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QUT ihbi
Institute of Health and Biomedical Innovation

IHBI ADVANCES

IN THIS ISSUE

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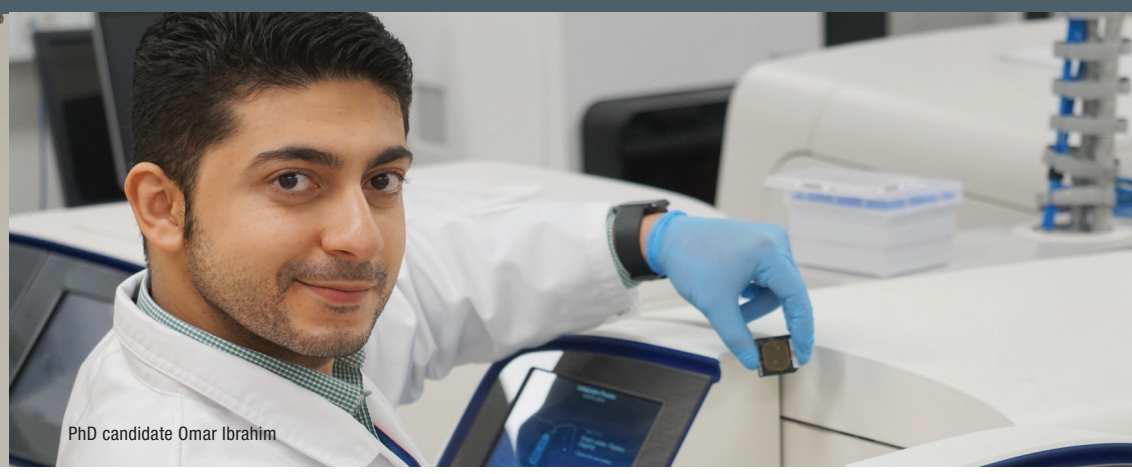
Dr Heidi Sutherland


PhD candidate Omar Ibrahim

People with concussion central to genomic research collaboration

Headache or migraine following a traumatic brain injury (TBI) is common and can cause significant healthcare burden and drastically affect quality of life. There are few reliable indicators to suggest who will have specific or long-term effects from TBI.

IHBI Executive Director Professor Lyn Griffiths is leading world-first research, aiming to identify genetic vulnerabilities that play a role in the way people react to concussion and whether they subsequently develop post-traumatic migraine.

Her team at IHBI's Genomics Research Centre is recruiting more than 100 people and their family members who have also experienced concussion. The research involves collaboration with neurologists from around Australia and New Zealand, and sporting organisations such as the Australian Institute of Sport and the AFL.

Using funding from the US Department of Defense, the research team will conduct in-house sequencing of each participant's DNA to identify mutations that result in people having a higher susceptibility to ongoing post-traumatic symptoms, including migraine.

Professor Griffiths says the research will identify biomarkers for diagnosing people and may also guide future therapeutic development.

'We aim to identify the genes that play a role in concussion development and response, investigating individual responses to treatment and developing precision medicine approaches for managing people with post-traumatic migraine,' she says.

'We will also collect data to analyse genetic, lifestyle, treatment response and psychological risk factors so that we can build a complete picture of post-concussion outcome.'

Research has already shown that mutations in one particular gene can cause a severe type of migraine that runs in families.

'For people with a specific mutation in this gene, even a minor head bump can lead to very severe post-concussion symptoms.

'This is an ion channel gene, controlling calcium release in neuronal cells. More recently we have identified another ion channel gene that also appears to play a role in concussion response.'

Professor Griffiths' research will focus on genetic mutations accounting for abnormal functioning of ion channels, key components in a wide variety of biological processes that involve rapid changes in cells following concussion and are particularly important in neurological functioning.

'Ion channels are clearly involved in the earliest stages of cellular response following a TBI and may represent a key player in symptom severity at the cellular and metabolic level,' she says.

After a TBI there is a cascade of events that can cause reduced blood flow to the affected areas, exacerbating attempts to recover and resolve energy starvation.

