Molecular and Gene Expression Studies of Migraine

Project Leader & Contact details
Professor Lyn Griffiths:
Email: lyn.griffiths@qut.edu.au
Phone: 07 3138 6100

A/Prof Rod Lea
Email: rodney.a.lea@gmail.com;

Dr Heidi Sutherland
Email: heidi.sutherland@qut.edu.au
Phone: 07 3138 0971

Background

Familial Hemiplegic Migraine (FHM) is a subtype of migraine characterised by severe migraine, accompanied by weakness, hemi-paralysis (hemiparesis), and in some cases extended coma. Although the pathogenesis of FHM remains unclear, the disease is considered to be a channelopathy. Several ion channel genes (CACNA1A, ATP1A2 and SCN1A) have been identified in large family studies as causing FHM. Within these three genes there is widespread allelic heterogeneity with >100 mutations reported to date. The Genomics Research Centre (GRC), currently undertakes diagnostic testing for the known mutated genes that cause FHM, as well as EA2, SCA-6 and CADASIL, and we have recently developed a customised diagnostic panel for the key genes using Next Generation Sequencing (NGS) technology. Of the FHM patients that undergo diagnostic testing <25% are positive for mutations in the known genes, suggesting that additional genes and mutations responsible for causing FHM are yet to be discovered. We hypothesise that whole exome sequencing using NGS technology will enable a comprehensive and cost-effective screen to uncover novel genes and mutations involved in FHM.

Hypothesis

Novel mutations in the CACNA1A, ATP1A2, SCN1A, NOTCH 3 and TRESK genes causing severe migraine and migraine-stroke related disorders, can be detected using Next Generation Sequencing (NGS) technology.

Aims

Perform whole exome sequencing (WES) of FHM patient samples that are negative for known FHM genes, and use variant prioritisation analysis and in-silico prediction methods to identify novel candidate mutations for functional assessment. This will be followed by validation of the pathogenicity of the selected novel mutations by developing a functional approach.

Approaches

The project will identify and assess novel genes and mutations in patients clinically diagnosed with FHM using WES and innovative functional analysis. Validation will include Sanger Sequencing and genotyping variants in extended case control cohorts and migraine families using HRM, RFLP and pyrosequencing methodologies. The identification of novel FHM genes will allow us to then extend our customised NGS targeted panel for a more comprehensive molecular diagnosis of FHM.

References

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