KCCG NEWS ISSUE 7

Looking back on 2017, we saw major political shifts towards enabling genomic medicine and research in Australia, with the release of the NSW Health genomics strategy and Australia's first National Health Genomics Framework.

With our research, we strive to demonstrate how genomics could be responsibly used in routine medicine and to incorporate new technologies that increase the value of genomic information at the point of care.

It's been thrilling to have both witnessed and participated in the extraordinary changes in the clinical genomics landscape and I'm sure that 2018 will hold as much excitement and revelation. KCCG would like to wish you all the best in the new year.

Marcel Dinger, Head of KCCG

Our new long read sequencing capability

Dr Martin Smith, Dr Kirston Barton and James Ferguson with the KCCG's new GridION sequencer.

Garvan has added long-read sequencing to its toolbox of systems to analyse human genomes, opening up new possibilities for research and deeper insights into the genetics of health and disease.

The Garvan is one of only two worldwide to have achieved certification to provide nanopore sequencing as a service, following the KCCG's acquisition of Oxford Nanopore Technologies' GridION sequencer.

Our Genomic Technologies team, who configured and now run the sequencer, recently claimed the world record for longest sequencing read (1.015Mb) using this technology. This is also the world's first continuous DNA sequence of more than a million bases.

Nanopore sequencing can read very long DNA and RNA molecules, including epigenetic marks. This technology also allows researchers to watch DNA and RNA

being sequenced in real-time, and even interact with their experiments while they are running.

“Nanopore sequencing provides alternative yet complementary capabilities to our existing short-read technologies, allowing us to rapidly identify genetic features that can be difficult to assess with other approaches, such as large genome rearrangements or epigenetic marks,” said Dr Martin Smith, Genomic Technologies Program leader at the KCCG.

Nanopore sequencing works by driving DNA or RNA molecules through thousands of tiny tubes, called nanopores, that sit in a membrane. As the molecules move through a nanopore, each base creates a disruption in the electric current. These disruptions are analysed to determine the sequence.

“Much of the function of the human genome remains a mystery. Nanopore sequencing represents an exciting new capability in our technology arsenal to better understand the genetic origins of disease and ultimately unlock further clinical value from the genome,” said A/Prof Marcel Dinger, Head of KCCG.

Research sequencing services will be made available in 2018 through the Garvan-Weizmann Centre for Cellular Genomics. For more information, please contact nanopore@garvan.org.au.

Technology updates

The Informatics team worked hard at the end of 2017, re-launching the Sydney Genomics Collaborative web portal with new back-end technologies and front-end features which provide improved annotations and cross-dimensional interactive charts. The portal provides access to the Medical Genome Reference Bank (MGRB) which now contains 2845 genomes.

The Informatics team have also finalised requirements for a computing hardware expansion for the Garvan Weizmann Centre for Cellular Genomics (GWCCG), which will provide transformative opportunities for the GWCCG and with spare computing resources being made available to KCCG and other Garvan researchers.

Staff profile

Clare Puttick works as a research assistant in the translational genome informatics team at KCCG. Clare brings a unique background in physics, mathematics and statistics to her role, but says that it was her passion for medical research that led her to KCCG.

“I wanted to do something that adds value to people’s lives, while also utilising my skills in mathematics and programming – KCCG seemed like a great fit.”

Clare works across a broad range of projects, with her key focus being the genome as it relates to mitochondrial disease. “There are many mitochondrial genomes per cell, and any number of those could have a pathogenic variant that is the cause of a person’s disease,” Clare says. “Often diagnosis involves a muscle biopsy, which is very invasive, especially for children. I’ve been working on a way of detecting these pathogenic variants in mitochondria in the blood, which means a muscle biopsy can be avoided.”

Clare recently received an award from the Australian Genomic Technologies Association (AGTA) for her poster presentation on ROHmer, another bioinformatics tool she has developed. ROHmer can help diagnose genetic disease in patients with consanguineous parents, by focusing the analysis on regions that are more likely to contain pathogenic variants in whole genome sequencing data. Clare is also in the early stages of developing an algorithm that can identify pathogenic cancerous variants in tumour samples.

“I really enjoy applying my skills to a diverse set of real biological problems,” Clare says about her role, “and I’m given lots of freedom to follow up any ideas that I have.” Clare also considers KCCG’s focus on translation-driven research to be a key strength of the group.

“The close connections to clinicians make the research we do here even more valuable. I work with a lot of very smart, passionate people every day who are striving to find answers that will benefit real people. I find that incredibly rewarding.”