TBI can also cause inflammation, which may contribute to the severity of symptoms.

The cascade can impact the health of neurons in the central nervous system. Energy depletion of neurons can last for around two weeks, correlating with the average length of time of recovery for mild TBI.

Neurons use ion channel receptors to convert chemical or mechanical messages into electrical signals.

Several studies have shown an important role relating to changes of various ions and neurotransmitters in the cascade of events after TBI. Many have an overlap with the neurotransmitters and ions known to be impacted in migraine, in people who have not experienced TBI.

'Therefore, it is reasonable to propose that similar genetic mechanisms may predispose some people to the same processes that perpetuate post-traumatic headache,' Professor Griffiths says.

TBI symptoms can vary significantly and can include migraine and persistent headache, cognitive deficit, confusion, slowed reaction times, personality changes, drowsiness and emotional changes. Symptoms of moderate or severe TBI may also include seizures, vomiting, nausea, weakness and increased confusion.

While most people have acute and relatively short-lived effects, some have symptoms persisting for years that result in a diagnosis of post-concussion syndrome.

WHAT WILL THE RESEARCH INVOLVE?

- **Recruiting more than 100 people**
- **Using whole exome sequencing on DNA samples to identify genes or genetic pathways that carry mutations common to people with post-traumatic headache**
- **Determining if detected mutations can be segregated into specific post-traumatic headache subtypes, such as tension-type headache, migraine or chronic migraine.**

WITH SO MANY GENES, WHERE DO YOU START? AND WHY?

Ion channel genes. Because of connections already identified between post-traumatic migraine and ion channel genes in people with Familial Hemiplegic Migraine type 1 and episodic ataxia type 2. Mutations in a specific gene cause both disorders.

WHAT ARE ION CHANNELS?

Key components in a wide variety of biological processes that involve rapid changes in cells, such as cardiac, skeletal and smooth muscle contraction, transport of nutrients and ions, T-cell immune activation and insulin release.

WHAT IS THE GENOMICS RESEARCH CENTRE?

Read more at research.qut.edu.au/grc

Personalised approach to limit adverse reactions to medicines

Adverse reactions to medications are a major cause of disease and death globally. Genomics shows promise in personalising dosing and prescriptions, limiting side effects and maximising therapeutic efficacy.

Sequencing manager Lisa Anderson

Genomics is the basis of research that Associate Professor Paul Leo conducts in IHBI laboratories at the Translational Research Institute, adjacent to the Princess Alexandra Hospital (PAH).

Using next-generation sequencing, Associate Professor Leo and his team at the Australian Translational Genomics Centre (ATGC) are analysing genomes to diagnose cancer as well as rare and heritable diseases. The genomic diagnostic service is offered to more than 2000 Queenslanders each year.

Building on this, the ATGC is collaborating with genomics company Illumina and genomics software company Biocomputing Platforms to launch a pharmacogenomics service, initially for PAH patients.

It involves screening for pharmacogenetic variants in a person's DNA, known to play a major role in increasing the risk of adverse drug reactions (ADRs) and in the varying individual response to many medications.

ADRs are responsible for about five per cent of hospital admissions and occur during six to 15 per cent of hospital stays.

In about 30 per cent of adverse reactions, pharmacogenomic variants affect the efficacy of medicines, suggesting that 30 per cent of ADR-related admissions may be predictable—and thus preventable—using pharmacogenomics.

Associate Professor Leo says the ATGC's genomics approaches will enable pharmacogenetic profiling for individual patients, optimising doses for therapeutics and preventing ineffective medication being prescribed. 'That will be of particular relevance in organ transplantation, antibiotic therapy and where patients are prescribed more than one medication,' he says.

'The pharmacogenomics service will enable implementation of pre-emptive genetic testing at low cost. The information will be available to inform clinicians of the risk of ADRs and the correct dose to use for many common medications, with the test result and its interpretation available prior to the medicine being prescribed.'

Better personalisation of medication dosages for patients will mean they have fewer side effects while still gaining the full benefit of the medication, Associate Professor Leo says.

