

## **DIFFICULTIES AND CONTROVERSIES INVOLVED IN IDENTIFYING MIGRAINE GENES FOR DRUG DEVELOPMENT**

**L.R. Griffiths<sup>1</sup>** N.J Colson<sup>1</sup> F. Fernandez<sup>1</sup>

S. Quinlan<sup>1</sup> J. MacMillan<sup>2</sup> D. Nyholt<sup>3</sup> R.A Lea<sup>1,4</sup>

<sup>1</sup> *Genomics Research Centre, Griffith Institute for Health and Medical Research, Griffith University, Gold Coast, Australia.*

<sup>2</sup> *Queensland Clinical Genetics Service, Royal Children's Hospital Health Service District, Brisbane, Qld, Australia*

<sup>3</sup> *Queensland Institute for Medical Research, Brisbane, Australia*

<sup>4</sup> *Environmental Science & Research, Wellington, New Zealand.*

Migraine is a common and debilitating neurological disorder with a significant genetic component. A number of genes involved in a rare and severe sub-type of migraine, termed familial hemiplegic migraine, have been identified, but although a number of linkage and association studies have been undertaken, the number and identity of the genes involved in the more common types of migraine have yet to be defined. Neurotransmitter pathways have been the main focus of studies investigating the molecular mechanisms of the disorder. However vascular and hormonal triggers disturbances also occur in migraineurs, as highlighted by alterations in cerebral blood flow and hormonal triggers of migraine and hence factors affecting these functions may also be involved. Genetic characterization of migraine is making steady progress with an increasing number of genomic susceptibility loci now identified on chromosomes 1q, 4q, 5q, 6p, 11q, 14q, 15q, 17p, 18q, 19p and Xq. The 4q, 5q, 17p and 18q loci involve endophenotypic susceptibility regions for various migrainous symptoms. In addition, candidate gene association studies have identified several susceptibility variants capable of altering vascular and hormonal, as well as neurological function. This presentation will focus on the difficulties involved in identifying the genes that play a role in the common types of migraine including the multifactorial nature of the disorder, the variable approaches that can be taken for gene mapping, the importance of stringency in diagnosis and sub-type classification, the role of linkage disequilibrium in defining causal or susceptibility variants, the power of linkage and association studies for gene identification, the need for replication of results and meta-analyses, the difficulties in identifying genes of modest effect, the potential for confounding due to population stratification and potential ethnic differences and the potential importance of pharmacogenetic interventions once genes have been identified.