

Gene therapy for glaucoma could have potential

Discoveries in glaucoma genetics are promising, but treatment through gene therapy is not imminent.

While genetic therapy may offer potential benefits to glaucoma risk assessment and treatment, the field is still in its early stages as scientists discover and research new glaucoma-associated genes.

About 10% of genes that determine risk of glaucoma have been discovered, so approximately 90% of genes that determine the risk are unknown, according to **Kang Zhang, MD, PhD**. He and his colleagues recently made an important finding in glaucoma genetics, localizing a gene on chromosome 2 that is associated with primary open-angle glaucoma in a black population.

Other key findings have included the LOXLI gene association with exfoliation and the discovery of the myocilin gene. **Ryo Kubota, MD, PhD**, and colleagues discovered the myocilin gene about 10 years ago and found that it was similar to the trabecular meshwork-induced glucocorticoid response protein, connected to the pathogenesis of chro-



Kang Zhang

mosome 1q-linked primary open-angle glaucoma. The discovery was an important first step in determining a causative gene for glaucoma, according to Dr. Kubota.

In an interview with Ocular Surgery News, he said the function of known genes for glaucoma has not yet been fully determined, rendering any potential gene therapy treatment a distant possibility.

“It is difficult to really figure out a way to modulate the protein without knowing the function,” he said. “And maybe the only way is to see if it’s a dominant mutation with a toxic byproduct – can we shut that down, that allele, so we have only a healthy protein product from healthy genes? That might be one possible way. We’re still in the very early infancy stage in terms of how we can treat glaucoma through gene therapy.”

Potential role of glaucoma genes

Genes could play several roles in glaucoma therapy, including determining risk and progression. Genome-wide association research has been paving the way for genetic discoveries in glaucoma by helping to pinpoint specific glaucoma genes in the genome, according to experts in the field.

“I think there are two major areas where we can really actually make some

great advances. One is to try to decipher the genetic underpinning of glaucoma,” Dr. Zhang told OSN. “The second thing is, we also have a variation in terms of drug therapy.”

Research by Dr. Zhang and colleagues found a strong predisposition for glaucoma in an Afro-Caribbean population of Barbados, West Indies.

The study looked at 249 glaucoma patients and 128 control subjects. Individuals with two copies of a mutant gene on a region of chromosome 2 were found to have a 20 times greater chance of having glaucoma than those who did not have the genetic mutation.

“This is also a very common mutation in the population. It’s present in about 40% of glaucoma patients, while it’s only present in about 5% of normal individuals,” Dr. Zhang said.

The finding of a potential genetic component in the Barbados population is a possible diagnostic marker for high risk of glaucoma development in that population, according to Dr. Zhang. The subjects with that mutation should be monitored regularly for disease development and progression.

Drug therapy in glaucoma could also be enhanced by pharmacogenomics, he said. By establishing each person’s genetic response to medications, more personalized medical therapy could enhance treatment effectiveness.

“For example, not all people respond to beta blockers in the same way, and this is all due to the underlying genetic variations of pharmacogenomics. I think efforts should be on trying to figure out which drug would be best for individual patients,” Dr. Zhang said.

Targeted therapy

A study by Sakurai and colleagues examined the relationship between polymorphisms of the prostaglandin F2 alpha receptor and latanoprost, finding that two single-nucleotide polymorphisms “correlate with a response to short-term latanoprost treatment in normal volunteers.”

The study concluded that the genotype of specific single-nucleotide polymorphisms might determine variability in an individual’s response to the drug. Such results could more accurately establish a patient’s receptivity to certain drugs, Dr. Zhang said.


The principles of pharmacogenomics may be able to be applied to other treatment modalities. Genetic analysis may help predict which patients will respond best to other interventions such as laser or incisional surgery.

Genetics may also provide a means to determine future risk and make an advanced diagnosis, **Hylton R. Mayer, MD**, told OSN. Subjects could one day be tested for glaucoma genes, determining risk for not only themselves but also for their children, he said.

“This could be fairly important for someone who has a strongly associated gene like the CYP1B1 gene, which is associated with congenital glaucoma,” Dr. Mayer said. “Another role for genetics in glaucoma could be stratification of patients who have higher or lower risk of progressive disease and visual loss.”

An additional role of genetics in glaucoma could be gene modification. The process could work by introducing DNA encoding for normal functioning proteins or by introducing healthier functioning cells that may improve aqueous outflow through the trabecular meshwork or reduce the susceptibility of the optic nerve to glaucomatous damage.

Dr. Zhang and colleagues are continuing to examine genes in the Barbados population, looking for a specific genetic defect.

Dr. Kubota said many more genes must be identified to find the common phenotype of glaucoma. “We should continue to do basic research to identify more genes and [see if] we can develop a new gene therapy, small molecule therapy or an RNA eye therapy-type of a new approach,” he said. – by Erin L. Boyle 

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