'Conversely, placing patients on a higher dose, when appropriate and safe, means that they will benefit from a medication that may otherwise be ineffective—while also incurring a cost for no benefit.'

Personalisation resulting from the ATGC's pharmacogenomics service will also provide significant time and cost savings to the health system. ADRs are estimated to cost Australian hospitals $1.2 billion annually. With the suggestion that about 30 per cent of admissions are predictable and preventable, savings of $360 million per year are possible.

Ahead of implementation, the ATGC will need to pass stringent accreditation tests for pharmacogenomics. The National Association of Testing Authorities (NATA) assesses laboratories for performance of tests and analysis against International Standards Organisation requirements.

'The ATGC are NATA accredited for the cancer genomics service and having a NATA-accredited pharmacogenomics facility would also enable other non-pharmacogenomics services using similar technologies to be offered, such as genetic risk testing for common heritable diseases including diabetes, arthritis, cardiovascular and mental health diseases,' Associate Professor Leo says.

'In those instances, early intervention improves prognosis and genomic risk testing has now been shown to have strong diagnostic performance.'

A GENOME

The genetic material of an organism, consisting of DNA.

GENOMICS

A field of biology focusing on the structure, function, evolution, mapping and editing of genomes.

PERSONALISED MEDICINE

Personalised medicine recognises that no two patients are alike and makes the best therapeutic choice for each person. It uses a person's genetic profile to predict whether that person will benefit from a particular medicine or have serious side effects.

THE AUSTRALIAN TRANSLATIONAL GENOMICS CENTRE

The ATGC's genomic diagnostic service is offered to more than 2000 Queenslanders, representing one of the largest programs of its kind in Australasia. The ATGC's screening identifies cancer-causing genetic mutations, leading to improved treatment outcomes, potentially fewer side effects and better survival rates for patients.

The website research.qut.edu.au/translationalgenomicsgroup/atgc


Dr Divya Mehta

Uncovering epigenetic changes linked to trauma and resilience

Stress-related disorders are the single largest contributor to years lived in ill health and reduce the total years of healthy life for Australians. Why some people develop psychiatric disorders after experiencing a traumatic situation and others do not is a key question for IHBI researchers.

IHBI molecular geneticist and biostatistician Dr Divya Mehta is working with trauma researcher Professor Jane Shakespeare-Finch to identify genes and environmental factors known to impact a person's response to stress and trauma—either positively or negatively.

Dr Mehta says epigenetics, the study of how the environment influences a person's genome, has the potential to provide insights in biological processes underpinning trauma responses.

'An often-studied epigenetic mechanism is DNA methylation,' she says. 'It is a process which changes the gene expression and the function of a gene associated with a particular response without changing the DNA's underlying sequence.

'In other words, DNA methylation switches on or off a segment of a gene in response to environmental challenges and changes.'

DNA methylation within specific genes has been associated with psychosocial stress, trauma and post-traumatic stress disorder (PTSD).

Dr Mehta's research is aiding identification of distinct DNA methylation changes in people with PTSD that accurately reflect specific environmental factors—such as whether they have experienced childhood abuse.

Her research is also providing evidence that epigenetics is dynamic and improvements in environmental factors can positively impact a person's response to stress and trauma. Physical exercise in veterans with PTSD proved beneficial, with altered DNA methylation of a specific gene known to be central to cognition and brain plasticity—assisting development, learning and memory.

Dr Mehta says there are subgroups in the Australian population more likely to experience potentially traumatic events as part of their occupation such as emergency service workers, police officers and military personnel.

Exposure to trauma has cascading negative consequences on health, underlining the importance of research that aims to understand post-trauma responses and facilitate prevention and treatment of mental health problems in the high-risk groups.

About 45 per cent of Australians experience a stress-related disorder during their lifetime. 'Stress-related disorders are severely debilitating disorders and pose a huge physical and emotional burden,' Dr Mehta says. 'There is an urgent need to precisely diagnose and treat the disorders.

