



*CURRENT MANAGEMENT*

# **CHILDHOOD** **Retinal Dystrophies**

*AND FUTURE HOPE*

Surprisingly simple measures can improve the lives of young people with retinal dystrophies. And some treatments are looking good in early trials.

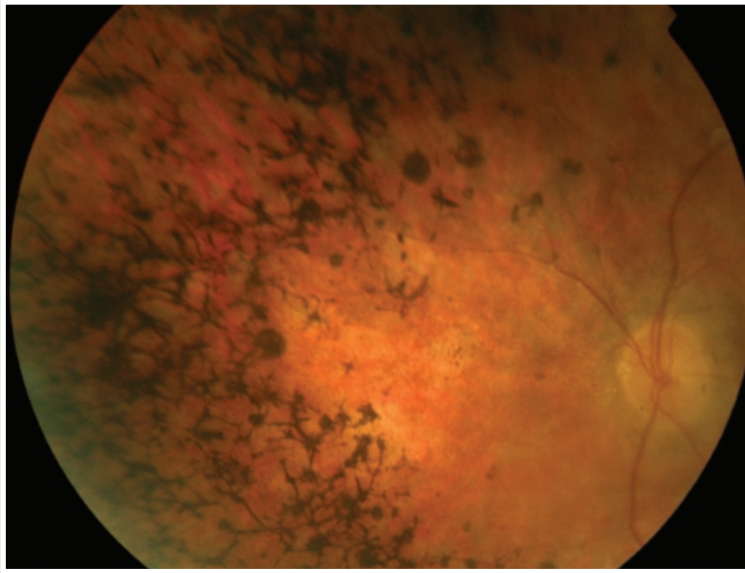
*By Barbara Boughton, Contributing Writer*

**T**o the dismay of both patients and physicians, ophthalmology currently offers no cures or therapies for inherited retinal dystrophies. These disorders result in progressive, sometimes blinding, vision loss during childhood. However, the science of diagnosing, genotyping and managing this broad and sometimes misunderstood group of diseases is rapidly advancing and, in the process, improving lives:

- Children with retinal dystrophies can benefit from a definitive diagnosis and attentive follow-up, which may include corrective lenses, low vision aids and treatment of accompanying genetic conditions.
- Identification of gene mutations—as well as the availability of genetic testing—has proven beneficial for patients and their families by allowing them to adjust to a future that includes visual disability.

More hearteningly, research is now substantial enough that effective therapies may not be such a distant dream:

- Human trials that treat a mutation in the RPE65 gene, which causes some cases of Leber congenital amaurosis, have produced promising results (see “Gene Therapy Study Results,” below).
- Two drugs, fenretinide and isotretinoin, have shown promise in early animal studies for treating Stargardt macular dystrophy. Although they are not being pursued aggressively by the drug makers, isotretinoin was shown to suppress the buildup of the toxic pigment lipofuscin, which leads to loss of vision in Stargardt disease. Likewise, fenretinide interferes with the production and accumulation of the toxin A2E that leads to lipofuscin deposits. Clinical trials of fenretinide are in place for treating age-related macular degeneration, though none are planned for Stargardt. “It could possibly work in Stargardt disease, but we may never find out



**Retina of child with Bardet-Biedl Syndrome.**

until we have clinical trials,” said Peter J. Francis, MD, PhD, associate professor of retinal and ophthalmic genetics at the Casey Eye Institute, Oregon Health & Science University in Portland. Dr. Francis noted as well that clinical trials of isotretinoin have not been initiated for Stargardt disease, and one possible reason is concern over the drug’s side effect profile.

### Surveying the Major Culprits

Despite the broad variety of inherited retinal dystrophies, some are more common than others. They include Stargardt macular dystrophy, retinitis pigmentosa, Usher syndrome, Leber congenital amaurosis and Bardet-Biedl syndrome, according to Arlene V. Drack, MD, associate professor of ophthalmic genetics at the University of Iowa in Iowa City.

Some of these conditions are also well-known for their accompanying systemic findings. Usher syndrome, for instance, is associated with deafness as well as vision loss, and Bardet-Biedl syndrome comes with a host of nonocular signs, including extra digits, obesity, development delay and renal disease, in addition to vision loss.

**When nothing looks wrong.** Two of the dystrophies—Stargardt and Leber—are not infrequently misdiagnosed, according to both Dr. Drack and Gerald A. Fishman, MD, director of the inherited retinal disease and electrophysiology section at the University of Illinois at Chicago. The reason? Although the retina is functionally impaired in these children, structural impairments may not show up in initial standard eye exams. Often children with these disorders see several physicians, including

ophthalmologists and neurologists, before being correctly diagnosed.