Grants and awards

The Tumour Genomics team won a silver medal at the Sydney Health Hack 2017 for their project to create an automatically annotated and machine-readable layer on top of the Australian Clinical Trials Registry (ANZCTR). Using information in the ANZCTR such as drugs, gene targets and cancer types, this tool helps match patients to clinical trials that target their specific cancer genomic profile.

A/Prof Marcel Dinger, Head of KCCG, was awarded an MTPConnect Project Grant for a project titled “Enabling Precision Cancer Clinical Trials: A molecular profiling platform for the Australian clinical trials industry”, along with consortium partners David Thomas, GIMR Genomic Cancer Medicine Program; Mark Cowley, KCCG Tumour Genomics Program; Michael Winlo, Linear Clinical Research; Illumina; NSW Early phase Clinical Trials Alliance; NHMRC Clinical Trials Centre and Genome.One.

Dr Martin Smith, Genomic Technologies Program leader, was awarded an ARC Project Grant titled “Charting the Human epitranscriptome” along with partner investigators.

Partnerships

Global Alliance for Genomics and Health

KCCG researchers are contributing to three genomic data initiatives selected as key Driver Projects by the Global Alliance for Genomics and Health (GA4GH).

GA4GH is an international alliance to accelerate the potential of genomic medicine and research to advance human health. It has struck formal collaborations with fifteen international genomic data initiatives. Other Driver Projects include Genomics England and the U.S. All of Us Research Program.

Australian Genomics Health Alliance

Australian Genomics Health Alliance is an NHMRC funded research collaboration of more than 70 organisations committed to integrating genomic medicine into healthcare in Australia.

A/Prof Marcel Dinger, Head of KCCG, co-leads their National Approach to Data Federation and Analysis research program, which is developing recommendations for guidelines and pilot infrastructure for a national data repository of clinical genomics information.

A/Prof Dinger says, “Key to our endeavours is the development of world-class genotype-phenotype databases and interfaces that link to international data sharing initiatives. We see remarkable opportunities to further refine these tools and super-charge their capabilities through closer engagement with GA4GH and with other Driver Projects.”

KCCG has also developed two data sharing tools used by Australian Genomics. Dr Warren Kaplan, Informatics Program leader, and his team built the Vectis platform, which provides the capabilities to house, query, filter and analyse genomic cohort data.

Dr Tudor Groza, Phenomics Program leader, and his team developed Patient Archive, which enables patient data management, collaborative diagnosis and knowledge exchange.

Other Australian Genomics Chief Investigators and Working Group members from the KCCG include Bronwyn Terrill and Dr Mark Cowley.

The Monarch Initiative and Matchmaker Exchange

Dr Groza is a principal investigator on the Monarch Initiative, an international collaboration that allows researchers to represent and compare phenotypes within and across species. The Phenomics team contributes data visualisation and text mining tools to this initiative.

Dr Groza contributed to the design and refinement of Matchmaker Exchange's API, which helps find diagnoses for patients with rare diseases by connecting people with similar phenotypes and genotypes.

"It is truly inspiring to see these initiatives converging and laying the foundation of the next generation of genomic healthcare, which will have a profound impact on the quality of life of patients," said Dr Groza.

Publications and conferences

Publications

Beth Signal, Dr Brian Gloss and A/Prof Marcel Dinger, along with Dr Timothy Mercer at the Garvan, published a paper titled Machine learning annotation of human branchpoints in Bioinformatics on 28 October. They developed a machine-learning algorithm to identify branchpoint elements solely from gene annotations and genomic sequence.

Dr Nenad Bartonicek, James Torpy, Dr Brian Gloss and A/Prof Marcel Dinger, along with researchers from the Garvan, had a paper published in Genome Biology on 28 December, titled Intergenic disease-associated regions are abundant in novel transcripts, which explores the transcriptional potential of genomic variants associated with disease risk in intronic and intergenic regions.