`New knowledge flowing from our research will enable risk prediction, better diagnosis, timely intervention and personalised treatment, with positive implications for health and wellbeing.'

While previous global research has focused on PTSD, few studies have examined epigenetic or gene expression changes associated with positive responses such as resilience—and none with post-traumatic growth (PTG).

'Resilience is the most common positive response and occurs when a person is able to bounce back after a traumatic event with adaptive coping strategies.'

Dr Mehta and Professor Shakespeare-Finch have conducted a world-first study of the epigenetics of PTG and resilience, finding that two stress genes—NR3C1 and FKBP5—are involved in post-trauma responses.

Continuing research involves paramedic students and aims to dissect cause from effect. The research will investigate DNA to determine whether the students have pre-existing DNA methylation markers or whether trauma induces specific DNA methylation changes that make them vulnerable or resilient.

It points the way for further research into how people can overcome the negative impacts of trauma after events such as COVID-19, bushfires, serious traffic accidents, domestic violence, childhood and work-related trauma.

'The good news about epigenetic processes such as DNA methylation is that they are dynamic and modifiable,' Dr Mehta says. 'Therefore, we can be the drivers of our own health outcomes to some extent, explaining why our DNA is not our destiny.'

DNA METHYLATION

A process which changes the gene expression and consequently the function of a gene associated with a particular response without changing the DNA's underlying sequence.

POST-TRAUMATIC STRESS DISORDER

A condition with triggers that can bring back memories of a trauma, accompanied by intense emotional and physical reactions.

POST-TRAUMATIC GROWTH

Positive psychological change experienced as a result of adversity and other challenges in order to rise to a higher level of functioning.


Professor Gene Tyson

Technology and collaboration aid bowel disease studies

Present treatments are unable to provide long-term remission for people with inflammatory bowel disease (IBD), allowing development of related diseases such as colorectal cancer and impacting quality of life. IHBI research uses genomics to improve IBD understanding and provide new treatment options.

Professor Gene Tyson is taking a multi-faceted approach to IBD research, with the aim of better understanding gut health, viruses and immunity—and ultimately developing a new class of medicines.

The work involves biology, genomics, microscopy, robotics, high-performance computing—and collaboration with industry and clinicians to ensure research findings align with manufacturing, regulatory processes and healthcare practices.

Professor Tyson has been appointed QUT Professor of Microbial Genomics and Director of the new Centre for Microbiome Research. He works with a multidisciplinary team in IHBI laboratories at the Translational Research Institute, adjoining the Princess Alexandra Hospital in Brisbane.

Professor Tyson says a healthy gut microbiome is vital not only in preventing IBD, but in supporting the body's immune response. 'The public awareness of the importance of the microbiome is increasing, and our aim is to understand the role that different microorganisms play in health and disease states,' he says.

A particular focus of his team's research is the spatial organisation of microorganisms in the mucosal epithelium, the outer layer of the gut lining that acts as a physical barrier. 'Bacteria that can penetrate and reside in this mucosal layer are uniquely positioned to influence host immune and metabolic functions,' Professor Tyson says. 'Disturbance in the mucosal barrier is a common characteristic of IBD.'

IBD research typically focuses on bacteria, but Professor Tyson is interested in overlooked components of intestinal microbial communities including drivers of disease such as fungi, viruses and DNA molecules called plasmids.

'Little of the prior research has captured the structural organisation of the intestinal microbiome, which provides important information on host-microbe interactions,' he says.

Microbial genomics is at the core of Professor Tyson's research, involving the study of microorganisms with their genetic material and providing insight in the diversity of microbes in a particular environment.

'The work is significant because it will help to bridge the gap between our understanding of the gut microbiome in IBD and the ability to transform the knowledge into clinical practice.

'Our team is uniquely placed for translating the knowledge. We have active engagements with qualified pharmaceutical companies who recognise that gut microbiome derived therapeutics are a revolutionary new class of medicine with highly desirable characteristics.'

In 2017, Professor Tyson co-founded Brisbane biotech company Microba with Professor Philip Hugenholtz to analyse the gut microbiome and develop new pathology services, therapeutics and diagnostics.