**Stargardt.** “There are no changes in the retina when Stargardt macular dystrophy first begins, so these children are often accused of malingering when they start to lose their vision,” Dr. Drack said.

“It’s potentially easy to miss the subtleties in this disease in the early stages because the telltale signs may not initially appear for several years,” Dr. Fishman added. However, he noted that one early sign of Stargardt disease is vision that cannot be corrected to 20/20.

When Stargardt is suspected, visual acuity and visual field testing are helpful tools in making a diagnosis, Dr. Drack said. Genetic testing can also help narrow the diagnostic differential because some children with Stargardt disease have a defect in the ABCA4 gene. This disorder generally causes gradual loss of central vision, although some patients may also lose their peripheral vision. Total blindness is rare.

**Leber.** In children with Leber congenital amaurosis, vision loss is early and is frequently severe. These children often present with nystagmus as well. Dr. Drack noted that without electroretinogram testing or a genetic blood assay, the disorder can be confused with oculocutaneous albinism, which also presents with poor vision and nystagmus.

### How to Manage the Patient

**Don’t believe the stereotypes.** One stereotype about retinal dystrophies is that they all lead to blindness, and, often, sudden blindness. But with the exception of Leber congenital amaurosis, most of these genetic diseases are quite slowly progressive. “There’s some unfortunate information on the Internet that creates a lot of anxiety among families,” said Dr. Francis. “That’s why it’s so important to provide an accurate diagnosis and prognosis—so that families know what lies ahead of them.”

In most cases, researchers and clinicians at the Casey Eye Institute are able to dispel patients’ and parents’ ideas that inherited retinal dystrophies lead to complete loss of vision, Dr. Francis said. And in many cases, adaptations in the child’s life can help him or her lead a normal functional life. A boy who’s talented in sports may need to channel energies into other areas as his vision gets progressively worse, for instance. “Many of our patients do very well with computer learning in school and end up going into the computer field and have successful careers,” Dr. Francis said.

“The biggest misperception on the part of both ophthalmologists and patients’ families is that

nothing can be done for these children, and so there's no reason for follow-up ophthalmologic care," Dr. Drack said. Yet many children with retinal dystrophies need to be carefully followed to treat associated eye conditions, she said.

**Refract the patient.** Simple corrective lenses can help a lot. "Glasses don't make the vision normal, but they can help these patients' vision be the best it can be. With glasses, they can use their vision maximally," Dr. Drack said.

**Filter the blue out.** Children with Stargardt can also be helped by brown or amber sunglasses, which decrease their exposure to blue light, according to Dr. Fishman. The disorder is marked by an accumulation of lipofuscin, which accumulates in the retinal pigment cells of the eye. Lipofuscin absorbs blue light, and then forms free radicals, which contributes to the destruction of rods and cones in the eye. Thus brown or amber sunglasses are potentially protective, Dr. Fishman said.

**Get a low vision assessment.** An evaluation by a low vision specialist is invaluable for all children with retinal dystrophies because they can benefit from an array of low vision aids that assist learning in the school setting, such as closed circuit television or computer monitors on which type can be enlarged. "What many people don't



**Retina typical of Leber congenital amaurosis.**

realize is that large-type books are very difficult to carry around, and they may not be appropriate. Acuity and visual fields have to be assessed in order to find the learning aids that will best suit the child," Dr. Drack said.

**Train for mobility.** Children who lose their vi-

## **Dr. Fishman Dispels Confusion**

Dr. Fishman has helped define the natural history of vision loss in a number of

retinal diseases, including retinitis pigmentosa, Leber congenital amaurosis, Stargardt disease and cone-rod dystrophy. He and his colleagues have also been categorizing a variety of subtypes of various juvenile onset macular dystrophies and correlating their expression with genetic mutations.

But not all inherited retinal disorders of childhood are dystrophies—or even progressive in their course. And they can be fraught with diagnostic confusion. In a recent conversation, Dr. Fishman addressed two of these disorders: achromatopsia and congenital stationary night blindness.

### **Why is congenital achromatopsia frequently misdiagnosed?**

The practitioner can examine these patients without seeing anything wrong with the clinical appearance of the retina. What's needed is an electroretinogram: It turns on the light in terms of diagnosis. When we do an electroretinogram in these children, the cone function is markedly impaired and sometimes not even electrically recordable at all.

