MCW researchers lead imaging study of patients with genetic color vision disorder in advance of AGTC gene therapy clinical trials

August 2016 - Motivated by an upcoming gene therapy trial sponsored by Applied Genetic Technologies Corporation (AGTC), researchers with the Medical College of Wisconsin (MCW) Advanced Ocular Imaging Program (AOIP) have undertaken leadership in a multicenter natural history study to analyze the structure of the eye’s color-detecting cone cells in patients with a genetic color vision disorder. The initial results, which appear in the current issue of Investigative Ophthalmology and Visual Science, show that high-resolution adaptive optics imaging could help physicians determine the potential effectiveness of these new gene therapies on various patients.

Congenital achromatopsia (ACHM) is a recessive disorder where function of the color-detecting cone cells in the retina is absent or severely reduced. According to the American Association for Pediatric Ophthalmology and Strabismus, ACHM affects about 1 in every 33,000 people and results in low visual acuity, light sensitivity and the absence of color vision. Researchers have found that achromatopsia is associated with a mutation in one of six genes, with two, CNGA3 and CNGB3, accounting for around 70 percent of all ACHM cases. AGTC’s clinical trial program for achromatopsia caused by mutations in the CNGB3 gene is currently enrolling patients, and the company is on track to release interim data in 2016.

“Patients living with achromatopsia today have no effective treatment options, but a growing body of evidence suggests that emerging gene therapies may have significant potential,” said study co-author Joseph Carroll, PhD, Richard Schultz, MD/Ruth Works Professor in Ophthalmology, professor of ophthalmology & visual sciences, biophysics, and cell biology, neurobiology and anatomy, and co-director of the AOIP at MCW. “Current data show significant variation in the degree of residual cone photoreceptor structure among patients with CNGB3-associated ACHM. As such, imaging tools that can accurately quantify the remaining cone population may aid in selecting patients who are most likely to benefit from gene therapy clinical trials and expedite the development of new therapies.”

Previous studies of gene-based therapies in animals with ACHM have shown that the presence of viable cone cells is required for restoration of cone function through gene therapy. For their natural history study, Carroll and collaborators recruited 51 patients with ACHM and a mutation of the CNGB3 gene. After initial examination, all traveled to the MCW AOIP for high-resolution imaging using optical coherence tomography (OCT), which enables in-vivo examination of retinal structure, and two types of adaptive optics scanning light ophthalmoscopy (AOSLO), which allows for noninvasive imaging of the eye’s rods and cones.

The results show significant variability in the structure and arrangement of the patients’ remaining cone cells, which could impact the effectiveness of different therapies and influence clinical trial data. “For example, consider a trial patient who shows no response to a given intervention,” the authors note in their results. “In the absence of accurate baseline information on residual cone structure, it would be difficult to determine if the lack of response is due to an ineffective treatment or whether there were simply too few cones to drive a change in visual behavior.” The study concludes that in conjunction with OCT, AOSLO will be an important imaging tool for assessing cone structure is the retinas of patients with diseases like ACHM.

“AGTC is committed to developing innovative adeno-associated-virus-based gene therapies to treat achromatopsia and other inherited diseases without adequate treatment options,” said co-author Jeffrey D. Chulay, MD, DTM&H, vice president...
and chief medical officer at AGTC. “The development of tools that can help assess individual patient status will be important for helping patients and physicians make informed decisions about the risks and benefits of enrolling in gene therapy clinical trials for ACHM. We believe the results of this study will help to enhance the design and recruitment of current and planned clinical trials to evaluate AGTC’s gene-based therapies for achromatopsia resulting from CNGB3 mutations.”

MCW co-authors include Alfredo Dubra, associate professor of ophthalmology & visual sciences, biophysics, and cell biology, neurobiology and anatomy, and co-director of the AOIP; Christopher S. Langlo, PhD, in the department of cell biology, neurobiology and anatomy; and Emily J. Patterson, PhD, Brian P. Higgins, Phyllis Summerfelt and Moataz M. Razeen, MD, in the department of ophthalmology & visual sciences.

Additional co-authors for the study include Laura R. Erker, PhD, Maria Parker, MD, Richard G. Weleber, MD, Paul Yang, MD, PhD, David J. Wilson, MD, Mark E. Pennesi, MD, PhD, and John Chiang, PhD, of Oregon Health & Science University; Frederick T. Collison, OD, and Gerald A. Fishman, MD, of The Chicago Lighthouse; Christine N. Kay, MD, and Jing Zhang, MD, of Vitreoretinal Associates in Gainesville, Fla.; Byron L. Lam, MD, of the University of Miami; and William W. Hauswirth, PhD, of the University of Florida.