15. A deletion in CFTR causes double trouble

Monica Runiewicz

Introduction: Cystic fibrosis is an autosomal recessive chloride ion channelopathy causing disruption of exocrine function of the pancreas, intestinal glands, biliary tree, bronchial glands and sweat glands. Pre-conception carrier screening for cystic fibrosis is common.

The molecular findings from an ARMS assay that required detailed analysis to arrive at the underlying molecular mechanism are presented.

Methods: The Elucigene CFEU2v1 kit detects 50 of the most common variants found in European populations, as well as the intron 9 (previously intron 8) polyT tract and adjacent TG repeat. It is a multiplex-fluorescent ARMS PCR assay which has two panels of primers – one panel targeting the specific variants and a second panel targeting the equivalent wild types, allowing the differentiation of variants in the heterozygous and homozygous states.

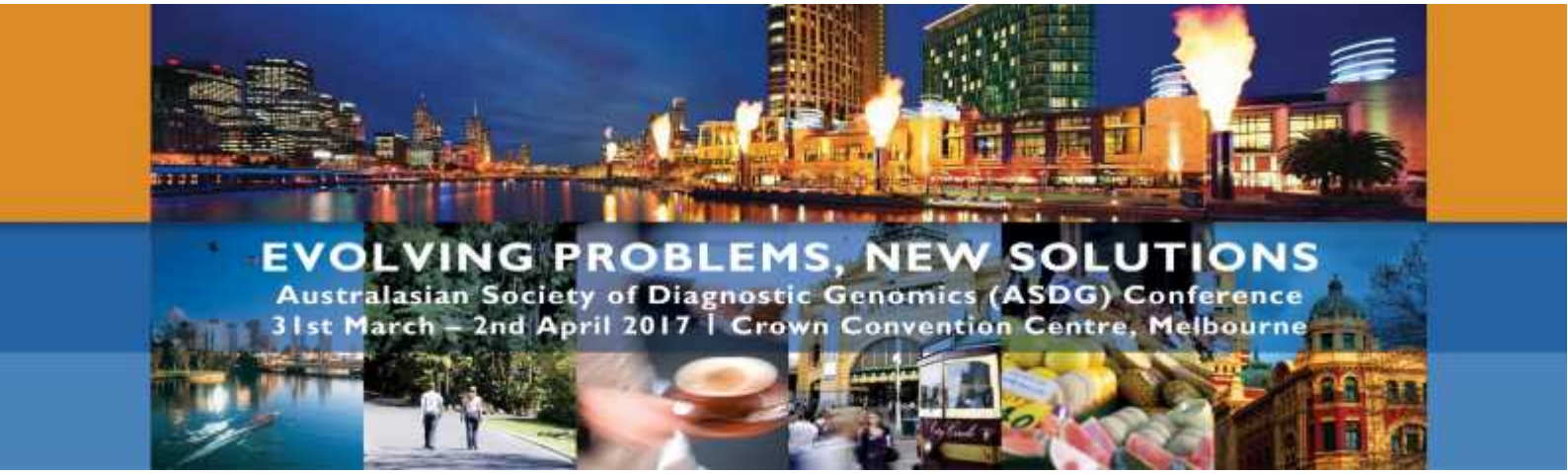
The assay also has the added benefit of being able to detect the presence though not the genomic location of small insertions and deletions within the amplicons as well as some variants other than the 50 that are targeted in the assay. Insertions and deletions alter the size of the PCR product produced while variants that fall under the assay primers can disrupt primer binding and thus reduce the amount of product produced. Both of these can be visualised on the assay electropherograms.

Results: A double peak was identified at one locus, suggesting an insertion or deletion, and a half-height peak at another locus, suggesting a variant disrupting the binding of one of the primers.

Following Sanger sequencing of all exons thought to potentially contain these two variants, only one variant was identified – *CFTR*:c.3874-64_3874-51del – a 14bp benign intronic deletion. This deletion was the cause of both anomalies in this individual's electropherograms. The single deletion appeared to cause two mutational signals by altering the size of one amplicon.

Biography

Monica is a Hospital Scientist in Molecular Genetics at SEALS Pathology, Prince of Wales Hospital. She is the team leader for the Community Genetics section of the laboratory and focuses on cystic fibrosis and other community-based screening.



16. Alport syndrome testing – 18 months experience with NGS

Louisa Sanchez [1], Evelyn Douglas[1], Linda Burrows[1], Kathy Cox[1], Maely Gauthier[2], Karin Kassahn[2], Sam Crafter[3], Lesley McGregor[4], Chris Barnett[4], Kathie Friend[1]

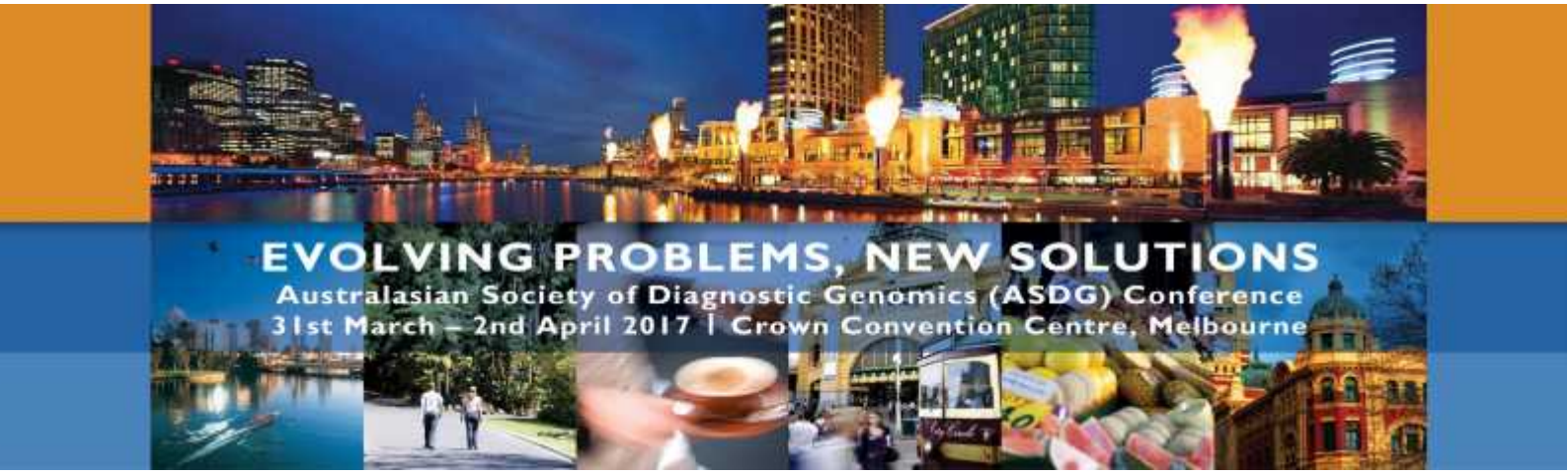
[1] Molecular Genetics Unit, SA Pathology, North Adelaide, South Australia
[2] Technology Advancement Unit, SA Pathology, Adelaide, South Australia
[3] Dept. of Nephrology, Women's and Children's Hospital, North Adelaide, South Australia
[4] South Australian Clinical Genetics Service, SA Pathology, North Adelaide, South Australia

Alport syndrome (ATS) is a disorder of the basement membrane characterised by glomerulonephropathy, resulting in renal failure, as well as sensorineural hearing loss and ocular anomalies. The majority of cases are X-linked, associated with variants in the *COL4A5* gene, including a large number of multi exon deletions and duplications. Autosomal recessive and autosomal dominant forms are associated with variants in the *COL4A3* and *COL4A4* genes. Rarely patients with ATS also have diffuse leiomyomatosis (ATS-DL), a benign neoplastic condition characterised by aberrant proliferation of well differentiated smooth muscle cells, involving the gastrointestinal, tracheobronchial and female genital tracts. A contiguous deletion of the 5' exons of *COL4A5* and *COL4A6* is commonly detected in patients with this phenotype.

Our laboratory (Genetics and Molecular Pathology, SA Pathology) has recently introduced screening of genes known to be involved in Alport syndrome using multiplex ligation-dependent probe amplification (MLPA – MRC Holland), in combination with Next Generation Sequencing using the Illumina TruSight One and NextSeq platform. Of the 20 cases completed to date, 3 patients have variants detected by MLPA, and a further 11 patients have reportable variants identified by NGS. No variants of clinical significance were identified in the remaining 6 patients.