### **Why is a precise diagnosis important in achromatopsia?**

These children will have difficulty with color vision, and they will be

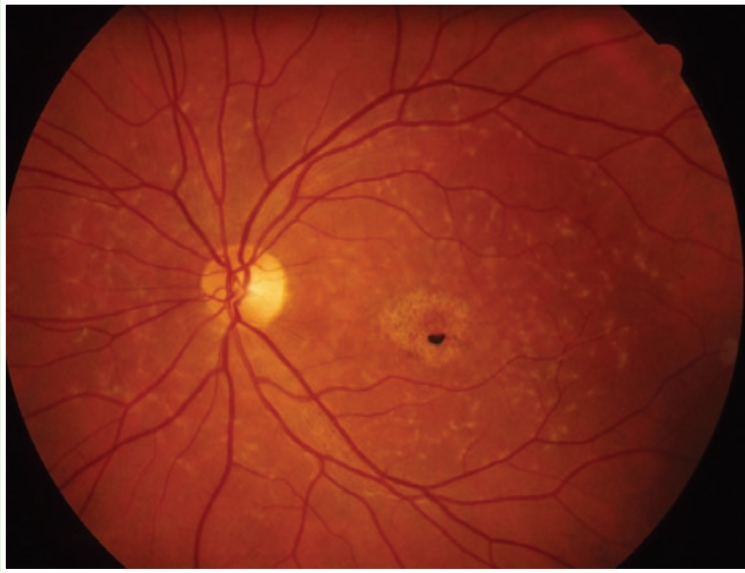
sensitive to light, so sunglasses are important. But it's helpful for the patient and family to know what it is and that it's not progressive. Genetics are also a part of the picture. Once we can correctly diagnose achromatopsia, we know that the parents have a 25 percent risk of having another child with the same disease. With a precise diagnosis and information about the genetics of the disease, parents can be properly informed.

### **What's important in correctly diagnosing congenital stationary night blindness?**

Often the ophthalmologist doesn't

see much wrong in the back of the eye in children with congenital stationary night blindness. But their vision can't be corrected to 20/20. So they may be sent to other physicians for evaluation, even a neurologist.

But one clinical sign of the disease is that they will often cling to their parents when it gets dark. They don't want to go outside, and they have to have light in their rooms. But when they get to a retina specialist who uses an electroretinogram, you obtain a very distinctive finding and consequently a proper diagnosis.



**Retina with Stargardt disease.**

sion slowly can also learn to function more ably through mobility training. “Often these children lose their vision so slowly that they compensate by using what vision they do retain,” Dr. Drack added. “But then their visual field gets so small that it’s not feasible or safe for them to walk around anymore. That’s why it’s important to constantly evaluate them, to see if a guide dog or cane travel may be a solution. Many people find renewed independence after receiving mobility training.”

**Join a study.** Finally, there is a great deal of research into retinal dystrophies. Patients and physicians can become involved in this research, which will eventually find treatments, according to Dr. Drack. And becoming involved in the research process is often empowering for patients and their families, Dr. Drack said, providing them a sense of engagement, if not control, over their situation.

### **Genetic Testing, With Caveats**

Genetic testing of retinal dystrophies is also valuable, but it can yield false positives or uncertain results, said Dr. Francis. “There’s a growing assumption that all patients with genetic disorders

should undergo available testing, but it’s only beneficial when the tests are evaluated by an expert and accompanied by a careful clinical evaluation by experienced ophthalmologists who’ve seen these disorders,” he said. “Blunderbuss genetic testing is not the best way to go.”

Because molecular testing can identify the genetic basis of a disease, it can also help doctors inform patients about the phenotype associated with a particular mutation. That helps inform patients and families about the course the disease may take.

**Knowledge base? Growing.** Genetic testing for inherited retinal dystrophies has made substantial strides over the past 10 years, according to Dr. Francis. “The amount of research knowledge we’ve gained about genetic mutations affecting retinal dystrophies is staggering,” he said. “There are upward of 50 gene mutations, for instance, that have been associated with retinitis pigmentosa.” Still, not all patients with a genetic retinal dystrophy will test positive for a genetic mutation. Only about 60 percent of patients with Leber congenital amaurosis, for instance, will receive a definitive diagnosis from genetic testing at this time, Dr. Drack said. The remaining 40 percent may have a genetic mutation that has yet to be discovered.