Researchers in Professor Tyson's team aim to develop a new class of medicines called live biotherapeutics, containing live microorganisms such as bacteria or yeast and often sharing common origins with probiotics.

Use of live biotherapeutic products in clinical application has shown great promise for reducing infection, stimulating innate immune responses and regulating metabolism in the gastrointestinal tract.

Australia has one of the highest global incidence rates of IBD, with more than 75 000 people affected. Hospital costs are estimated at $100 million per year, with an additional cost of $380 million due to productivity losses and IBD management.

Decreased quality of life is also a major consequence for people with IBD, including the disruption to routine activities and impact on education, work productivity and social functioning.

INFLAMMATORY BOWEL DISEASE

A chronic, relapsing inflammatory disorder driven by complex interactions between environmental factors, microbes and immune responses—especially in genetically susceptible people.

MAIN SUBTYPES

Ulcerative colitis is characterised by diffuse inflammation that is confined to the colon. Crohn's disease can involve any part of the gastrointestinal tract.

INCIDENCE

Australia has one of the highest rates in the world, affecting about one in 250 people aged five–40 years.

TREATMENT

Figures show at least one widely used therapy for mild to moderate IBD cases has response rates between 40–70 per cent and remission rates of 15–20 per cent.

SURGERY

More than 30 per cent of people with IBD require at least one surgical intervention in their lifetime.

Unique genetic mutations at the core of chronic disease research

Life expectancy of Aboriginal people is much lower than other Australians, in part due to an apparent genetic predisposition to chronic diseases. IHBI research aims to better understand the genetics that cause the diseases to improve early detection and prevention strategies.


Dr Shivashankar Nagaraj

From 1980 to 2010, the average age at natural adult death of Aboriginal people on the Tiwi Islands was 56.7 years, while it was 53 years for the 82 per cent of people dying of chronic disease.

More than 20 per cent of Tiwi adults have diabetes, with rates of renal replacement therapy among the highest in the world. Death rates from cardiovascular disease are more than three times those of non-Indigenous Australians.

Dr Shivashankar Nagaraj aims to address the reduced life expectancy, leading a research collaboration and using $1.6 million in funding from the Federal Government's Genomics Health Futures Mission. The collaboration involves joint leadership with Professor Wendy Hoy from the University of Queensland and partners from the Australian National University, the US and India.

THE COLLABORATIVE TEAM

- **Dr Shivashankar Nagaraj, IHBI**
- **Professor Wendy Hoy and Dr Aideen McInerney-Leo, the University of Queensland**
- **Dr Brendan McMorran, Australian National University**
- **Dr Ryan Taft, Illumina Inc, US**
- **Professor Cheryl Winkler and Dr Jeff Kopp, National Institute of Diabetes and Digestive and Kidney Diseases, US**
- **Professor Graeme Suthers, Sonic Genetics**
- **Dr Rohit Gupta, IIT-Chennai, India**

The Tiwi people initiated the research in 1987, reaching out to epidemiologist Professor John Mathews at the University of Melbourne to ask why their rates of diabetes were so high.

The research continues to involve the Tiwi people through the establishment of a steering committee, involves wide community engagement, and includes training of Indigenous students in genetics, bioinformatics and genetic counselling.

'Our primary focus is to investigate and understand genetic predisposition for developing chronic kidney disease and associated conditions such as diabetes, cardiovascular disease and high blood pressure,' Dr Nagaraj says.

'Better understanding of genetic contributions to disease can lead to earlier, accurate diagnosis and inform targeted prevention strategies and precise, personalised treatments.'

The research will build on a pilot study that used whole genome sequencing to reveal novel founder mutations in the DNA of Tiwi people. The mutations are believed to be associated with chronic disease.

A founder mutation is a genetic alteration frequently found in a population with a history of geographical or cultural isolation in which one or more of the ancestors was a carrier of the altered gene.