Biography

Louisa is a medical scientist working in the Molecular Genetics Unit at SA Pathology in Adelaide, South Australia.



Poster Prize Candidate

17. Molecular testing for imprinting disorders at Monash Health

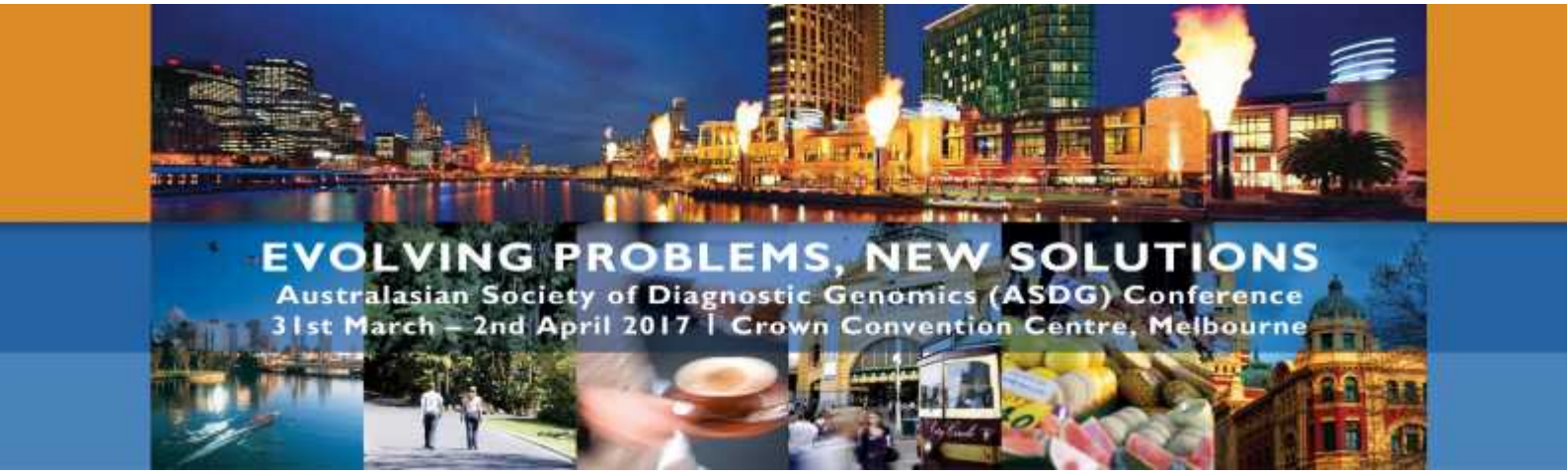
Priscillia Siswara[1], Nadine Taubenheim[1], Elizabeth M. Algar[1,2]

[1] Genetics and Molecular Pathology Laboratory, Monash Health, 246 Clayton Road, Victoria, 3168
[2] Hudson Institute of Medical Research, 27-31 Wright Street, Victoria, 3168

Disorders of genomic imprinting are rare developmental disorders in which either the maternal or paternal allele, is monoallelically expressed. Imprinting is conserved in mammals and constitutes part of a higher order system of gene regulation to control the expression of developmentally critical genes. Imprinting is maintained in locus control regions by several mechanisms including CpG methylation, histone acetylation/deacetylation and antisense transcription. The Genetics and Molecular Pathology laboratory at Monash Health provides genetic testing for human imprinting disorders including Beckwith-Wiedemann syndrome (BWS), Russell-Silver syndrome (RSS), Prader-Willi syndrome (PWS), Angelman syndrome (AS), and Albright hereditary osteodystrophy (AHO) using methylation specific MLPA (MS-MLPA®). In four years the laboratory has been referred 794 cases for 11p15.5 imprinting centre 1 and 2 (IC1 and IC2) testing, 67 cases for *SNRPN* (15q11) testing, and four cases for *GNAS* (20q13.32) investigation. Common 11p15 alterations in BWS were detected in 110 cases including 5 with *H19* hypermethylation, 77 with *KCNQ1OT1* loss of methylation (LOM), 27 with uniparental isodisomy (UPD), one with a *CDKN1C* mutation and three had copy number variations (CNVs). In RSS, 36 cases were positive for H19 LOM. Mosaicism presents a challenge in ascertaining BWS and RSS. MS-MLPA® is only able to detect to a lower limit of 20% mosaicism for UPD 11p15. SNP array testing is recommended in test negative cases with clinical features. A diagnosis was confirmed by methylation analysis in 12% of referred cases with suspected PWS or AS where the parental origin of the deleted chromosome or UPD was established. None of four cases with AHO were positive for *GNAS* abnormalities. MS-MLPA® is an efficient method for identifying imprinting defects in these disorders, however has some limitations including sensitivity towards sample quality, sample source and a comparatively high limit of detection.

Biography

Priscillia Siswara is a medical scientist at the Genetics and Molecular Pathology Laboratory, Monash health. She did her undergraduate degree at University of Washington, Seattle and holds a masters degree in laboratory medicine from Royal Melbourne Institute of Technology.



18. Seeing the whole picture – integrated view of CNVs, AOH, and sequence variants for Improved results

Alessio Venier[1], Andrea O'Hara[1], **Soheil Shams**[1]

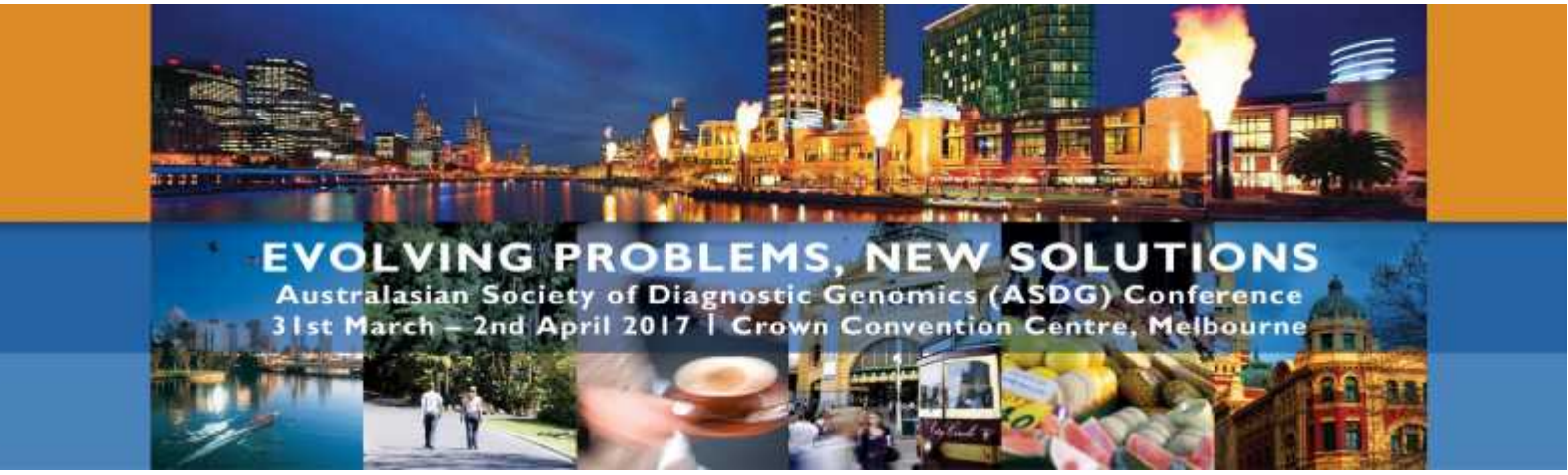
[1] BioDiscovery, Inc. 715 North Douglas Street, El Segundo, CA, 90245

Given the separate technologies used to detect CNVs, AOH, and Sequence Variants (SNP Microarrays for CNVs and AOH, and NGS for Sequence Variants), this data commonly has been reviewed in isolated silos. This segregation has also been exaggerated by the separate expertise in Cytogenomics and Molecular Genetics. However, as the fields are now coming together, the importance of an integrated view of the data has become even more apparent. Here we present a new system that can integrate data from any array as well as NGS platforms to create a single genomic view of structural changes in a sample. The data is presented in a view familiar to cytogenomicists with aberrations displayed across an ideogram with supporting evidence for each call (e.g. probes from arrays and reads from NGS). Historical data and outside database knowledge is integrated into this view allowing the analyst access to all information needed to make assessments of the results. We will demonstrate the utility of this system using a few samples with compound heterozygous aberrations that are detected using different technologies. This includes a case with a microdeletion detected by custom exon array and SNV detected with a custom targeted NGS panel. Another case includes a variant in a large region of homozygosity.

