PhD Project Opportunities

Centre of Research Excellence in Neurocognitive Disorders (CRE-NCD)

About the CRE in Neurocognitive Disorders

Neurocognitive Disorders (NCDs) are one of the largest unmet challenges in health care, due to their lifelong nature, high management costs, prevalence and frequent recurrence within families. The development of effective therapies has been hampered by the heterogeneity in the underlying genetic aetiologies, and hence biology, of NCD. A dynamic Centre of Research Excellence in Neurocognitive Disorders (CRE-NCD) has been established to transform the diagnosis and characterization of NCD through the application of genomic technologies, including whole exome sequencing (WES) and whole genome sequencing (WGS). This will be achieved through a co-ordinated network of experienced clinicians and researchers to enhance fundamental knowledge about the genetic basis of neurocognition and the investigation of targeted treatment strategies in relation to biological pathways. This program will achieve its goals through a national approach with improvements in clinical phenotyping, genomic diagnostics, common data analysis and reporting standards. The aim is that within the next 5 years, all Australians with NCDs will have access to genomic testing, achieving a diagnosis in >50%. A molecular diagnosis with an accurate genotype-phenotype classification is essential for defining an aetiology for families, improving patient management, predicting recurrence risk, and for the successful design of targeted therapeutics. The CRE-NCD team comprises researchers and clinicians with internationally recognized leadership and track records in neurogenetics research, genomics, bioinformatics, functional analysis, health economics and clinical practice.

PhD projects - $27,200 per year plus laboratory support over 3 years for relevant projects

Several PhD projects are available through the CRE-NCD for highly motivated scientists or physicians across Australia. Desirable qualifications and skills include medical graduates or first class Honours degree (or equivalent) in Biomedical Science, Neuroscience, Genetics or related field with particular skills relevant to the PhD project (molecular biology, cell biology, economics, bioinformatics, clinical phenotyping).

Applications: Please send your CV and a one page expression of interest to: c.evans@neura.edu.au

An interview process will follow for successful applicants. For specific project enquiries, please contact the project supervisors as listed below.

Applications close: Open until filled

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Centre of Research Excellence in Neurocognitive Disorders (CRE-NCD)

1. **The genomics of intellectual disability (ID) – NeuRA, University of New South Wales, Sydney, NSW**

This project will apply massively parallel sequencing, the development of bioinformatics tools and functional validation in families with ID. The workpages in the PhD will include (1) definition of the broad clinical phenotyping and molecular mechanisms in a retrospectively and prospectively selected population with neurocognitive disorders of at least 200 families (2) exploration non-coding and CNV mechanisms (3) study of non-coding mechanisms in detail through the intersection with ENCODE data in WGS studies where WES has not defined an aetiology (4) the identification of novel Mendelian disease genes with follow-up animal and functional studies. Phenotypes relating to specific mutations will be sought in iPS cells and an initial study on variable expressivity and non-penetrance will be performed in families with recurrent mutations that do not always result in neurocognitive disorders. Non-penetrance mechanisms will be sought in specific syndromes by including interrogation of divergent CNVs proximate to the known gene locus or relating to more distant functional elements.

Enquiries to: Associate Professor Tony Roscioli (tony.roscioli@health.nsw.gov.au) and Dr Carey-Anne Evans (c.evans@neura.edu.au).

2. **Delivering 3D facial analysis for precision phenotyping for diagnosis and management of NCDs – Genetic Services of Western Australia, Perth, WA**

Up to 50% of children with moderate to severe intellectual disability [ID] have associated craniofacial anomalies or dysmorphic features. Finding individuals with similar facial features currently relies on the comparison of photographs of undiagnosed children at medical meetings or via written descriptions in phenotyping databases. The 3dMD photography system is now available in three states and provides an opportunity to compare and contrast 3D photography within and between ID biological pathways. This project will investigate the utility photography in the diagnosis and sub-phenotyping of individuals with ID. Research projects will include (i) enhancing the accuracy and extent of HPO term extraction in comparison to 3D facial data (ii) creating the means to integrate 3D and 2D photography with text and genomic data, and associated knowledge management platforms databases; (iii) refinement of existing 3D facial data analysis modules and data visualisations; and; (iv) to investigate the health economic potential of pre-screening with 2D/3D photography to determine diagnostic utility.

