Save Sight Society Grant – Interim Report Feb 2016 3711333

Elucidating the Genetic defect in North Carolina Macula Dystrophy – a rare retinal disease using Exome sequencing

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Amount funded $23067

Award activated: 31/03/2016

This grant was submitted for the SSS round in May 2015, and reviewed on 11th September 2015 at the ORIA research review committee, notification of funding 10th December 2015, and funds finally available end of March 2016. There are obvious delays between the grant submission, review, notification of success, and activation of grant funding, in a rapidly moving field, resulting in 10 months between submission and activation of the grant.

An On-line publication appeared in Ophthalmology on Oct 24, 2015, by Kent Small's group entitled *North Carolina Macular Dystrophy Is Caused by Dysregulation of the Retinal Transcription Factor PRDM13.* (Published Jan 2016)
This paper identified in 12 families (with 141 members), 3 point mutations in an upstream regulatory region (DNAse1 hypersensitivity region) of a developmental gene *PRDM13* (mutations entitled V1(6 families), V2 (3 families), and V3 – one family), as well as a duplication of the *PRDM13* gene in one family, and a duplication of a gene at a second choromosal locus *(IRX*), in a further family. Of note these changes were found by next generation sequencing, specifically genome NGS.

From award activation, further patients and family members were examined and recruited.
Our cohort now exists of 8 probands, which includes 3 families with clear AD inheritance (11 individuals affected), and 5 other probands with no family history, and parents found to be normal on examination. The phenotypes have been reviewed carefully, and are consistent with NCMD, suggesting there may be a de novo mutation rate, as is observed in many other developmental ocular disorders. The lack of family history however has meant these individuals have been classified as congenital toxoplasmosis. The ethnic makeup consists of

3 Caucasian, 2 Polynesian, 1 Cambodian, 1 Sri Lankan, and 1 Pakistani proband. The Ocular genetic unit was without a research technician until August 2016, and when our new technician commenced, we decided to specifically target the known genes and regulatory regions described in the Small Paper 2016[1], and a different duplication subsequently found in a further family[2].

The entire DNAse1 Hypersensitivity region has been sequenced in full; none of the prior variants, nor new ones, were identified. We screened for the known duplications, which were not present. We have screened 18 of the 19 exons of *PRDM13*, with no obvious pathogenic variants identified that segregated with disease. At this point we will revert to the original plan of undertaking next generation sequencing, as it would appear that structural variants (i.e. copy number variants/ large deletions or duplications) are the most likely cause for disease in these individuals. Our original hypothesis that our families have a unique genetic cause for their disease based on ethnicity is therefore likely correct. I have been in personal communication with Kent Small, who is collaborating with us in our ventures.He has a further We are just completing the final amplicon of *PRMD13,* and are researching using NZGL services, or an overseas NGS service which is likely to be cheaper, faster, and bioinformatics support can be provided by Kent Small's team.

We have $11,000 of consumable funding remaining (budgeted $15,000 for exome sequencing at NZGL, including bioinformatics support) – fortunately prices have dropped since May 2015, and genome NGS is likely possible for 8 probands.

1. Small KW, DeLuca AP, Whitmore SS, et al. North Carolina Macular Dystrophy Is Caused by Dysregulation of the Retinal Transcription Factor PRDM13. *Ophthalmology*. 2016;123:9-18.

2. Bowne SJ, Sullivan LS, Wheaton DK, et al. North Carolina macular dystrophy (MCDR1) caused by a novel tandem duplication of the PRDM13 gene. *Molecular vision*. 2016;22:1239-47.