The Primary Open-Angle African American Glaucoma Genetics study

Primary open-angle glaucoma (POAG) is a familial disease affecting 53 million people worldwide, with individuals of African descent making up a disproportionate number of those affected. A multidisciplinary research team from the Ophthalmology Department at University of Pennsylvania, led by Principal Investigator Joan O'Brien, MD, is investigating the genetics of glaucoma in individuals of African ancestry. The Primary Open-Angle African American Glaucoma Genetics (POAAGG) study has now enrolled more than 10,200 individuals from Philadelphia, making it one of the largest African-ancestry cohorts recruited in a single city. Findings from this study will help to develop personalised diagnostic and therapeutic strategies for this understudied and overaffected minority population.

Over three million people in the US live with a debilitating eye disease, glaucoma, but perhaps only half of them are aware that they have this disease. This is because glaucoma is an insidious disease with few symptoms associated with onset in early stages. A number of affected individuals do not even notice that anything is wrong with them until they have already lost a significant portion of their vision, since the loss is gradual and usually affects their peripheral vision first. Primary open-angle glaucoma affects around 90% of glaucoma patients, and when vision loss occurs it cannot be reversed. Further, though existing treatments can help to slow disease progression in some patients, no cure exists and its etiology remains poorly understood.

Individuals of African descent are five times more likely to develop glaucoma than European Americans, and are up to 15 times more likely to experience loss of vision due to the disease. Notwithstanding these statistics, African-ancestry individuals are a radically understudied group. Unfortunately, this is a recurrent theme throughout genetic research; as of 2019, only 2% of participants in genome-wide association studies were of African descent.

Photo credit: Peggy Peterson.

The Primary Open-Angle African American Glaucoma Genetics (POAAGG) study is currently redressing this imbalance. Principal Investigator Dr Joan O'Brien, and Project Manager Rebecca Salowe, describe how their multidisciplinary research team in the Ophthalmology Department at the University of Pennsylvania is investigating the genetics of glaucoma in Black individuals. In addition to addressing a pressing public health need and a health disparity, the POAAGG study aims to keep Penn Medicine and its patients at the forefront of transformations in ophthalmology, bringing precision to both the understanding and treatment of eye disease.

PRIMARY OPEN-ANGLE GLAUCOMA

Primary open-angle glaucoma (POAG) is a familial disease affecting 53 million people worldwide, and African Americans make up a disproportionate number of those affected. Glaucoma usually involves a build-up of fluid within the eye: as pressure inside the eye increases, the fluid cannot drain properly. If left untreated, this increase in pressure may damage the optic nerve, which connects the eye to the brain in order to process visual information. While the cause of POAG is not fully understood, factors including age, ancestry, and family history increase the risk of developing the disease.

Currently, medical interventions aim to improve drainage or to reduce the pressure in the eye before it causes irreversible damage: treatments include eyedrops, laser treatment, or surgical procedures. Unfortunately, not all glaucoma cases respond to current treatments, and practitioners are unable to prevent vision loss in approximately one-third of patients. Furthermore, some patients who develop POAG think that their vision problems relate to natural ageing, rather than indicating a progressive disease. When they do finally consult a doctor, this therapeutic delay can mean that vision loss is permanent.

THE POAAGG STUDY

Clinicians at the Scheie Eye Institute realised that they needed to be able to identify glaucoma patients earlier and provide more effective and personalised therapies. O'Brien, an ocular oncologist specialising in ocular genetics – whose prior research has already advanced diagnostic and treatment options for several diseases including retinoblastoma and ocular melanoma – wondered if exploring the genome would reveal clues about the biological basis of glaucoma. This information could allow for development of earlier and more precise diagnostic and therapeutic interventions for these most at-risk patients.

'The majority of glaucoma studies to date have been conducted in cohorts of European or Asian descent,' explains O'Brien. 'This impedes translation of findings into clinical action for the most affected group. Genetic variation detected in other populations may not be relevant in people of African ancestry.' The Scheie Eye Institute researchers, therefore, needed to carry out their own study, focusing on the Black population of Philadelphia. Synthesising data from genetics, bioinformatics, phenotyping, imaging, and structural genomics, together with numerous next-generation sequencing techniques, the POAAGG team aimed to understand the increased burden of POAG in Black people.

With initial funding of $11.25m in 2014 from the National Eye Institute, the POAAGG research team was able to recruit more than 10,250 African Americans from Philadelphia – one of the largest African-ancestry cohorts that has ever been enrolled in a single city. The participants agreed to be re-contacted and could be monitored over time for progression of the disease.