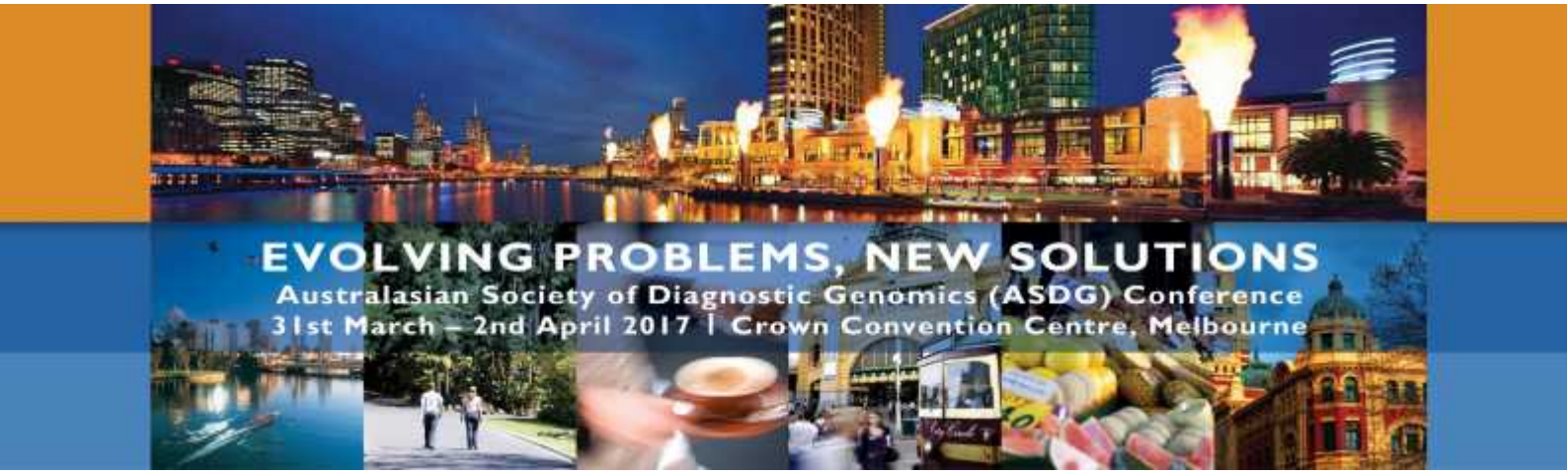
Biography

Dr. Soheil Shams is the founder and President of BioDiscovery, Inc. a privately held bioinformatics company based in El Segundo, California established in 1997. He received his Masters and Ph.D. degrees from University of Southern California in 1986 and 1992 respectively in the field of Computer Engineering. He has been a pioneer in the field of microarray image and data processing having invented many of the basic approaches to array analysis resulting in numerous issued US patents. Under the direction of Dr. Shams, BioDiscovery has played a pioneering role in development of software tools for conducting array based research and more recently in clinical application of arrays in cytogenetic and molecular genetic diagnostics as well as Next Generation

Sequencing (NGS) data analysis. Prior to founding BioDiscovery, he was a Sr. Member of Staff at Hughes Research Laboratories (HRL) in Malibu and taught undergraduate and graduate classes in Artificial Intelligence, Machine Perception, and Data Mining at UCLA. His research interests span a wide range with concentration on pattern recognition technologies and parallel processing



architectures. He has worked with many of the pioneering scientist in microarray research and has authored over 50 technical publications and book chapters.



Poster Prize Candidate

19. Diagnosing two syndromes with one test

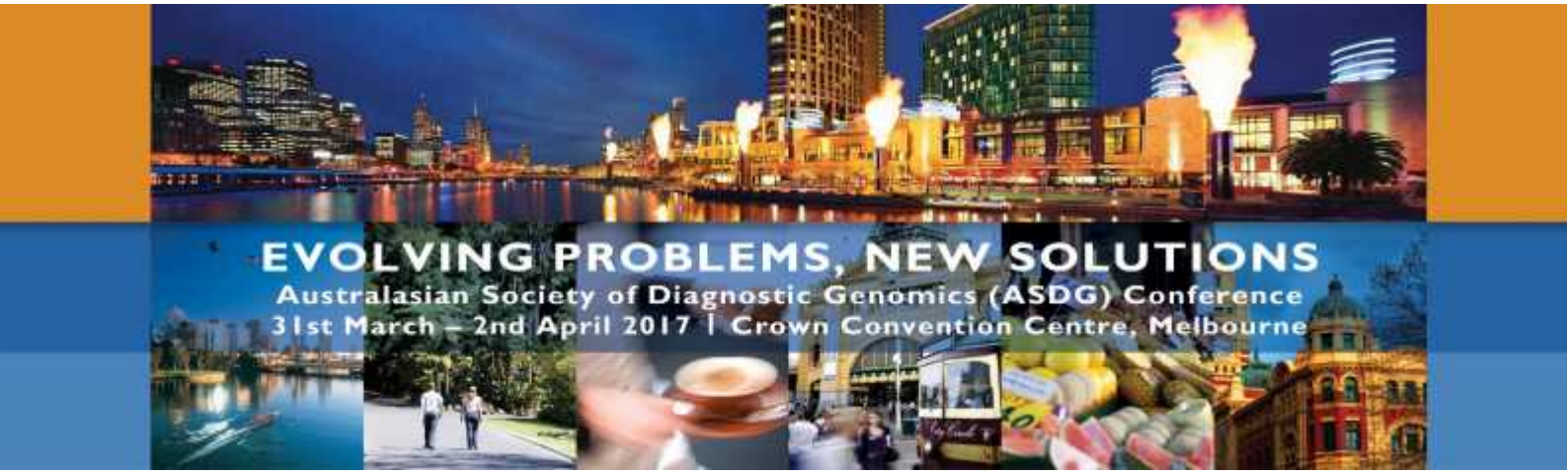
Ling Sun[1], Lucy Gugasyan[1], Matthew Hunter[2], Abhijit Kulkarni[1]

[1]Cytogenetics, Monash Health, 246 Clayton Road, Clayton, 3168, VIC
[2]Monash Genetics, Monash Health, 246 Clayton Road, Clayton, 3168, VIC

Orofaciodigital syndrome has an estimated incidence of 1 in 50,000 to 250,000 newborns, most of which are due to abnormalities in the *OFD1* gene on the X chromosome. This syndrome is inherited in an X-linked dominant pattern and is seen mostly in females. CGH microarray analysis performed on a one week old female with clinical features including *in utero* growth retardation (IUGR), cleft palate, wide set eyes, and tri-lobed tongue showed a ~0.42Mb copy number loss in Xp22.2 encompassing the *OFD1* gene. Additionally, a copy number gain of ~6.15Mb in 6q24 was also detected. This change is associated with 6q24-related transient neonatal diabetes mellitus (TNDM). TNDM is present in infancy and usually resolves within the first few months of life, although it often recurs later. IUGR is also a typical characteristic of affected individuals. Further investigation showed this patient to have hyperglycaemia and abnormal digits. We therefore present a rare case of a newborn who was diagnosed simultaneously with orofaciodigital syndrome and TNDM.

Biography

Ling Sun is a medical scientist at Monash Health, specialising in cytogenetics and molecular genetics. Previously, Ling worked as a laboratory assistant at St. Vincent's Hospital, where she discovered her interest in clinical diagnostics. She graduated with honours from the University of Melbourne with a degree of Biomedical Science.



20. Maternal Y chromosome derived copy number variant causes false positive klinefelter syndrome (XXY) sex chromosome results during noninvasive prenatal testing

Absera Tsegay[1], Nicola Flowers[1], Olivia Giouzeppos[1], Grace Shi[1], Damien Bruno[1], Mark Pertile[1,2]

[1]Victorian Clinical Genetics Services, Murdoch Childrens Research Institute, Melbourne, Australia.
[2]Department of Paediatrics, University of Melbourne, Parkville, Australia.