'We identified significant numbers of deleterious founder mutations,' Dr Nagaraj says. 'Multiple variants were present in all Tiwi samples and absent in other populations, with some variants strongly associated with chronic kidney disease. The genes represent critical therapeutic targets.'

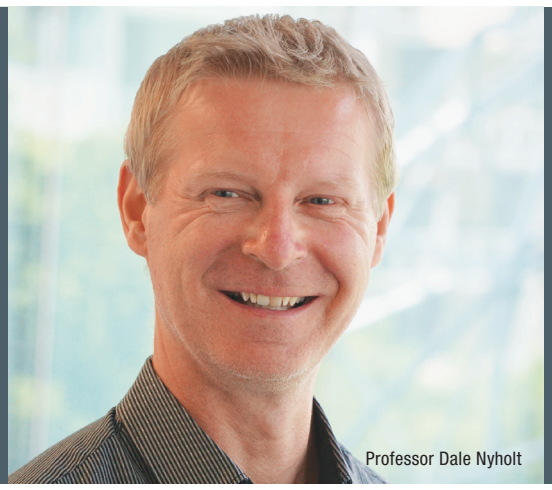
Dr Nagaraj says the new research will increase the number of people involved to nearly 500, providing DNA for whole genome sequencing to define the genetic architecture and its association to serious chronic disease.

Among the outcomes to flow from the research are the establishment of a catalogue of known genetic mutations associated with common chronic disease in Tiwi Aboriginal people. Aligned with the catalogue will be use of big data analytics and artificial intelligence to model risk predictions.

'The models can identify individual risks, stratifying each person and guiding clinicians in their preventative intervention efforts,' Dr Nagaraj says.

Pharmacogenomics analysis will be used to uncover links between genetic patterns and sensitivity to—or adverse reactions to—commonly-prescribed medication.

'Significant numbers of Tiwi adults—including our DNA donors—are receiving at least one chronic disease medicine, so scope to inform genomic-guided therapeutic dosage and prediction of benefit or adverse reactions is broad,' Dr Nagaraj says.



Professor Dale Nyholt

Evidence of shared genetics for endometriosis and migraine

Comorbidity is the existence of two or more medical conditions simultaneously, regardless of whether one causes the other. Endometriosis and migraine co-occur in people more than expected by chance, but the cause and biological mechanisms underlying their comorbidity remain unknown.

IHBI Professor Dale Nyholt and PhD candidate Emmanuel Olorunleke Adewuyi are investigating the genetic overlap between the two disorders.

They have discovered some genetically controlled biological pathways associated with both endometriosis and migraine and identified three genes—two of which have not previously been reported for either condition. The findings have been published in *Genes*.

COMORBIDITY

The occurrence of two or more diseases in a person at one time.

COMMON COMORBIDITIES

- **arthritis with cardiovascular disease**
- **arthritis with back pain**
- **cardiovascular disease with back pain**
- **back pain with mental health conditions**
- **asthma with mental health conditions**

WHY IT IS IMPORTANT TO IDENTIFY COMORBIDITIES

Understanding can provide vital information for prevention, management and treatment.

THE PUBLICATION

Shared Molecular Genetic Mechanisms Underlie Endometriosis and Migraine Comorbidity

www.mdpi.com/2073-4425/11/3/268

Confirming the shared genetics enables a combining of knowledge of the two disorders, providing insight into their underlying biology and ultimately improving healthcare by identifying undiagnosed disorders.

'Our study supports the importance of a concurrent screening for migraine in patients presenting with—or being investigated for—endometriosis,' Mr Adewuyi says. 'Clinicians should start exercising a heightened suspicion for migraine in endometriosis patients.'

Endometriosis is one of the leading gynaecological disorders, affecting six–10 per cent of women of reproductive age and 35–50 per cent of women with infertility worldwide. Endometrial tissue grows outside of the uterus and patients have varying degrees of pelvic, menstrual, abdominal, bowel and lower-back pain.

Active migraine, with symptoms in the past 12 months, has an estimated global prevalence of 14.7 per cent, making it the most disabling neurologic disorder and the third most common illness worldwide. A typical migraine is a recurrent and episodic headache of moderate to severe intensity.