Initially, the team recruited patients from ophthalmology clinics at the University of Pennsylvania. In later years, the study expanded enrolment to two external sites, including Temple University (Jeffery Henderer, MD) and the private practice of a Scheie Eye Institute alumnus (Windell Murphy, MD). 'This broad-based, large-scale outreach strategy, including partnerships with several local ophthalmologists who generously volunteered to open their clinics to the study, gave us access to a broader pool of patients,' explains Salowe. Approximately 1,600 patients were also recruited from the Penn Medicine Biobank (a collection of DNA samples from consenting patients at Penn Medicine).

Photo credit: Peggy Peterson.

A community outreach event at a North Philadelphia Health Fair.

It is well-known that individuals of African ancestry have been mistreated in past research studies and are dramatically under-represented in genetic research. This disparity, together with negative experiences within the healthcare system, can discourage Black Americans from trusting in medical research. 'These types of hesitations and reservations have negative effects on people of colour who are not participating in very important research,' Marquis Vaughn, Community Outreach Director for the study, explains. 'It takes away the chance for this community to be a part of powerful new treatments.'

Aware of these past abuses and hesitations, the POAAGG study team sought to employ a framework of cultural humility that was sensitive to the needs of Black people. Partnership with community leaders, strong African American representation on the study team, provision of financial assistance with transportation, and assistance with insurance options, are several examples of how the team sought to prioritise patient comfort and access to glaucoma specialists.

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POAAGG'S GLAUCOMA AWARENESS CAMPAIGN

The study team also sought to reach individuals in Philadelphia who may not have access to healthcare providers or insurance. To reach these individuals, the team launched a multimedia glaucoma awareness campaign in 2018. A primary goal of the campaign was to increase awareness of the elevated risk of glaucoma in the Black population, with particular emphasis on the importance of receiving early treatment. Secondly, free glaucoma screenings with fellowship-trained glaucoma specialists, many of whom are of colour, were offered to all interested individuals, regardless of insurance status. Lastly, all eligible individuals were offered the opportunity to enrol in the POAAGG study.

Researchers partnered with WURD Radio, which is the only Black-owned talk radio station in Pennsylvania. This Philadelphia-based radio station, which has been under the leadership of President and CEO Sara Lomax-Reese for more than a decade, has a wide listener base. WURD Radio invited two POAAGG glaucoma specialists, Dr Eydie Miller-Ellis and Dr Ahmara Ross, onto the show for an interview. They discussed the study, highlighting the free glaucoma screenings, and answered listeners' questions, which allowed them to allay any fears regarding the genetic study. WURD Radio also ran advertisements with a phone number for listeners to schedule a free glaucoma screening, and broadcast testimonials from study participants. As

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Photo credit: Scott Spitzer..

part of the campaign, the study team also distributed information flyers and postcards at locations such as hair salons, barber shops and public transport stops.

The researchers explained to patients that the genetic study was unlikely to provide any direct benefit to them as participants, but could ultimately lead to better treatment options for their children and grandchildren. The majority of participants, however, reported that benefitting others in the future was a large motivator for joining the study. As Selam Zenebe-Gete, lead Clinical Research Coordinator for the POAAGG study, explained, 'The glaucoma screenings were useful in recruiting patients from the community to the POAAGG study, but their deeper importance lay in diagnosing new disease and connecting community members with key glaucoma care resources.'

RESEARCH FINDINGS AND DISSEMINATION

The POAAGG study has generated genome-wide association data on 7,765 individuals and whole-exome data on 8,082 individuals. These data are now being integrated with a vast clinical and imaging dataset to find genetic variants that increase the risk of POAG in African-ancestry individuals.

One of the unique features of the POAAGG study is the extensive phenotypic information gathered on glaucoma patients. 'The study prioritised the collection of detailed phenotypic information on glaucoma cases during exams by glaucoma specialists,' says Salowe. 'These measurements ranged from more traditional clinical values, such as intraocular pressure and visual field testing, to more precise and unique measurements, such as optical coherence tomography and stereo disc photos, which were further curated at Scheie Image Reading Center.'

Not only did the POAAGG research team produce invaluable new research for an under-studied portion of the population, but they also provided key information for other researchers on how to approach recruitment of participants from underrepresented groups. Follow-up interviews with patients from the campaign found that half of them enrolled in the study because of a desire to help others avoid suffering from glaucoma. The study team collaborated with the Annenberg School for Communication and the School of Public Health at UPenn to publish results from detailed interviews in *Preventative Medicine Reports* and *Health Communications*.

We hypothesise that glaucoma, much like cancer, is not one, but many diseases with a spectrum of underlying causes and genetic differences.