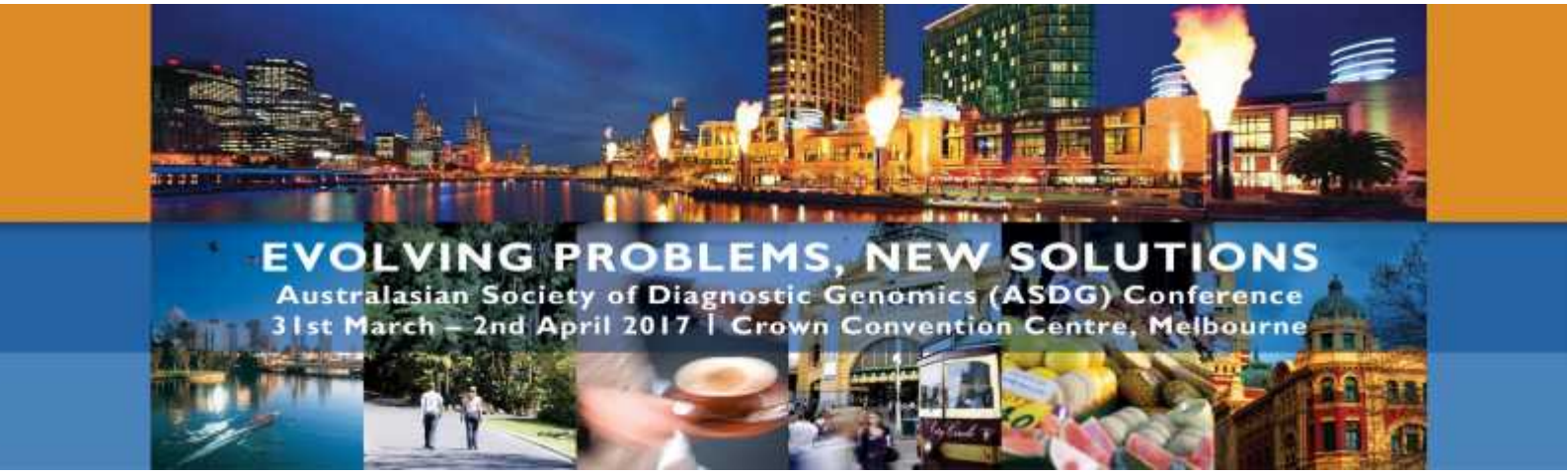
Noninvasive prenatal testing (NIPT) uses massive parallel sequencing to test cell free DNA (cfDNA) isolated from maternal plasma. The major component of the cfDNA is maternally derived, while the fetal component is derived from the placental trophoblast. The specificity of NIPT for sex chromosome aneuploidies (SCA) is reduced in comparison to trisomy 21, which results in an increased frequency of false positive findings. In particular, maternal 45,X mosaicism and 47,XXX complements have been implicated in false positive NIPT SCA results.

Here we present three cases of XXY results reported as high risk by NIPT but which were false positive findings. Diagnostic prenatal testing returned normal results in two cases, while a third case was associated with female genitalia on second trimester ultrasound scan after the patient declined prenatal diagnosis. In all three cases, chromosomal microarray (CMA) performed on maternal blood indicated the presence of a 1.5 Mb Y chromosome derived copy number variant (CNV).

These cases demonstrate a maternal biological cause for each false positive XXY NIPT result. In our patient cohort, 10/13 (77%) high risk XXY results have been confirmed in the fetus, while 3/13 (23%) were false positive results caused by a maternal Y chromosome derived CNV. Where an XXY NIPT result is not confirmed after diagnostic testing, maternal CMA testing should be considered.

Biography

My name is Absera Tsegay most people know me as Sera. I am a Medical Scientist at Victorian Clinical Genetics Services for about a year and and 6 months now and i work as part of the Noninvasive prenatal testing (NIPT) team.



21. Familial alzheimers disease exclusion testing and an incidental finding: A PGD case.

Andrea P. Twomey[1], Paisu Tang[1], Anke E. Kohfahl[1], David Amor[2], Sharyn E. Stock-Myer[1]

[1]Virtus Diagnostics, Melbourne IVF, 344 Victoria Parade, Victoria 3002
[2]Department of Paediatrics, University of Melbourne, Level 2, West Building Royal Children's Hospital, 50 Flemington Road, Victoria 3052

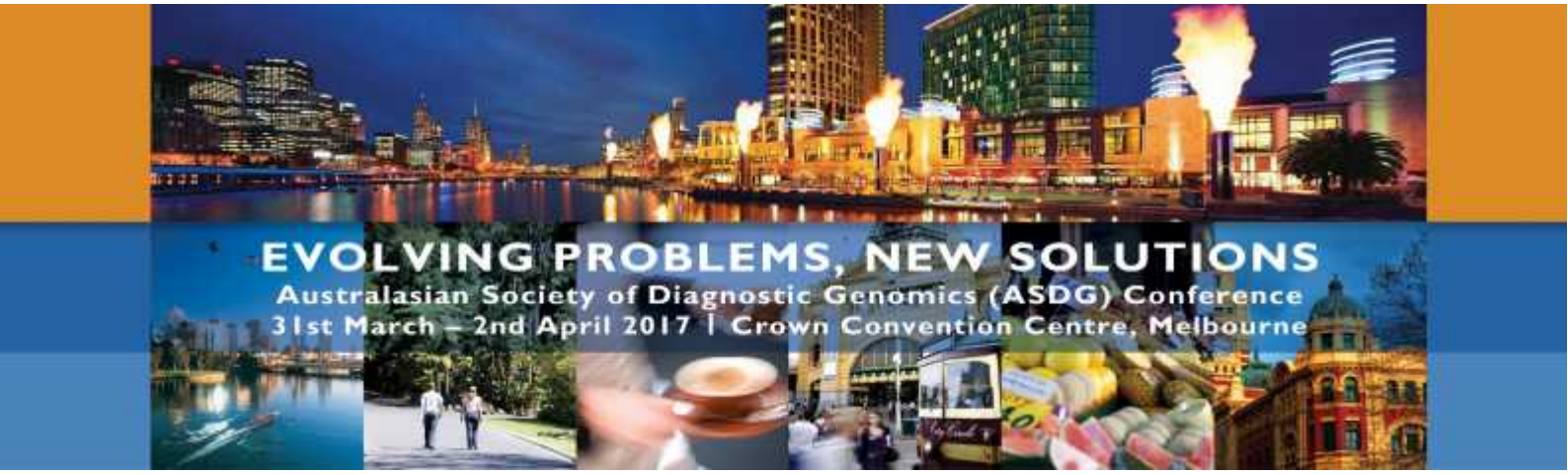
Exclusion testing allows couples to avoid having an affected child without having to undergo genetic testing themselves for the condition. Embryos which inherit the haplotype passed on from the affected grandparent are deemed to be 'at risk' and therefore not suitable for transfer. We offer exclusion preimplantation genetic diagnosis (PGD) testing using Karyomapping technology to couples at risk of inheriting late onset single gene diseases. This technique utilises approximately 300,000 SNPs spread across the genome in the form of a SNP array which is used to perform linkage analysis as well as detect chromosome imbalances.

We recently provided PGD to a couple seeking exclusion testing for Familial Alzheimers Disease caused by a known pathogenic mutation in the PSEN1 gene that had been previously detected in her affected parent. In their first IVF cycle, from 11 embryos tested none was suitable for transfer, having been diagnosed as at risk of carrying the affected allele or having aneuploidy. During analysis an incidental microdeletion at Xp22.31 was detected in several male embryos and subsequently found in the mother. On further investigation this microdeletion was determined to be a risk factor for autism and we were requested to also test for this in future cycles. In the following IVF cycle Karyomapping was used to analyse for the presence of this Xp22.31 microdeletion as well as for the initial exclusion test for Familial Alzheimers disease.

Exclusion testing using Karyomapping linkage analysis allows us to offer PGD to couples wishing to avoid having a child with a late onset disease without the need for direct mutation detection. However this technology can also reveal incidental findings which may influence future clinical decisions.