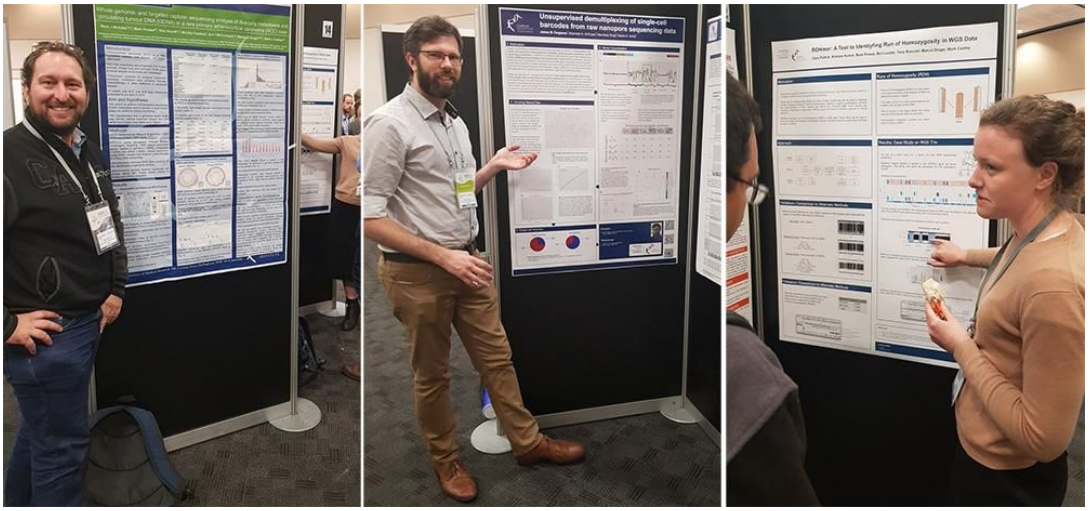
Dr Mark Cowley and Dr Velimir Gayevskiy contributed to a paper titled EPG5-Related Vici Syndrome: A Primary Defect of Autophagic Regulation with an Emerging Phenotype Overlapping with Mitochondrial Disorders, in JIMD Reports in November. The paper outlines the case of a child who received a diagnosis of Vici syndrome through whole genome sequencing.

Conferences

Australasian Genomic Technologies Association

Five KCCG researchers presented at the Australasian Genomic Technologies Association (AGTA) conference, which ran from 30 October to 1 November:

1. Dr Brian Gloss (Translational Genome Informatics): High Resolution Temporal Transcriptomics of Mouse Embryoid Body Development Reveals Complex Expression Dynamics of Coding and Noncoding Loci
2. Clare Puttick (Translational Genome Informatics): ROHmer: A tool to identify Run of Homozygosity in whole genome sequencing data
3. James Ferguson (Genomic Technologies): Unsupervised demultiplexing of single-cell barcodes from raw nanopore sequencing data
4. Dr Mark McCabe (Tumour Genomics): Whole Genome- And Targeted Capture- Sequencing Analysis Of Dual Lung Metastases And Circulating Tumour DNA (ctDNA) In A Rare Primary Adrenocortical Carcinoma (ACC) Case
5. Dr Martin Smith (Genomic Technologies): Big Data From a Small Device: Real Time Genomics with Nanopore Sequencing



Dr Mark McCabe, James Ferguson and Clare Puttick at AGTA 2017.

Clare Puttick won AGTA Best Student Poster Presentation Award for her poster, which described the development of 'ROHmer,' a bioinformatics tool developed to help find diagnoses by focusing complex genomic analysis to regions that are more likely to contain a particular type of damaging variant. She presented examples of how ROHmer has helped obtain diagnoses for patients in research projects.

James Ferguson won AGTA Late-Breaking Poster Award for his poster, which presented a new method of exploring gene expression in single cells, in a poster entitled 'Unsupervised demultiplexing of single-cell barcodes from raw Nanopore sequencing data.' The new method more than doubles the amount of informative data from these technologies, allowing the observation of entire molecules within single cells more efficiently.

Invited talks and seminars

Tanya Dwarte (Master of Genetic Counselling student supervised by Bronwyn Terrill and Marcel Dinger), delivered a Capstone presentation on her two-year research project with KCCG. Her presentation, titled "Evolving landscape of genetic counselling in the genomic era", was delivered at the Kolling Institute, in Sydney on 24 November.

Manuel Sopena-Ballesteros, Big Data Engineer in the Informatics Team, presented on KCCG's computing infrastructure at the OpenStack Summit, 6 - 8 November in Sydney.

A/Prof Marcel Dinger, Head of KCCG, talked on genomics in the clinic, transforming healthcare, and bridging research and clinical practice in a series of talks in Korea (Seoul), Sydney, the Gold Coast and New Zealand (Aukland).

Dr Mark Cowley, Tumour Genomics Program leader, gave talks on translating cancer genomics to the clinic and precision genomics in Sydney, Adelaide and Brisbane.

Dr Martin Smith, Genomic Technologies Program leader, spoke on big data and nanopore sequencing in Adelaide and the US (New York).

Tanya Dwarte presenting at the Kolling Institute.

In the media

KCCG team members were featured in online stories from Garvan and the Australian Genomic Health Alliance on 18 October about genomic data initiatives selected as key Driver Projects by the Global Alliance for Genomics and Health (GA4GH).