The POAAGG study has also shown that ophthalmology tools can fail Black patients. For instance, the standard optic-nerve database integral to an eye-imaging machine did not correspond to what they observed in healthy Black patients. This observation has the potential to mislead clinicians' judgements regarding the risk of African American glaucoma.

$6.6MILLION GRANT RENEWAL

The research team was recently awarded a renewal of $6.6m from the National Eye Institute to continue their investigation for another five years. This will enable them to identify further variants associated with glaucoma in African ancestry individuals. O'Brien remarks, 'Our long-term goal is to translate this information into more personalised and targeted diagnostic and therapeutic strategies for this overaffected and understudied population.'

The POAAGG team has a strong translational research background, adapting research discoveries into therapeutic interventions to benefit patients. So far, they have developed a process to derive retinal ganglion cells (a type of neuron located near the inner surface of the retina) and retinal organoids (minute self-organised three-dimensional tissue cultures derived from stem cells) from induced pluripotent stem cells (those cells that can self-renew by dividing). These cells are most affected by POAG. They are also well-equipped to conduct novel cell-based and animal-model studies with gene editing approaches and multiomic analysis – combining datasets of different omic groups, eg, genomics, proteomics, metabolomics, etc – to better understand the pathogenesis of glaucoma.

Behind the Research

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Research Objectives

The Primary Open-Angle African American Glaucoma Genetics (POAAGG) study investigates the genetics of glaucoma in individuals of African ancestry.

Detail

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Bio

Joan O'Brien, MD, is chairman of the Ophthalmology Department at University of Pennsylvania. Her ocular genetics research has greatly advanced diagnostic and treatment options for several diseases, including retinoblastoma, ocular melanoma, and glaucoma. Today, her research focuses on elucidating the genetics of glaucoma in African ancestry individuals.

Funding

- National Eye Institute (grant #1RO1EY023557-01)
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- F M Kirby Foundation
- Research to Prevent Blindness
- The UPenn Hospital Board of Women Visitors
- The Paul and Evanina Bell Mackall Foundation Trust
- Regeneron Pharmaceuticals

Collaborators

Glaucoma Specialists

- Eydie Miller-Ellis, MD (Professor of Ophthalmology)
- Prithvi Sankar, MD (Professor of Ophthalmology)
- Victoria Addis, MD (Assistant Professor of Ophthalmology)
- Qi Cui, MD, PhD (Assistant Professor of Ophthalmology)
- Ahmara Ross, MD, PhD (Assistant Professor of Ophthalmology)

Research Personnel

- Venkata R Murthy Chavali, PhD (Assistant Professor of Ophthalmology)
- Harini Gudiseva, MSc, MS (Research Project Manager)
- Jie He, MD (Research Specialist)
- Dave Collins (Consultant)

Clinical Research Staff

- Rebecca Salowe, MSE (Project Manager and Scientific Writer)
- Roy Lee, MS (Database Manager)
- Marquis Vaughn (Community Outreach Director)
- Selam Zenebe-Gete (Clinical Research Coordinator)

Biostatisticians and Reading Center

- Maureen Maguire, PhD (Emeritus Professor of Ophthalmology)
- Gui-shuang Ying, MD, PhD (Carolyn F. Jones Professor of Ophthalmology)
- Ebenezer Daniel, MBBS, MS, MPH, PhD (Director of Scheie Image Reading Center)

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Scheie Eye Institute
Penn Medicine

Personal Response

What is the most rewarding aspect of the POAAGG study to date?

"The engagement of many participants within the city of Philadelphia, supported by community leaders, has allowed us to overcome health disparities in this population. This overaffected and understudied group will hopefully become the most-studied population within our city. The willingness of participants to be re-contacted has provided an opportunity to understand progression of this disease and the underlying causes of vision reduction.

What are your future plans?

Our research team will continue its journey towards identifying the determinants of glaucoma and translating this information into personalised diagnostic and therapeutic strategies. The richness and scale of the POAAGG study's data will support future glaucoma studies, along with collaborations across disciplines, improving treatment options for future generations. In the next five years of our grant renewal, we plan to construct a disease-risk model, conduct a meta analysis with other glaucoma cohorts, and correlate phenotypes with genetic variants. Our team also intends to analyse extensive whole-exome sequencing data to identify rare and familial POAG variants. Finally, we plan to evaluate these variants for functional significance using relevant cellular and animal-model systems.

We hypothesise that glaucoma, much like cancer, is not one, but many diseases with a spectrum of underlying causes and genetic contributors. If proven to be true, we can then name the subtypes of disease and develop precise, targeted treatments for each form. This dataset can also be used to investigate many other diseases that over-affect African ancestry populations, such as hypertension or diabetes."