

# Genetic Testing Sheds Light on Degenerative Eye Disease

The molecular definition of the genetic basis of disease provides a unique adjunct to the clinical care of patients with hereditary retinal degenerations.

REVIEWED BY RADHA AYYAGARI, PhD

**G**enetic testing in ophthalmology can provide vital information about complex retinal diseases, particularly when used to confirm an ophthalmologist's diagnosis. In a review of molecular testing for hereditary retinal degenerations conducted over a 5-year period at the University of Michigan Kellogg Eye Center, scientists were able to confirm a clinician's diagnosis in half of the cases.<sup>1</sup>

The testing took place in the laboratory of Radha Ayyagari, PhD, Director of Kellogg's Ophthalmic Molecular Diagnostic Laboratory and was reported in the *Archives of Ophthalmology*.

Dr. Ayyagari and her colleagues reported on 350 genetic tests conducted since 1999. For each test described in the current study, the scientists analyzed one or more of eight genes known to cause diseases of the retina, according to a news release from the University of Michigan. Of the 350 tests, 266 were performed to confirm a clinician's diagnosis, by far the most common reason the test was ordered. Another 75 tests sought to determine whether an individual was a carrier of a disease, and as such may pass it to offspring. Nine tests were requested to determine if a nonsymptomatic individual had inherited the mutation that had caused the disease in other family members: In predictive tests, a negative predictive test result indicates that the individual is not likely to develop the genetic eye condition that is present in the family.

## CONFIRM OR RULE OUT DIAGNOSIS

Dr. Ayyagari's team determined the molecular basis of the disease in half of 266 tests conducted to confirm a diagnosis. The researchers said these results are significant because many retinal diseases present similar symptoms, and it is

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sometimes difficult for even the most skilled specialist to distinguish one from the other. By comparing a patient's DNA to DNA from normal individuals, scientists deliver information needed to confirm or rule out a diagnosis.

More than 130 genes associated with retinal diseases (ie, retinitis pigmentosa and macular degeneration) have been identified to date, according to the report. The authors wrote that genetic testing for ophthalmic conditions is a relatively new and evolving practice.

"Molecular diagnostics does not replace the necessary expertise of the ophthalmologist; rather, it adds a new tool to the ophthalmologist's diagnostic arsenal," Dr. Ayyagari said.

In the report, there is one case in which parents with no family history of retinal degeneration requested genetic testing in hopes of revealing the specific nature of their son's eye disease. They also wanted to know whether the younger son, who was experiencing more subtle symptoms, had the same disease or a milder vision problem due to a different disease. Testing revealed that both boys had mutations in the gene linked to Stargardt's macular degeneration.

## GENETIC COUNSELING

Dr. Ayyagari noted that genetic counseling is a crucial part of the genetic testing process. The family must pre-

## MOLECULAR DIAGNOSTIC TESTING FOR INHERITED EYE DISEASES

The University of Michigan Kellogg Eye Center offers state-of-the-art testing in its Ophthalmic Molecular Diagnostic Laboratory. The Ophthalmic Molecular Diagnostic Laboratory provides testing of genes causing:

### Retinal Dystrophy Phenotypes

Gene	Related eye disease
ABCA4	Stargardt's macular degeneration
Bestrophin	Best's macular degeneration
CEP290	Leber's congenital amaurosis
CNGA1	Recessive retinitis pigmentosa (RP) and other early-onset retinal diseases
CRB1	Recessive RP and other early-onset retinal diseases
CTRP5	Recessive RP and other early-onset retinal diseases
EFEMP1	Malattia Leventinese /Doyme honeycomb dystrophy
ELOVL4	Dominant Stargardt's-like macular degeneration
MERTK	Recessive RP and other early-onset retinal diseases
PDE6A	Recessive RP and other early-onset retinal diseases
PDE6B	Recessive RP and other early-onset retinal diseases
RDS	Pattern dystrophy
	Butterfly macular dystrophy
	Adult-onset foveomacular dystrophy
	Bull's eye maculopathy
	Adult-onset Best's disease
	Late-onset dominant macular degeneration
	Additional RDS phenotypes
RGR	Recessive RP and other early-onset retinal diseases
Rhodopsin	Recessive RP and other early-onset retinal diseases

RLBP1	Recessive RP and other early-onset retinal diseases
RPE65	Recessive RP and other early-onset retinal diseases
TIMP3	Sorsby's fundus dystrophy
TULP1	Recessive RP and other early-onset retinal diseases

### Corneal Dystrophy Phenotypes

Gene	Related eye disease
Bigh3	

### Indications for molecular diagnostic testing:

- Clinical diagnosis for patients with signs and symptoms of disease.
- Presymptomatic testing for individuals who do not have the disease but, given family history, are at risk for the disease.
- Carrier testing for individuals who may carry a gene mutation that can be passed on to children.

### Comprehensive services include:

- Certified laboratory testing (CLIA ID# 23D0964501)
- Written report of results for the patient
- On-site genetic counseling for patients both before and after testing.
- The pretest session educates patients about the scope of testing and helps them set realistic expectations; the post-test session will help patients interpret results and their implications for the patient and family members.

For additional information, contact [eyegetest@med.umich.edu](mailto:eyegetest@med.umich.edu)

pare for all possible test results, understand the implications of test results for the patient and other family members, and be aware of the limitations of genetic testing. If physicians do not have the time or skills to provide this background, Dr. Ayyagari urges them to refer their patients to genetic counselors.

The study also reported that a diagnosis could not be confirmed in half the tests conducted. "It is very difficult for patients to understand that the test may not be definitive," Dr. Ayyagari said. "Genetic testing may not always yield the definitive results we receive in other kinds of testing, such as blood tests for cholesterol levels."

### STILL HAVE A WAYS TO GO

A related point of confusion, according to the report, is that an inconclusive result does not necessarily rule out a diagnosis for a given disease. Limitations still exist in technologies for genetic testing, Dr. Ayyagari explained. In addition, very slight genetic variations believed to be benign may have either a cumulative effect or may alter the way another gene functions. Finally, while there has been great progress, scientists have yet to identify all the genes that contribute to disease of the retina.

"Tomorrow we may discover a new gene that explains

many of the previously inconclusive test reports," said Dr. Ayyagari.

In an accompanying report, Stephen Daiger, PhD, of the University of Texas Health Science Center, writes on the promise of genetic testing for eye disease.<sup>2</sup> He said, "Across all of the categories of inherited retinopathy, careful screening of known disease genes leads to the detection of pathogenic mutations in 25% to 90% of patients; an extraordinary accomplishment."

It is to the patient's advantage to have a molecular diagnosis on file, Dr. Ayyagari said. "When treatments begin to emerge for these complex genetic diseases, the individual's genotype may determine whether a new treatment will be the one that works for that patient." ■

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1. Downs K, Zacks DN, Caruso R, et al. Molecular testing for hereditary retinal disease as part of clinical care. *Arch Ophthalmol.* 2007;125:252-258.

2. Daiger SP, Bowne SJ, Sullivan LS. Perspective on genes and mutations causing retinitis pigmentosa. *Arch Ophthalmol.* 2007;125:151-158.