Biography

I have more than 20 years experience working as a scientist in human molecular genetic diagnosis. I helped set up molecular genetic diagnostic testing at Monash Medical Centre and have worked in preimplantation genetic diagnosis at Virtus Diagnostics (Melbourne IVF) for the past 8 years.
I am a certified member of the Human Genetics Society of Australasia (Diagnostic Genomics).



22. Two rare pathogenic copy number gains on chromosome 10

Violeta Velkoska-Ivanova[1], Ellen Casey[1]

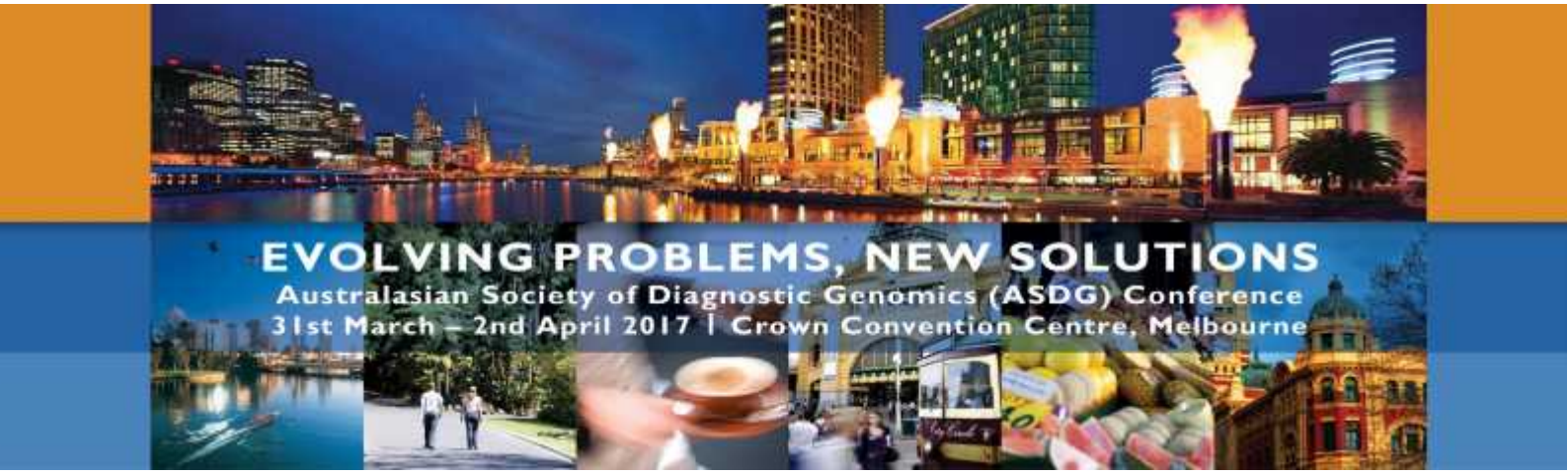
[1]Australian Clinical Laboratories, Clayton, Melbourne

Case 1:

Trisomy 10p is a relatively well-characterized chromosomal abnormality that may occur through a variety of cytogenetic mechanisms including malsegregation of familial balanced translocation, duplication or supernumerary chromosome. However, cases of true complete trisomy 10p are rarely reported and are useful to further delineate the trisomy 10p syndrome.
We present a 15 year-old patient with IQ=50, profound developmental delay and additional minor abnormalities. His molecular karyotype showed a variable gain of DNA segments mapped to the short arm of chromosome 10 in 10%-15% of this patient's genome. Additional studies were undertaken and parental molecular karyotyping followed. The proband's final karyotype is:
mos 47,XY,+mar[15]/46,XY[45].ish?r(10)(p15.1p11.1) (WCP10+,CEP10+,PTEN-).
arr 10p15.1p11.21(4,280,637-37,083,941)x2~3 *dn*
The mosaic pattern, together with the variable segmental copy number seen by microarray is consistent with a small supernumerary chromosome, most likely a ring. The mechanism of this ring formation and its interpretation with SnP microarray is discussed.

Case 2:

A three day -old term newborn with normal antenatal scan was referred for molecular karyotyping with hand and feet abnormalities, with three middle toes and second and third fingers missing bilaterally. The SnP microarray analysis has shown a male result with an approximately 0.43 megabase interstitial duplication of chromosome region 10q24.31q24.32. This duplication involves genes associated with Split Hand Split Foot Malformation 3 (SHFM3)- a contiguous gene syndrome of chromosome region 10q24 (OMIM#246560 http://www.omim.org/entry/246560 SHFM3).The rare condition and its phenotype will be discussed.



23. Severe haemophilia A caused by a duplication in the factor VIII gene covering exons 7 to 9

Jeremy N Wells[1], Kerryn M Weekes[1], Wendy M Hutchison[1], Ruoxin Li[1], Asif Alam[1], Anastasia Adrahtas[1], Elizabeth M Algar[2], Zane S Kaplan[3]

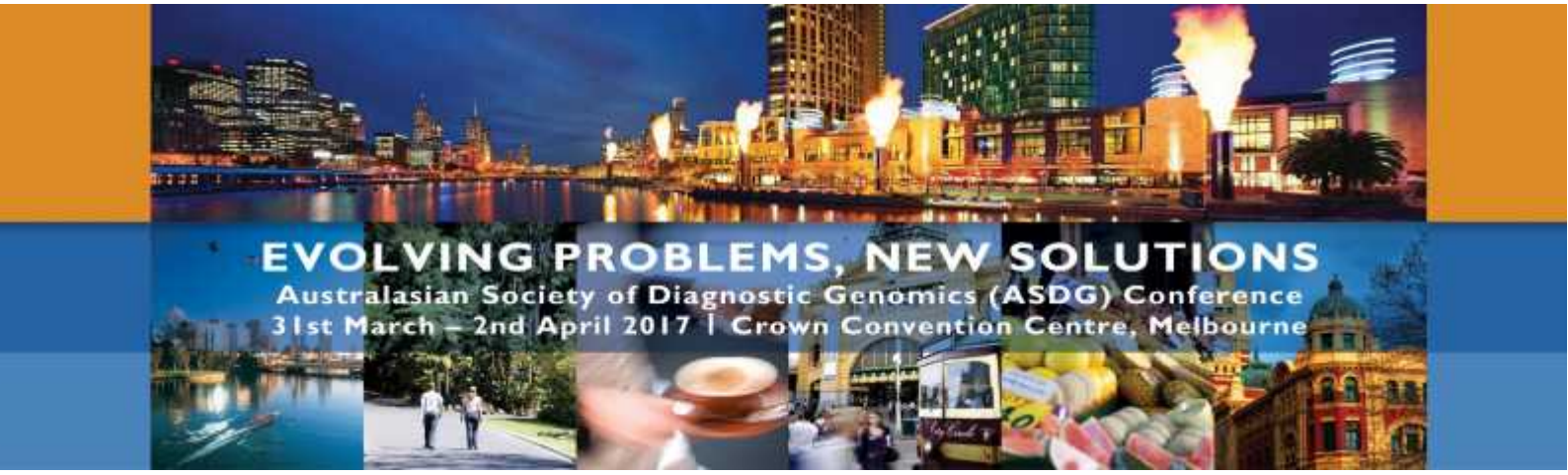
[1] Thalassaemia & Haemophilia Molecular Reference Laboratory, Level 3 Monash Medical Centre 246 Clayton Road, CLAYTON, VIC, 3168, jeremy.wells@monashhealth.org
[2] Genetics and Molecular Pathology, Level 3 Monash Medical Centre 246 Clayton Road, CLAYTON, VIC, 3168
[3] Medical Therapy Unit, Level 2 Monash Medical Centre 246 Clayton Road, CLAYTON, VIC, 3168

Haemophilia A is a recessive X-linked disorder caused by mutations of the Factor VIII gene (F8) that lead to a reduction in the amount of factor VIII protein produced. Factor VIII protein is involved in the blood coagulation pathway, with phenotypes classified according to the factor VIII activity ranging from mild (>5%), moderate (1-5%), to severe (<1%). Reported mutations in F8 include single base substitutions, small indels, and inversions affecting intron 22 and intron 1. Less frequently observed are large deletions and duplications of various lengths in the gene. With the wide-spread adoption of additional molecular techniques, such as multiplex ligation-dependent probe amplification (MLPA), novel mutations in F8 are being discovered.