Enquiries to: Associate Professor Gareth Baynam (Gareth.Baynam@health.wa.gov.au)

3. **The application of functional genomics for disease gene discovery in children with orphan phenotypes – Murdoch Children's Research Institute, Melbourne, VIC**

Despite recent successes in the application of next generation sequencing technologies as a means of shortening the diagnostic odyssey for children with suspected monogenic disorders, there remain many children, particularly those who have an apparently unique phenotype, who remain unsolved. This PhD project will focus on children with novel/unique phenotypes in which intellectual disability/developmental delay is a prominent feature, harnessing genomic technologies to identify novel candidate genes. We will then call on the functional genomic resources available through the CRE and beyond to confirm their functional relevance. During the course of this PhD candidature we anticipate identifying at least three novel ID genes and functionally characterizing them.

Enquiries to: Professor John Christodoulou (john.christodoulou@mcri.edu.au)

4. **The application of genomic testing in adults with intellectual disability - Murdoch Children's Research Institute, Melbourne, VIC**

We hope to recruit a high quality medical graduate/trainee to undertake a clinical and genomic study of adults with intellectual disability. The proposal is to recruit two cohorts of adults with ID, one being adults with ID referred to adult genetics clinics and the other being adults with intellectual disability who have not been referred to genetics, who will be recruited from other clinics that cater to the needs to adults with intellectual disability. All adult patients will undergo clinical assessment and traditional investigations (e.g. microarray, FXS) and will be offered genomic testing via exome sequencing. We will collect and assess data regarding diagnostic yields of clinical assessment, microarray and exome sequencing. We will also study the interest of families in exome sequencing, the acceptability of testing and the clinical utility of genetic testing results. In addition, we will also offer families/guardians the opportunity to receive secondary findings from exome sequencing, and assess interest and uptake of these analyses. A health economic analysis will also be performed comparing ID in older populations to those with paediatric onset.

Enquiries to: Professor David Amor (david.amor@mcri.edu.au)

5. **The cost effectiveness of triaging access to WGS and WES: Australia and the UK – Macquarie University, Sydney, NSW**

Currently there is a backlog of patients with ID seeking a molecular diagnosis. However, there is a limited workforce to provide genomic diagnostics and related services such as genetic counselling. Even public subsidies of the full price of WGS would not immediately overcome all barriers to access to the technology due to training and workforce issues. Early genomic diagnosis is however critical due to the degenerative nature of some disorders, the potential for effective treatment in a small proportion of cases during a critical window of development and the importance to families of understanding the likelihood of recurrence and reproductive planning. The capacity to triage patients most likely to have a condition that has a genetic cause could play an important role in maximising the cost effectiveness of genomic testing. This PhD research program will focus on the benefits to the individual and society of genomic diagnostics and the most cost-effective mechanisms for their delivery. Comparisons will be made between panels, WES and WGS. Links to other PhD projects will be encouraged including those investigating 2D and 3D photography which could identify those patients with ID most likely to benefit from early access to genomic sequencing, with a potential concomitant increase in the diagnostic rate and cost effectiveness of the use of WES/WGS.

Enquiries to: Professor Deborah Schofield (deborah.schofield@mq.edu.au); philippa.smith@mq.edu.au

6. **Functional characterisation of NCD genes and therapies using Cell models – University of the Sunshine Coast, QLD**

Drug discovery is beginning to provide pathway specific therapies for individuals with NCD. At least 8% of current diagnostic targets have effective pathway specific treatments in the Deciphering Developmental Disorders (DDD UK) study. This number is likely to increase given the steep rise in the number of interventional trials in NCD (clinicaltrials.gov). Ensuring the presence of accurately diagnosed NCD patient cohorts available for trial inclusion represents a clear translational opportunity. Within the CRE group we have experience in collaborating and/or in co-ordinating a number of large multicentre trials in disorders associated with NCD, where the outcome measure is improvements in psychosocial and cognitive domains. This PhD project will allow patients with a common genetic diagnosis or a common biological aetiology to be identified and will be a great enabler for the access of Australian patients into clinical trials. Professor Robert Harvey will design overall strategies to allow for pharmacological testing in molecular and cellular models with a view to future clinical testing with pharmacological endpoints, as well as selecting the most interesting compounds relevant to canonical NCD pathways. The CRE-NCD will translate this to other gene families in NCD and will share findings with the broader CRE-NCD consortium.

Enquiries to: Professor Robert Harvey (r.j.harvey@usc.edu.au)

7. **Gene and variant discovery in large, mapped, unresolved families with X-linked neurocognitive disorders – The University of Adelaide, SA**

X-chromosome linked intellectual disabilities, XLID affect approximately 1.7 per 1,000 males and are caused by mutations in genes on the X-chromosome. XLID disorders are genetically heterogeneous with coding and non-coding variant aetiology. In excess of 131 XLID genes have been identified however, about 1 in 3 of the published syndromic and non-syndromic XLID families are without a known cause. Distinct clinical features and linkage data suggest different genetic causes in these families. This constitutes a major gap in our understanding of neurocognitive disorders and not just on the X-chromosome. These remaining unsolved, large XLID families form a unique and valuable resource for identifying causative genetic events, which likely involve regions outside the exome including conserved regulatory regions of coding genes, non-coding genes, and other functional genomic elements. These novel variants and genes can be efficiently detected as the responsible loci are mapped within a specific, small chromosomal region.

