

## Neurogenetics Laboratory, Department of Genetic Medicine, Women's and Children's Hospital



### Head: A/Prof Jozef Gecz

Identification of genes and understanding of molecular mechanisms leading to intellectual disability represents a challenge of significant medical importance. Over the last decade, we have identified in excess of 26 genes involved in various forms of intellectual disability and epilepsy. As part of our recent, international effort (supported by the Wellcome Trust Sanger Institute in Cambridge, UK), we have re-sequenced 737 X-chromosome genes in probands from 250 families and thus generated a catalogue of novel and candidate genes implicated in these disorders. While the causative nature might seem obvious for some changes identified (e.g. protein truncation mutations), many others need to be tested using more sophisticated approaches (e.g. unique missense changes). In addition to the gene discovery projects we are also actively involved in the study of molecular consequences of some of these using cell and animal models. We have multiple opportunities for highly nationally and internationally competitive Hons and PhD projects.

#### The areas of project opportunities include;

- \* Recruitment of families and mapping genes for X-linked mental retardation, non-syndromic forms in particular.
- \* Identification of novel genes by novel exon capture and massive parallel re-sequencing approaches.
- \* Molecular mechanism of ARX gene associated pathology with the emphasis on polyalanine expansion mutations.
- \* Characterisation of the animal model (conditional KO) of the Phf6 gene associated with the obesity & mental retardation syndrome BFLS.
- \* Understanding of the role of non-sense mediated mRNA decay pathway(s) in mental retardation.

#### To achieve our goals we are supported by a network of fantastic national and international collaborators:

1. Drs. A. Hackett and M. Field, Genetics of Learning Disability service of NSW, Newcastle, Australia).
2. EURO MRX Consortium (Prof. J. Chelly Paris, France; Prof. H. Ropers Berlin, Germany; Prof. B. Hamel Nijmegen, Holand; Prof. C. Moraine Tours, France and Prof. J-P. Fryns Leuven, Belgium).
3. Prof. M. Stratton & Wellcome Trust Sanger Institute, Cambridge, UK. Collaborative project of complete X-chromosome gene set re-sequencing in 250 families with intellectual disability.
4. Prof D. Geschwind, UCLA, Los Angeles, USA. Collaboration on the systematic expression profiling and copy number investigations in families with XLMR.

#### Relevant and latest publications:

- P. Strømme et al. Mutations in the human ortholog of Aristaless cause X-linked mental retardation and epilepsy, *Nature Genet.* 30: 441-445, 2002.
- Lower et al., Mutations in PHF6 are associated with Börjeson-Forsssman-Lehmann syndrome. *Nature Genet.* 32(4):661-5, 2002.
- Tarpey PS et al. Mutations in UPF3B, a member of the nonsense-mediated mRNA decay complex, cause syndromic and nonsyndromic mental retardation. *Nature Genet.* 39(9):1127-33, 2007.
- Froyen G, et al. Submicroscopic duplications of the hydroxysteroid dehydrogenase HSD17B10 and the E3 ubiquitin ligase HUWE1 are associated with mental retardation. *Am J Hum Genet.* 82(2):432-43, 2008.
- Chiurazzi P et al. XLMR genes: update 2007. *Eur J Hum Genet.* 16(4):422-34, 2008.
- Dibbens L, et al. X-linked protocadherin 19 mutations cause female-limited epilepsy and cognitive impairment. *Nature Genet.* online publication, May 12 2008.

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