An affected male in which previous investigations for severe haemophilia A had not detected any substitutions, indels, or inversions was investigated further with MLPA. An unreported duplication of exons 7, 8, and 9 in the F8 was detected. We present here the family affected by this duplication.

Biography

Jeremy has been working as a medical scientist with Monash Health since 2011 after graduating from Monash University with a Bachelor of Science (Genetics).



24. An unbalanced mosaic structural chromosome abnormality: A case study

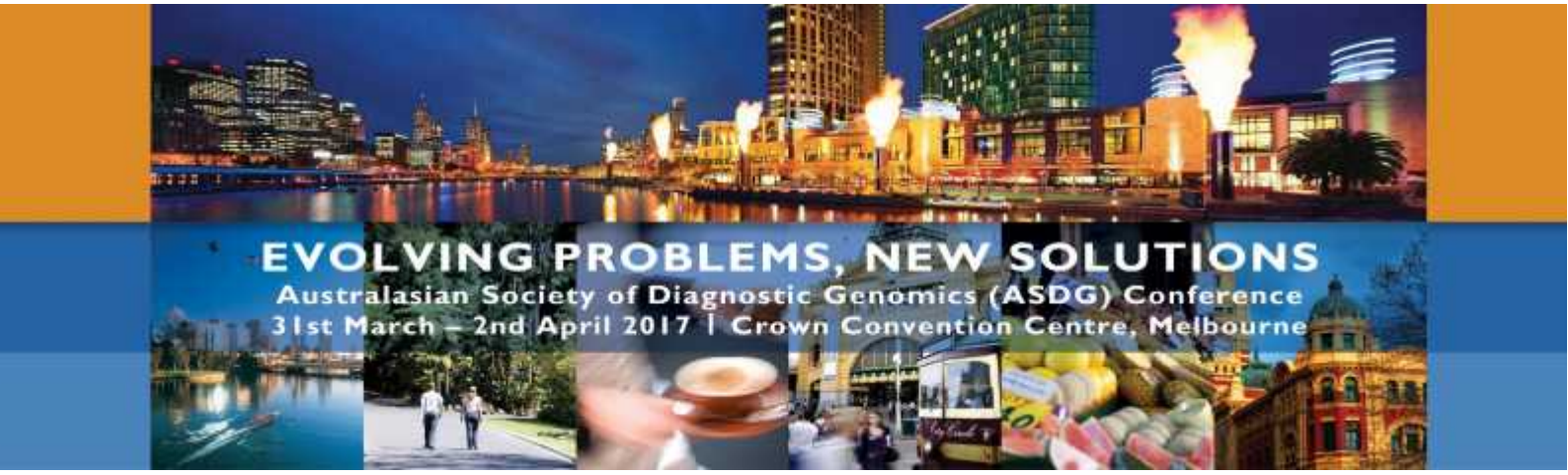
Helen Z Wilkin[1], Amanda Beament[1], Annie Falcone[1], Lucy Gugasyan[1], and Abhijit Kulkarni[1]

[1] Cytogenetics, Monash Pathology, Monash Health, Clayton, Victoria

Somatic mosaicism for an unbalanced structural chromosome anomaly is a rare phenomenon. Due to the rapid cell population turnover, cytogenetic testing of blood may not be sufficient to detect this mosaicism and may therefore require analysis of an alternate tissue such as fibroblasts. Phenotypically, a skin pigment anomaly such as hypomelanosis of Ito, can be suggestive of a mosaic unbalanced chromosome abnormality and analysis of more than one tissue type is therefore beneficial. We report the identification of a mosaic unbalanced structural chromosome 13 anomaly in the skin but not detected in the blood of a newborn.

Biography

Helen has worked in Cytogenetics in four countries – the UK (where she grew up), USA (on an exchange program), New Zealand and several labs in Australia. She has experience in both constitutional and haematological cytogenetics, but has most experience in the prenatal field. She has been an associate assessor for the ASDG QAP program for three years.



25. Immunohistochemistry as a screening tool for FISH testing in the diagnosis of double hit lymphoma

Emile Sansakda-Phillips[1], Emma-li Yit[1], Fiona Webb[1], Maya Latimer[2,3], Adrienne Morey[3,4], Dipti Talaulikar[2,3]

[1] Cytogenetics department, The Canberra Hospital, PO Box 11, Woden, ACT, 2606
[2] Haematology department, The Canberra Hospital, PO Box 11, Woden, ACT, 2606
[3] The Australian National University, Acton, ACT, 2601
[4] Anatomical Pathology department, The Canberra Hospital, PO Box 11, Woden, ACT, 2606

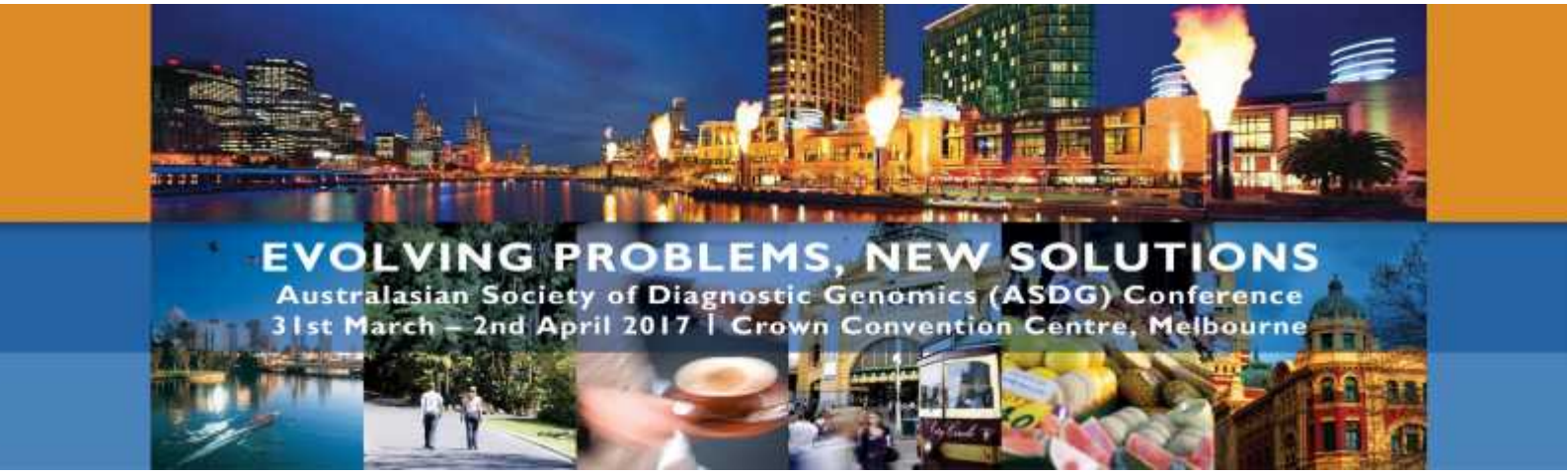
Background: Double hit lymphoma (DHL) is a subtype of diffuse large B-cell lymphoma (DLBCL) characterised by the presence of *c-MYC* and *BCL2 and/*or *MYC* and *BCL6* gene rearrangements on Fluorescence *in-situ* Hybridisation (FISH). Double expressor lymphomas (DEL) are DLBCL cases with high expression of *MYC* and *BCL2* proteins on immunohistochemistry (IHC). DHL and DEL are associated with a poor outcome with DEL being associated with a less adverse outcome.

Aims: Given the high cost of FISH testing to establish a diagnosis of DHL, and the lack of definitive guidelines for selecting cases for FISH, we conducted this study to determine whether *c-MYC* IHC could be used as a screening tool. Our second aim was to determine whether FISH analysis could be reliably performed on tissue sections.

Methods: Laboratory data on IHC and FISH tests performed on DLBCL (n=14) and Burkitt lymphoma (BL) (n=1) cases between 2015 and 2016 was extracted and analysed. A cut-off value of 40% was used to determine positivity on IHC for *c-MYC*. FISH studies were performed in-house (on fresh or Formalin Fixed Paraffin Embedded (FFPE) tissue sections) (n=13) or as sendaways (n=2).

