University of Pennsylvania

Annual Progress Report: 2009 Nonformula Grant

Reporting Period

June 1, 2013 – May 31, 2014

Nonformula Grant Overview

The University of Pennsylvania received $4,600,000 in nonformula funds for the grant award period June 1, 2010 through May 31, 2014. Accomplishments for the reporting period are described below.

Research Project: Project Title and Purpose

Improving Vision and Preventing Visual Impairment in Rural Amish and Urban African Americans - We propose to assess methods for improving treatment of visual impairment for Age-Related Macular Degeneration; determine the genes associated with Age-Related Macular Degeneration in African Americans; phenotype Amish and African American subjects with Age-Related Macular Degeneration to determine characteristic retinal signs associated with genetic risk variants; determine the extent of cortical plasticity in advanced Age-Related Macular Degeneration; and identify disparities in vision care within the African American community.

Duration of Project

6/1/2010 - 5/31/2014

Project Overview

The overall goal of this project is to investigate the genetic and environmental determinants of Visual Impairment, to develop new methods of treatment to delay its progression, and enhance the use of remaining residual vision. In particular, this project will focus on Age-related Macular Degeneration (AMD), which is the leading cause of Visual Impairment in Pennsylvania. The research aims are to (1) enhance vision rehabilitation for African Americans with central visual impairment, (2) determine the genetic and environmental modifiers in AMD, (3) determine visual cortex function in response to the central visual deficit seen in AMD, and (4) identify the barriers for minorities that prevent access to vision care.

To address the need for enhancing vision rehabilitation, a clinical trial will be performed comparing home vs. office-based rehabilitation in 60 African American subjects with visual impairment to determine if there is an advantage of one method over another. To assess the genetic and environmental modifiers in AMD, African American and Amish case/controls will be genotyped for risk variants and phenotyped for retinal changes with advanced imaging technology. To address the need to understand visual cortex function in AMD subjects with

central visual deficits, 40 subjects will undergo extensive testing with functional MRI to determine if there has been any remapping and shift of visual cortical responsiveness. To identify the reasons for minorities having poor access to vision care, faculty at Lincoln University in collaboration with other faculty participating on this project, will develop and test a study protocol to identify the hurdles that impede access to vision care in African Americans.

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Other Participating Researchers

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Elise Ciner, OD, Sarah Appel, PhD, Marcy J. Graboyes, MSW, LSW, ACSW, Ruth Y. Shoge, OD, Erin Draper, OD – employed by Salus University
Daniel Weeks, PhD – employed by University of Pittsburgh
Judith Thomas, PhD, Patricia Joseph, PhD – employed by Lincoln University
Jeffrey Henderer, MD – employed by Temple University Health System
Omesh Gupta, MBA, MD – employed by Temple University School of Medicine

Expected Research Outcomes and Benefits

(1) Of the 50 states, Pennsylvania has the 4th highest prevalence of visual impairment and blindness. Age-related Macular Degeneration is the leading cause of Visual Impairment in Pennsylvania. The outcome of our project will be improved methods to treat and diagnose Age-related Macular Degeneration resulting in earlier therapeutic intervention to prevent and slow progression of this blinding disease. Slowing progression will lead to less advanced disease which will impact the overall prevalence of Visual Impairment in Pennsylvania.

(2) Ethnic, cultural and socio-economic factors contribute to the poor access of African Americans (AAs) to essential visual rehabilitative services and must be addressed to ensure that individual needs, rather than these modifiable factors, determine the potential for AAs to achieve successful outcomes. We expect that an understanding of these factors will lead to increased access to essential vision rehabilitative services and improved vision.

(3) There is a need to empower the African American community in Philadelphia to perform vision screening and refer subjects to appropriate facilities for continued vision care if needed. We will train lay screeners from the community to educate their communities so services can be continued beyond the grant period. This will result in less visual impairment long-term due to

better education and access for community members.

(4) The future of stopping visual impairment will depend on preventing progression from early disease to later blindness. This project will identify modifiable risk factors in Age-related Macular Degeneration, such as diet and smoking behavior, and target subjects with these risks with interventions to reduce these risk factors. This reduction in risk factors will result in a decrease in prevalence of Visual Impairment.

Summary of Research Completed

Aim 1: Vision Rehabilitation Research for African Americans with Central Vision Impairment (VISRAC)

Recruitment was completed on 12/17/13. The initial targeted goal of 48 patients completing the study was reached.

Aim 2. Genetic and Environmental Modifiers in AMD

Subaim 2A. Genotyping of Candidate Genes in African Americans
The target for this study was 400 cases and 400 controls. Recruitment is finished (397 cases and 427 controls, Table 2).

Subaim 2B. Genotyping of Candidate Genes in the Amish
The target for this study was 200 cases and 100 controls.
We have completed genotyping of 397 cases and 427 controls. Genotyping was just completed on the Illumina Exome Chip. Analysis of this data has started.

Subaim 2C. Phenotyping of AMD subjects
<u>The target for this study was 160 AA and Amish patients.</u>
<u>Phenotyping by Jacobson group</u>. In the current period (July 1, 2013 – July 23, 2014) we continued the phenotyping substudy (Jacobson group). Our main goal was to complete our analyses of the detailed features of AMD in African-American (AA) patients and compare the results to those of Amish AMD patients. Following on our observations in non-neovascular (intermediate) Amish AMD, we studied the AA AMD patients with spectral-domain optical coherence tomography (and autofluorescence imaging in a subset). Macular location and characteristics of large drusen (≥125 μm) were determined. Thickness of photoreceptor laminae was quantified overlying drusen and in other macular regions.