KCCG researchers Clare Puttick and James Ferguson were featured in a Garvan online story on 10 November congratulating five early career researchers who received awards at the annual conference of Australasian Genomic Technologies Association (AGTA), and Epigenetics 2017.

KCCG's MTPConnect award for a tumour profiling platform, was headlined in an article from the Australian Financial Review, on the projects recently funded by the 2017 MTPConnect Project scheme.

KCCG's integration of nanopore sequencing into its genomics capabilities was covered in a Garvan online story, and our certification and record breaking read were featured by Oxford Nanopore.

Events

Annual Australian Clinical Genomics Symposium

Panel (Mary-Anne Young, Prof John Christodoulou, Prof Fowzan Alkuraya, Prof Les Beiseker, Dr Cliff Meldrum, A/Prof Julie McGaughran and A/Prof Clara Gaff) and A/Prof Marcel Dinger at AACGS 2017

Garvan (KCCG) and the Australian Genomics Health Alliance organised the second Annual Australian Clinical Genomics Symposium, which was held in Melbourne on 17 to 18 November.

Attendees included more than 170 geneticists, genomicists, medical specialists, genetic counsellors, project officers, educators and ethicists.

The national steering committee, co-chaired by A/Prof Marcel Dinger and Prof John Christodoulou (Chair of Genomic Medicine, Murdoch Children's Research Institute and Co-lead of Australian Genomics Health Alliance) and including Bronwyn Terrill,

Education and Communication Program Leader, put together a wide ranging program covering current best practice and challenges, mainstreaming, screening and personalised prevention. A/Prof Marcel Dinger spoke during the proceedings about his vision for making genomic information accessible to link clinical practice with research and enable clinicians to use this information throughout an individual's lifetime to inform care and prevention.

Two world renowned clinical genomics experts brought an international perspective, Professor Fowzan Alkuraya, Saudi Human Genome Project and Head of the Development Genetics Unit at the King Fasial Specialist Hospital and Research Centre, and Professor Leslie Beiseker, Chief of the Medical Genomics and Metabolic Branch at the National Institutes of Health. Experts from Australia came from a wide range of disciplines, highlighting the impressive progress made in clinical genomics over the past year.

You can watch interviews with AACGS speakers about the conference and the future of clinical genomics on Garvan's YouTube channel.

The event was financially supported by Genome.One and Murdoch Children's Research Institute. Illumina Inc. supported the international speakers and the Australian Digital Health Agency also provided support for the food and beverage at the event.

Sydney Genomics Collaborative Scientific Symposium

Dr Warren Kaplan and Dr Mark Cowley presenting at SCGSS 2017

KCCG hosted the third Sydney Genomics Collaborative Scientific Symposium on 27 November 2017.

The symposium updated more than 70 clinical and research attendees on the Collaborative programs and grants. Nine of the Collaborative grant holders updated attendees on research into the genomic basis, diagnosis and treatment of diseases such as schizophrenia, congenital heart disease, blinding eye diseases, cardiomyopathies, melanoma, skeletal disorders, epilepsy and Mendelian disorders. The Symposium also featured an international speaker, Dr Adam Ameur who spoke about SweGen, a Swedish population study with some similarities to the MGRB.

A number of KCCG staff presented at the symposium:

- A/Prof Marcel Dinger, "Overview of the Sydney Genomics Collaborative and Program Impact"

- Dr Warren Kaplan, “Variant Atlas cohort analytics platform”
- Dr Mark Cowley, “Genome analytics in the Molecular Screening and Therapeutics Trial (MoST)”

The event finished with a discussion about NSW research, futures and funding models between attendees and Chief Medical Officer, Dr Kerry Chant.

Showcase

KCCG hosted their sixth capabilities showcase on 9 November, showcasing KCCG’s diverse capabilities in processing huge genomic data sets, computer-assisted interpretation of clinical records and engagement with patients and clinicians.

Presentations included KCCG Head A/Prof Marcel Dinger on the challenges of genomic diagnosis, Phenomics Team Leader Dr Tudor Groza on data sharing in rare disorders, and KCCG PhD student and Genome.One genomicist Dr Lisa Ewans on diagnosing rare, genetic disease.

We will run three more showcases in 2018. If you are interested in attending any of our showcases please contact us.

Welcoming new team members

KCCG has recruited Amanda Chau as an Education Project Officer in the Education and Communication Program and Carla Aguilar, a visiting masters student in the Tumour Genomics Program.

If you would like to receive our quarterly newsletter, please sign up here. You can also connect with us on Twitter and LinkedIn.