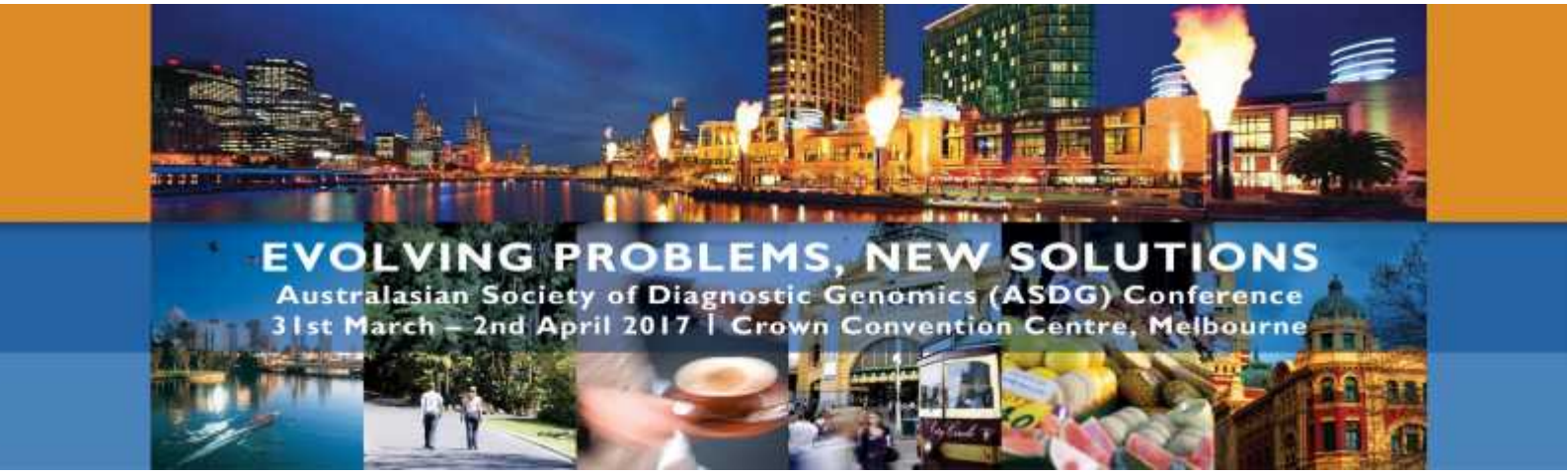
Results: 7 cases of DLBCL were diagnosed to be DEL. Of these, the average expression was 67% for *c-MYC. BCL2* expression was positive in 14 cases (quantitative data was not available). FISH for *c-MYC* was positive in 6 cases including one case of BL. FISH for *BCL2* was positive in 8 cases with 3 cases being DHL and 1 THL. All 4 cases were DEL.
Overall, 11 cases were tested using FFPE tissue with reportable results obtained for all cases.

Conclusion: In our laboratory, *c-MYC* IHC appears to be a good screening tool and FPPE is a feasible method for FISH analysis for DHL. A more substantial data set is being curated to expand the cohort.



Biography

Scientists from the cytogenetics department in ACT Pathology, The Canberra Hospital



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Barton, Ms Narelle	Sullivan Nicolaides Pathology	QLD
Batzios, Mrs Cris	Victorian Cancer Cytogenetics Service	VIC
Beddow, Mrs Rachel	Wellington Regional Genetics Laboratory	New Zealand
Belluoccio, Daniele	Agilent Technologies	
Bonaccorso, Oliver	Qiagen	
Boys, Ms Amber	Victorian Clinical Genetics Services	VIC
Brooks, Mr Ian	Victorian Clinical Genetics Services	VIC
Burns, Mr Ian	Victorian Clinical Genetics Services	VIC
Buzzacott, Ms Natasha	Pathwest Diagnostic Genomics	WA
Chan, Ms Hui Yu	Genomic Diagnostics	VIC
Chiu, Miss Eleanor	Royal Hobart Hospital	TAS
Claxton, Karen	Auckland City Hospital	New Zealand
D'Achille, Ms Pina	St Vincent's Hospital Melbourne	VIC
D'Cunha, Dr Glenn	Australian Genome Research Facility	VIC
De Fazio, Mr Paul	Monash Health	VIC
Diano, Mr Giuseppe	Royal Hobart Hospital	TAS
Dixon-McIver, Dr Amanda	Igenz	New Zealand
Drake, Dr Kylie	Canterbury Health Laboratories	New Zealand
Dun, Ms Karen	Royal Hobart Hospital	TAS
Duncan, Brad	Illumina	
Elvidge, Gareth	Illumina	
Fenn, Miss Mahony	Western Diagnostic Pathology	WA
Field, Mr Peter	Virtus Diagnostics - QFG Genetics	QLD
Flanagan, Mr Daniel	Victorian Clinical Genetics Services	VIC
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Fraser, Ms Rachel	SA Pathology	SA

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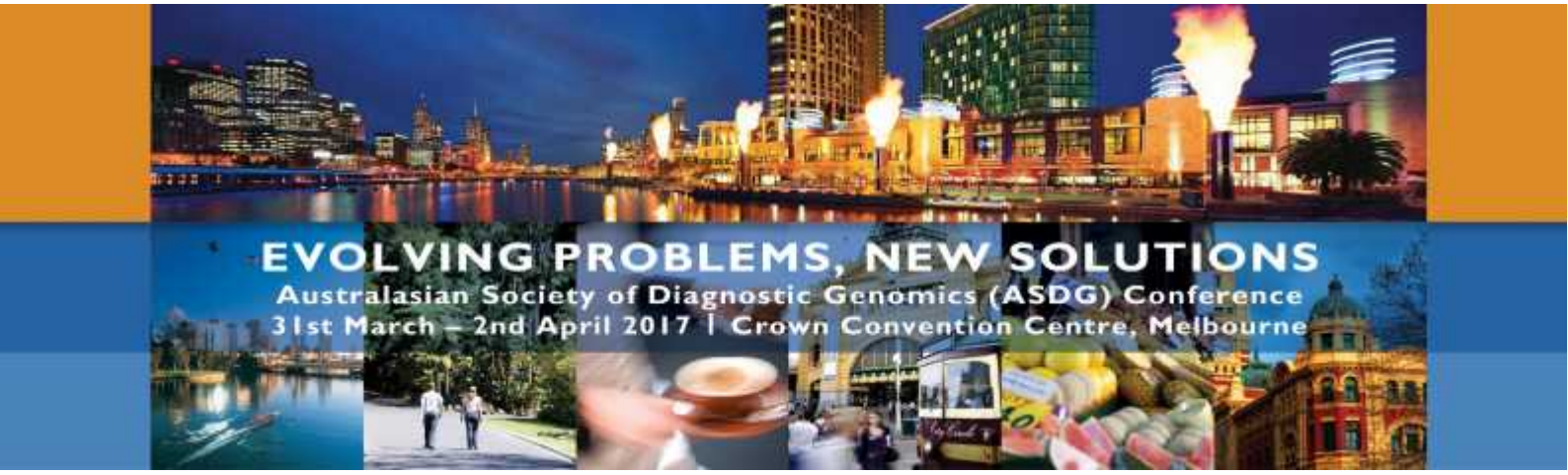