**The relief of a diagnosis.** “It’s helpful for families to have a definitive genetic diagnosis,” said Niamh Stover, a genetic counselor at Oregon Health & Science University. “When we can define a condition at the molecular level, we can use information from the scientific literature to give the family a more accurate prognosis, and guess how fast or how slowly the disease might progress. If the test tells us whether the disorder is X-linked, dominant or recessive, it also allows us to counsel the parents about family planning,” she said.

Identifying a genetic mutation can also tell a patient and their family whether they might be eligible for any cutting-edge treatments, including gene therapy. And while gene therapy trials are now ongoing only for patients with the RPE65 mutation causing Leber congenital amaurosis, scientists anticipate that many more gene trials will eventually be in place.

### **Gene Therapy Study Results**

**Leber.** Three different Leber gene therapy studies, each with a different team of scientists, were published last year.<sup>1-4</sup> In one study, funded by the National Eye Institute, researchers found that day vision improved 50-fold and night vision by 63,000-fold in three patients, compared with pre-treatment levels 90 days earlier.<sup>3,4</sup> All subjects in the study were adults with significant visual impairment from birth due to the RPE65 mutation.

### **WHERE TO GO FOR TESTING**

Many large universities with retinal eye centers have genetic counselors on staff who help arrange for genetic testing. Ophthalmologists can also find centers that offer genetic testing through the National Eye Institute, [www.nei.nih.gov](http://www.nei.nih.gov), the Foundation Fighting Blindness, [www.blindness.org](http://www.blindness.org) and through GeneTests, [www.genetests.com](http://www.genetests.com).

They all received subretinal injections to replace the nonfunctioning gene with an adeno-associated virus gene vector. Only one patient experienced an adverse event—an asymptomatic macular hole, which may or may not have been due to gene therapy.<sup>1</sup> Despite this event, the patient’s retinal function improved.

“These trials demonstrate the potential benefits of gene therapy for treating ocular disease,” said Paul A. Sieving, MD, PhD, director of the NEI. “They have also caught the attention of researchers working on gene therapy in other disciplines. Although there’s still a long way to go in understanding the biology of the disease treated in these trials, we are encouraged by their success,” he said.

**Targeting younger Leber patients.** Researchers are now hoping to extend the benefits of gene transfer to children with Leber because young patients are most likely to benefit, given that the degeneration of their retinas is at an earlier stage than most adults with the disease, said J. Timothy Stout, MD, PhD, MBA, vice president of commercialization strategies at Oregon Health & Science University in Portland and professor of ophthalmology at OHSU’s Casey Eye Institute.

Children with Leber are already being treated in one gene therapy trial at Children’s Hospital of Philadelphia, Dr. Drack said.

**Studies for other dystrophies.** Research is under way on gene therapy for other retinal dystrophies, including Stargardt disease. “These trials are very encouraging for a variety of reasons,” Dr. Stout said. “Gene therapy has struggled in the past because of safety issues. But we’ve come a long way in making sure the vectors that are introduced with gene therapy are much safer than they were

years ago. Second, this is a population of patients with a blinding disease, and we know that we have a delivery system that targets the right cells. It points the way toward therapeutic options,” he added.

**On the near horizon.** Dr. Stout is one of several researchers who will be overseeing a new multicenter trial that will attempt gene therapy for patients with the RPE65 mutation. The trial will use an adeno-associated virus vector to deliver the treatment and will be used first in adults. If the treatment proves safe, it will be expanded to cohorts of patients aged 8 to 18. The patients will be followed closely by the study’s data and safety monitoring committee and the FDA. Dr. Stout anticipates following all the patients enrolled in four different cohorts of the trial for 15 years or more.

Dr. Stout reiterated the disappointments of the past as well as the glimmers of optimism for patients who otherwise have none. “The field of gene therapy has not had a completely smooth course. But we think and hope that gene therapy for Leber congenital amaurosis may safely treat patients for whom there is no therapeutic alternative,” he said. “We hope it will really push the cause of treating genetic retinal dystrophies forward.”

1 Maguire, A. M. et al. *N Engl J Med* 2008;358(21):2240–2248.

2 Bainbridge, J. et al. *N Engl J Med* 2008;358(21):2231–2239.

3 Cideciyan, A. V. et al. *Proc Natl Acad Sci* 2008;105(39):15112–15117.

4 Hauswirth, W. W. et al. *Hum Gene Ther* 2008;19:979–990.

## MEET THE EXPERTS

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