Retina Australia
Research Progress Report – Research Funding 2014

"Finding genetics answers for Leber congenital amaurosis using next-generation sequencing"

Eye Genetics Research Group
Children's Medical Research Institute
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Save Sight Institute
University of Sydney

Investigators:
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The Eye Genetics Research Group is using next-generation sequencing (NGS) to identify novel disease genes and variants causing blinding eye diseases in humans. Model systems are used to determine the underlying pathophysiological mechanisms and for preclinical work to develop new treatment strategies for the vision impairment.

Leber congenital amaurosis (LCA), is a severe form of retinal degeneration with onset usually in infancy. Clinical features include lack of ocular fixation, photophobia, nystagmus and strabismus. Over 20 causative disease genes have been identified. LCA can occur in isolation or in association with other systemic features such as developmental delay or dysmorphic features. LCA usually shows an autosomal recessive mode of inheritance, although autosomal dominant forms also occur. There is marked genetic heterogeneity with each genetic defect representing a small proportion of cases, and there are an estimated 40% of cases due to unidentified disease genes. There has been a bottleneck in genetic diagnosis in LCA, because of the large number of genes that need to be tested. We have applied NGS techniques to LCA in this project, to overcome this bottleneck.

In this project we performed NGS strategies including exon capture of protein-coding exons in the genome followed by NGS in patients and families with LCA. Overall, we identified known and novel variants in LCA disease genes in 60% of patients and families, consistent with previous reports using these approaches. Several candidate novel disease genes are under further investigation. Due to the success of this project, we have developed an NGS pipeline, which can now be applied for further patients with this condition.

Findings from this work have been presented at the Australian and New Zealand Society of Retinal Specialists Annual Meeting, Sydney, June 2014 (1), Orthoptics Australia Annual Scientific Conference, Brisbane, November 2014 (2), the Royal Australian and New Zealand College of Ophthalmology Annual Scientific Congress, Brisbane, November 2014 (3) and will be presented at the 9th Congress of Asia Pacific Vitreo-Retina Society, Sydney, July, 2015 (4), the Retina Australia National Congress, Melbourne, October 2015 (5) and the Human Genetics Society of Australasia Annual Scientific Meeting, Perth, August 2015. Publication from this work is in preparation for journal submission (6). Support from Retina Australia is gratefully acknowledged in publications and presentations of this work.

The sequencing and bioinformatics pipelines, and preliminary results obtained in this project, have been applied to provide preliminary data for an NHMRC project grant application for 2016: "Pathways to treatment in blinding genetic retinal eye diseases."

Publications & Presentations:

1) Jamieson RV. Retinal genetic testing: what can we do in 2014? Australian and New Zealand Society of Retinal Specialists Annual Meeting, Sydney, 14 June 2014. **(Invited Speaker – Retina Australia support recognised in acknowledgement slide)**

2) Jamieson RV. Next-generation sequencing for patients and families with retinal and developmental eye diseases. Orthoptics Australia Annual Scientific Conference, Brisbane, 23-26 November 2014. **(Invited Speaker – Retina Australia support recognised in acknowledgement slide)**

3) Jamieson RV, Ma A, Prokudin I, Sabri A, Nash B, Cheng A, Flaherty M, Grigg J, Ho G, Bennetts B. Application of genomics and next-generation sequencing to genetic diagnosis in developmental eye and retinal diseases. Royal Australian and New Zealand College of Ophthalmology Annual Scientific Congress, November 2014. **(Conference presentation – Retina Australia support recognised in acknowledgement slide)**

4) Jamieson RV, Nash B, Grigg JR, Sabri A, Greenlees R. Pathways to therapy for retinal dystrophies: combining genomics, genome engineering and functional studies. 9th Congress of Asia Pacific Vitreo-Retina Society. Sydney, 31 Jul – 2 Aug, 2015. **(Abstract submitted – Retina Australia support to be recognised in acknowledgements)**

5) Jamieson RV. Genomics, gene correction and understanding function: pathways to therapy for retinal dystrophies. Retina Australia National Congress, Melbourne, 23-25 October 2015. **(Invited Speaker – Retina Australia support to be recognised in acknowledgement slide)**

6) Sabri A, Nash B, Ma A, Prokudin I, Sabri A, Mohapatra S, Cheng A, Flaherty M, Ho G, Bennetts B, Lamey T, De Roach J, Grigg JR, Jamieson RV. Next-generation sequencing and clinical correlations in Leber congenital amaurosis. In preparation, March 2015. **(Retina Australia support recognised in acknowledgements)**

Budget: Funds were expended on consumables and next-generation sequencing for this project, detail attached.