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Giouzeppos, Ms Olivia	Victorian Clinical Genetics Services	VIC
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Harrington, Mr Tom	Victorian Clinical Genetics Services	VIC
Herron, Karl	Agena	
Hills, Ms Louise	Victorian Clinical Genetics Services	VIC
Howden, Ms Amanda	Melbourne Pathology	VIC
Hughes, Dr Quintin	Western Australian Centre For Thrombosis And Haemostasis (WACTH)	WA
Hutchison, Ms Wendy	Monash Pathology	VIC
Ivory-Church, Ms Jessica	Sullivan Nicolaides Pathology	QLD
Kaur, Mrs Sharanbeer	Sydney Children's Hospital Network Westmead	NSW
Kaur, Ms Livia	Victorian Clinical Genetics Services	VIC
Korte, Mrs Louise	SA Pathology	SA
Kulkarni, Dr Abhijit	Monash Health	VIC
Kyriazis, Mr Andrew	Custom Science Pty Ltd	VIC
Lall, Mrs Paula	Victorian Clinical Genetics Services	VIC
Legaie, Roxane	Monash University	VIC
Lucas, Mr Christopher	NSW Health Pathology	NSW
Lunke, Dr Sebastian	Murdoch Children's Research Institute	VIC
MacKinnon, Dr Ruth	Victorian Cancer Cytogenetics Service, St Vincent's Hospital	VIC
Manser, Ms Rebecca	Victorian Clinical Genetics Services	VIC
Mao, Miss Jackie	Sophia Genetics	VIC
Martic, Dr Mirjana	Preimplantation Genetics- Virtus Diagnostics	VIC
McBride, Rob	Illumina	
McCarthy, Ms Catherine	Virtus Diagnostics	QLD
McDonald, Lachlan	Illumina	
McLaughlin, Mrs Vanessa	Victorian Clinical Genetics Services	VIC
Moore, Ms Sarah	SA Pathology	SA
Muller, Arne	Zeiss	
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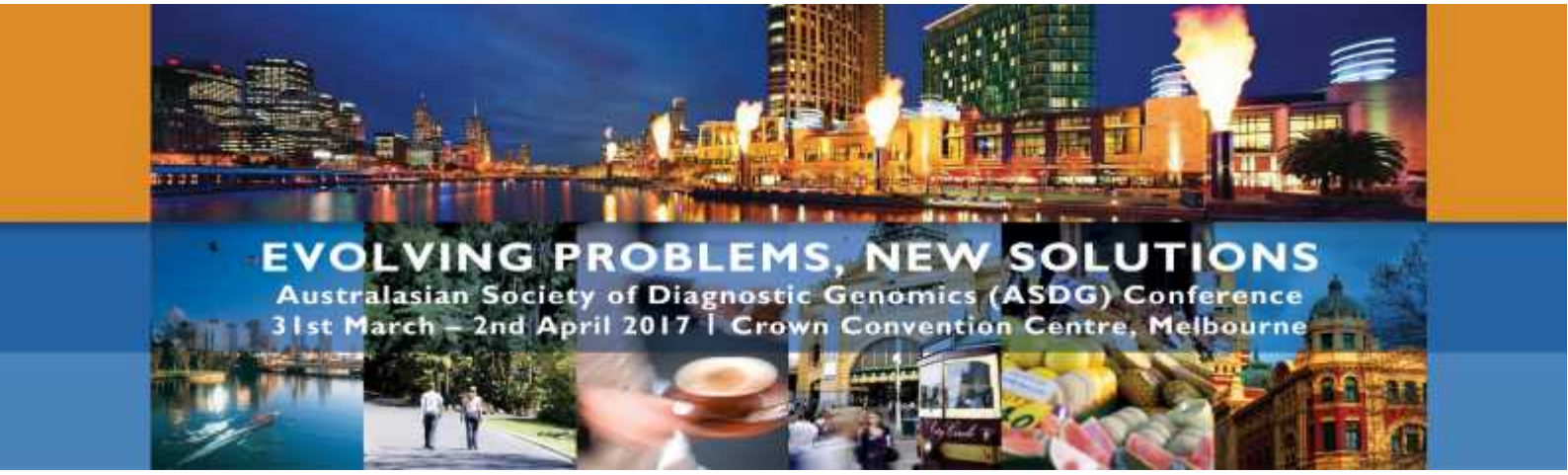

Ngo, Mr Con	Sydney Genome Diagnostic	NSW
Nguyen, Ms Oanh	Sullivan Nicolaides Pathology	QLD
Nguyen, Nam	Abbott	
Norris, Ms Fiona	Victorian Clinical Genetics Services	VIC
O'Connell, Gail	Illumina	
O'Malley, Ms Frances	St Vincent's Hospital Melbourne	VIC
Ong, Miss Jennifer	The Children's Hospital At Westmead	NSW
Payne, Mike	ThermoFisher	
Pertile, Dr Mark	Victorian Clinical Genetics Services	VIC
Peters, Dr Greg	Children's Hospital Westmead	NSW
Petrovic, Mrs Vida	Victorian Clinical Genetics Services	VIC
Phillimore, Ms Hazel	Victorian Clinical Genetics Services	VIC
Pollock, Miss Charmaine	Sullivan Nicolaides Pathology	QLD
Ricci, Maria	Qiagen	
Richter, Miss Melinda	Virtus Diagnostics - QFG Genetics	QLD
Ritchie, Miss Anna	Victorian Clinical Genetics Services	VIC
Robinson, Mrs Samantha	Children's Hospital Westmead	NSW
Robinson, Ms Samantha	Sullivan Nicolaides Pathology	QLD
Ross, Ms Janet	Waikato District Health Board	New Zealand
Runiewicz, Miss Monica	NSW Health Pathology	NSW
Sanchez, Ms Louisa	SA Pathology	SA
Sansakda-Phillips, Mr Emile	Canberra Hospital	ACT
Shams, Soheil	BioDiscovery	
Shi, Mrs Grace	Victorian Clinical Genetics Services	VIC
Siswara, Ms Priscillia	Monash Health	VIC
Squires, Sally	ThermoFisher	
Stock-Myer, Dr Sharyn	Virtus Diagnostics Melbourne IVF	VIC
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Tang, Dr Paisu	Virtus Diagnostics	VIC
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Twomey, Ms Andrea	Virtus Diagnostics	VIC
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Velkoska-Ivanova , Ms Violeta	Cytogenetics Department, Australian Clinical Laboratories	VIC

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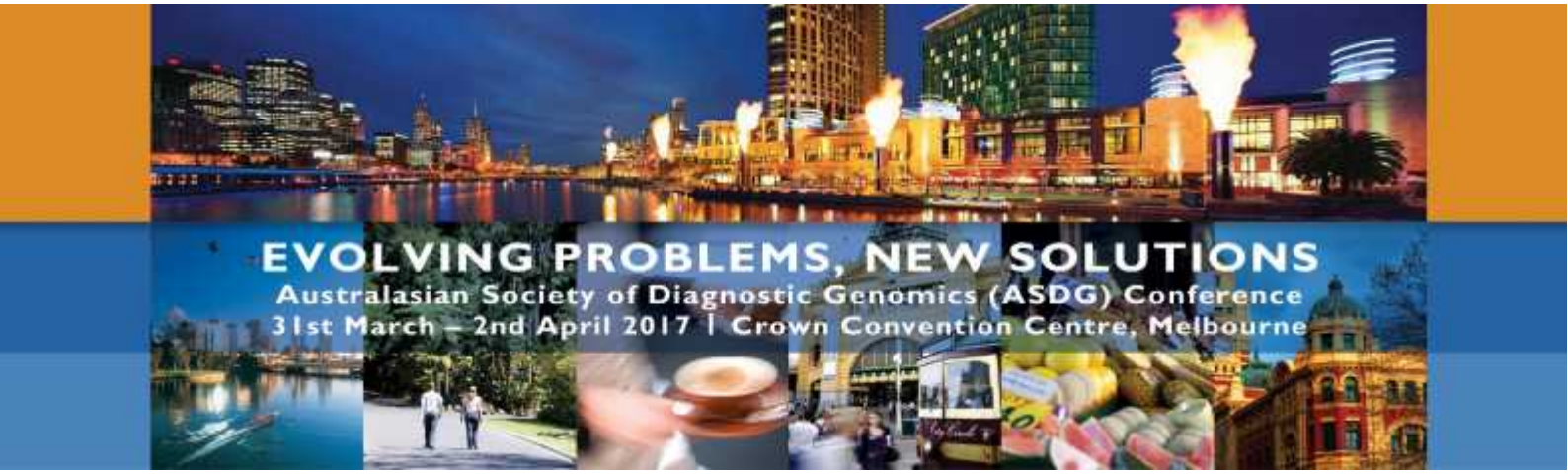

Voghoei, Ms Sue	Victorian Clinical Genetics Services	VIC
Weekes, Ms Kerryn	Monash Health	VIC
Wells, Mr Jeremy	Thalassaemia & Haemophilia Molecular Reference Laboratory	VIC
Weston, Miss Kathryn	Western Diagnostic Pathology	WA
Whelehan, Cormac	ThermoFisher	
Whiteley, Karen	Illumina	
Wilkin, Ms Helen	Monash Pathology	VIC
Williams, Miss Lorna	Victorian Clinical Genetics Services	VIC
Wright, Mr Dale	The Children's Hospital At Westmead	NSW
Yit, Ms Emma-li	Cytogenetics, ACT Pathology	ACT
Yuen, Bryan	MetaSystems	
Ziino, Ms Melinda	Australian Genome Research Facility	VIC
Zordan, Mr Adrian	St Vincent's Hospital Melbourne	VIC