Qualitative observations that preceded our quantitative studies revealed a spectrum of severity of disease in our AA patients and these observations were comparable to earlier published studies. Drusen were associated with normal autofluorescence, or locally increased or decreased autofluorescence. Cross sectional images by optical coherence tomography (OCT) showed drusen as elevations of the retinal pigment epithelium (RPE) layer. Some eyes showed numerous small patches of increased and decreased autofluorescence and subretinal drusenoid deposits which contrasted to the sub-RPE location of typical drusen. There was also (in some AA-AMD patients) amorphous-appearing hyperreflective material beneath the foveal region with

apparently thinned foveal and surrounding outer nuclear layer (ONL). Images representative of advanced AMD with central geographic atrophy were present in one patient. The atrophic areas had markedly reduced autofluorescence. OCT showed increased choroidal reflectivity and disruption of normal retinal laminar architecture with loss of ONL in the atrophic region. Another notable OCT feature in the advanced AMD eye was thickened subretinal material across the central retina.

Reference:

Sadigh S, Luo X, Cideciyan AV, Sumaroka A, Boxley SL, Hall LM, Sheplock R, Feuer WJ, Stambolian DS, Jacobson SG. Drusen and photoreceptor abnormalities in African-Americans with intermediate non-neovascular age-related macular degeneration. Curr Eye Res. 2014 Jun 9:1-9.

Phenotyping by Contrast sensitivity. Our work over the past year has focused on the analysis of the data we collected during the previous three years. In total, we scanned 39 subjects, of which 22 subjects were excluded due to inability to fixate during the experiment or inability to observe the stimulus, even at high contrast. Of the 17 valid subjects, 9 were control subjects and 8 were experimental subjects. Among these 17 subjects, we successfully measured sensitivity data at 41 targets, each of which consisted of a series of iso-eccentric positions on the retina that, based on the subject's funds photograph, crossed either a blood vessel (17 targets), a druse (8 targets), or neither (16 targets). Measurements at each location consisted of a sensitivity-vs-position curve, where the positions were finely spaced across the location of interest. In order to determine if we were able to accurately measure the contrast sensitivity at our target locations, we first asked if we observed a dip in sensitivity for those targets located over a retinal blood vessel, as compared to those targets that overlapped with neither a blood vessel nor a druse. We tried a number of automated approaches to this problem, none of which were satisfactory. As an alternative, we asked three human raters to categorize each sensitivity-vs-position curve, presented masked as to subject and target position, as either containing or not containing a dip in sensitivity. All three raters agreed on their ratings of 10 of 16 control positions and 10 of 17 blood vessel positions. For control subjects, both sensitivity and specificity for all three raters were between 60 and 90%, indicating an above-chance classification accuracy and suggesting that localized contrast sensitivity in control subjects was accurately measured by the experiment. For experimental subjects, however, sensitivity and specificity were not above chance and thus our measurements are not able to reliably indicate contrast sensitivity at the precision required to determine whether such sensitivity is reduced over the location of drusen. We believe, the reason for the difference between control and experimental subjects is related to their ability to fixate reliably. This in turn may be related to age.

In addition to finalizing our analyses of the contrast sensitivity experiment, we also finalized and published a paper on an unsupervised learning method for determining the classes (long-, medium-, or short-wavelength-sensitive) and positions of the cones in the photoreceptor mosaic of the retina. This project grew out of an effort to understand how changes in the sensitivity of patches of retina, e.g. by the presence of drusen in macular degeneration patients, might affect the visual system's representation of the photoreceptor mosaic. In our paper, we found that our unsupervised learning technique was capable of learning both the classes and positions of the

retinal cones from visual experience alone. This paper was published in *PLOS Computational Biology*: Benson NC, Manning JR, Brainard DH (2014) Unsupervised Learning of Cone Spectral Classes from Natural Images. PLoS Comput Biol 10(6): e1003652. doi: 10.1371/journal.pcbi.1003652.

Aim 3. Brain structure and function in response to changes in visual experience

This project was completed at the end of the third year due to the lack of subjects that fit the criteria for FMRI testing.

Aim 4A-C: Pilot Study to Identify Barriers for Routine Eye Care

Completed two years based on original proposal and is no longer ongoing.

Aim 4D: Student Internships
The milestone for this reporting period was to provide a student internship to a minority graduate student recruited from the University of Pennsylvania or Temple University or Lincoln University and a student internship to a minority undergraduate student recruited from Lincoln University.

Table 1.

	Cumulative Total as of 5/31/2014
New Enrollees	56
Withdrew	8
Active/In Progress	0
Completed Trial (Target=48)	48

Table 2. African American AMD Genotyping – Aim 2, Sub Aim 2A

Month: 5/31/2014								

Cumulative (to date totals)*	**All Sites**	**Penn**	**Temple**	**Salus**	**Wills**	**Ilin.**	**Kres.**	**Corn.**
Enrolled Controls	427	350	34	43	0	0	0	0
Enrolled Controls – Genotyped	427							
Enrolled Cases	397	223	36	50	34	6	23	25
Enrolled Cases – Genotyped	397							