Similar to endometriosis, migraine impacts women in their reproductive and most productive years.

Mr Adewuyi says the research has leveraged membership of the International Endogene Consortium and the International Headache Genetics Consortium to access data for analysis, covering more than 17 000 cases of endometriosis and more than 59 000 cases of migraine. Additional data was secured from the United Kingdom Biobank.

He says multiple statistical methods were used to analyse the large data sets, ensuring a comprehensive assessment without lifestyle or environmental factors distorting the results.

'Our findings further confirm the comorbidity of endometriosis and migraine,' he says, 'with shared genetically controlled biological mechanisms underlying the co-occurrence of the two disorders.

'Biological mechanisms related to sex hormone activities—as well as inflammatory and immune system dysfunction, among others—are implicated by the pathways.'

Mr Adewuyi says the three identified genes drive cellular processes including cell growth, metabolism, development of new cells and programmed cell death, also called apoptosis.

In turn, the cellular processes activate other mechanisms that can result in development of the endometrial tissue.

In the case of people with migraine, the cellular processes result in the release of the protein CGRP, long associated with the disorder. How CGRP causes migraine remains unclear.

Mr Adewuyi says proof of the link between CGRP and migraine provides further evidence of the protein's importance as a target for therapeutic treatment.

EXECUTIVE DIRECTOR'S REPORT

IHBI is building research capacity, with the establishment of the **Centre for Genomics and Personalised Health**. The centre's research identifies the molecular basis of disease and uses it for better diagnosis and more targeted treatments. Training the next generation of translational genomics scientists is also a major objective.

Genomics is a field of biology focused on the structure, function, evolution, mapping and editing of genomes—a person's complete set of DNA, including all genes.

Our genomics research covers diagnostics, stem cells, links with chronic disease, ageing and adverse reaction to therapeutics, bioinformatics and statistical analysis.

The centre is the second to be established at IHBI, joining the Centre for Biomedical Technologies, with its focus on improving how we treat complex medical cases stemming from injuries, infection and age-related issues.

It is part of a move to establish QUT centres representing high-quality and focused activity aligning to the university's key research strengths.

This edition of *IHBI Advances* showcases the research conducted as part of the Centre for Genomics and Personalised Health involving patients, clinicians, the community and industry.

The **Australian Translational Genomics Centre** offers a diagnostic service for cancer and heritable diseases to many Queenslanders—and is building on this to screen DNA for people at increased risk of adverse reactions to therapeutics.

Under the leadership of **Associate Professor Paul Leo**, the ATGC aims to prevent the five per cent of hospital admissions that result from adverse reactions.

Dr Shivashankar Nagaraj has research that involves up to 500 people providing DNA, building a catalogue of known genetic mutations and training of Indigenous students. He aims to understand the genetics that cause chronic diseases in our Indigenous populations.

Researchers at the **Genomics Research Centre** also aim to understand genetic vulnerabilities, with a focus on trauma-induced concussion and post-trauma symptoms and response. It involves more than 100 people and collaboration with sporting organisations and neurologists across Australia and New Zealand.

Dr Divya Mehta is working with paramedic students to identify genes and environmental factors known to impact a person's response to stress and trauma—either positively or negatively.

Professor Dale Nyholt and PhD candidate **Emmanuel Olorunleke Adewuyi** have leveraged membership of two global consortia to identify shared genetics between endometriosis and migraine—a world first that underscores QUT strength in the field and points the way for a suitable target for therapeutic treatment.

Professor Gene Tyson has collaborative research bridging biology with genomics and using microscopy, robotics and high-performance computing to better understand and treat inflammatory bowel disease.

With genomics driving scientific discovery in fields as diverse as cancer, migraine, concussion, post-traumatic stress disorder and inflammatory bowel disease, the endeavours of the Centre for Genomics and Personalised Health have across-the-board relevance and potential for major clinical impact.

Enjoy this edition of *IHBI Advances*.

Professor Lyn Griffiths
Executive Director, IHBI

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