This PhD project will aspire to address at least some of the following, specific research questions:

1. Well-characterized XLID families with negative findings from X-exome sequencing (n=21) have unusual coding or non-coding mutation in a known or novel XLID gene. A range of state-of-the-art genomic investigations shall be undertaken including whole genome sequencing, transcriptomics and methylomics of cell lines derived from affected individuals of these families to identify and prioritise potentially causative variants.
2. Prioritised, novel coding and non-coding variants will be assessed using a variety of computational tools before we embark on molecular and cellular assessment of select few of these variants using patient derived cell lines and where appropriate also CRISPR/Cas9 human ES cell models.
3. Tools and approaches developed as part of this XLID project will be applied to unresolved singleton ID cases from the NCD CRE to attempt to develop a workable framework for unresolved, likely genetic cases of NCD.

Enquiries to: Professor Jozef Gecz (jozef.gecz@adelaide.edu.au), Dr Mark Corbett (mark.corbett@adelaide.edu.au) and Dr Mike Field (Mike.Field@health.nsw.gov.au).

8. **Optimising the use of the 2D computer-vision FaceMatch algorithm to enhance opportunities for novel intellectual disability (ID) gene discovery and reduce time to diagnosis of syndromic ID – The University of Newcastle, NSW**

The FaceMatch research team is seeking a PhD candidate with a background in computational and biomedical science. FaceMatch aims to facilitate novel gene discovery and the interpretation of variant data by using advanced 2D computer facial recognition technology to match the faces of children with similar features. Up to 70% of individuals with ID remain undiagnosed following DNA sequencing of the known ~1500 developmental disorder genes, and there are a large number of ID genes still to be characterized. Classifying the pathogenicity of novel syndromic ID genes requires molecular confirmation in at least a second

or a cluster of individuals with an overlapping phenotype. Up to 50% of children with moderate to severe ID have associated craniofacial anomalies. Finding individuals with similar facial features currently relies on doctors comparing photographs of undiagnosed children at medical meetings or via written descriptions in phenotyping databases. The recently launched FaceMatch platform [Facematch.org.au] allows dual parent/doctor or doctor-only participation to enable the collection of facial images, phenotypic and DNA variant data via a secure international website. This project will involve 1) Determining the optimal diagnosis algorithm strategy and parameters, and the influence of factors such as age, ethnicity and gender. 2) Facilitating novel gene discovery for individuals with a range of genetically heterogeneous forms of intellectual disability. Through collaboration with participating doctors and research groups, the aim is to reduce time to genetic diagnosis and facilitate novel ID gene/genetic mechanism discovery.

Enquiries to: Doctor Tracy Dudding-Byth (Tracy.Dudding@hnehealth.nsw.gov.au)

9. **Functional Analyses of ID/ASD genes in *Drosophila* – external PhD, Nijmegen (position filled).**

Intellectual Disability (ID) and comorbid autism spectrum disorders (ASD) are among the biggest unsolved medical problems of modern societies. The current understanding about the underlying neuronal mechanisms is limited and no treatment is available. This project will investigate genes, molecular networks, and neuronal mechanisms underlying ID/ASD using *Drosophila* as a model organism. We will focus our functional analyses on phenotypes that we have previously shown to be affected in a large number of ID/ASD *Drosophila* models, such as habituation learning or synapse development. The Ras-MAPK pathways, one of the most frequently disrupted pathways in ID/ASD, will be studied in depth as a proof of principle. Further ID/ASD genes forming molecular networks will also be investigated. In addition to the experimental work in *Drosophila*, we will establish the correlation of specific *Drosophila* and clinical ID/ASD phenotypes to demonstrate their predictive value for (subsets of) ID disorders and empower such phenotypes as a support tool in ID/ASD diagnostics. Furthermore, we will determine whether cognitive phenotypes in *Drosophila* ID models are reversible at adult stages and proceed to testing candidate drugs for their ability to reverse such defects. We expect this project to yield fundamental knowledge and novel tools that will be applicable in diagnostics and for testing treatment strategies.

Project leader: Associate Professor Annette Schenck (Annette.Schenck@radboudumc.nl)