Jules Stein Eye Institute
U C L A

Clinical Update

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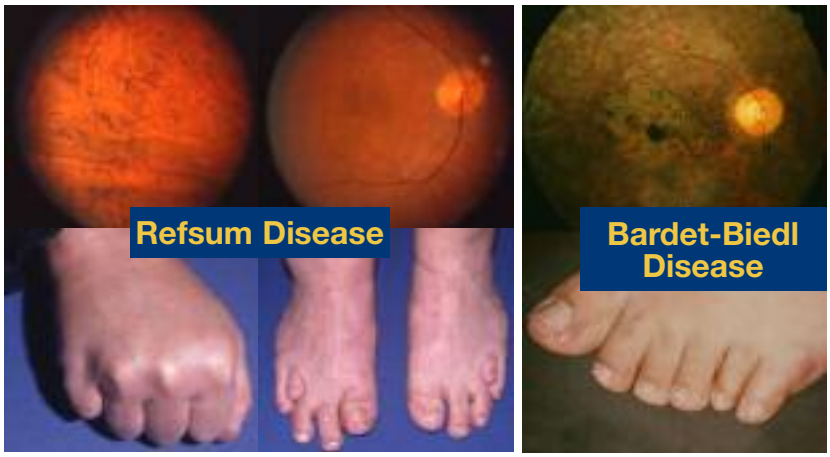
Integrating Molecular Genetics in Ophthalmic Practice



Right: Look beyond the eye findings to determine if other abnormalities may define a syndrome. Note the abnormal hands and feet in these two cases of progressive retinal degeneration. The first case is a woman with Refsum disease, a treatable form of retinal degeneration due to an inability to metabolize phytanic acid. The second case is a patient with mutations in both copies of one of the 11 known genes that cause Bardet-Biedl disease, which is associated with polydactyly, truncal obesity, hypogonadism, mental retardation and renal disease.

As more information emerges about molecular genetics and eye diseases, ophthalmologists should become well-versed in the role genes play in a wide range of disorders and obtain thorough and accurate family histories from their patients, according to Michael B. Gorin, M.D., Ph.D., the Harold and Pauline Price Professor of Ophthalmology at UCLA's Jules Stein Eye Institute. Dr. Gorin says many molecular diagnostic tests can now help determine whether patients and their family members are at risk for particular diseases. However, clinicians must recognize the impact these tests can have on families and patients, the limitations of these tests, and the need to recognize when molecular diagnostic testing may not be appropriate.

"We now know that many genetic conditions are encountered in ophthalmology practice," says Dr. Gorin. Some are straight forward, including congenital cataracts and congenital glaucoma, hereditary corneal and retinal dystrophies, retinoblastoma, and genetic syndromes with ocular findings. Increasingly, though, other conditions are proving to have a strong genetic component. These include conditions as common as non-congenital glaucomas, age-related macular degeneration, common and pathologic myopia, amblyopia and strabismus. Moreover, Dr. Gorin notes, "When you look deeper, you realize that genetics contribute to age-related cataracts and uveitis, and that a number of other conditions have genetic components we have yet to understand, including vaso-occlusive disease and diabetic retinopathy."

Molecular ophthalmic genetics refers to the identification of variations in specific genes that contribute to the risk for developing ocular disease and/or modifying the response to medications. The simple model — a variant in a single gene almost guaranteeing a certain disease — rarely applies to the many, more common conditions ophthalmologists observe, Dr. Gorin notes. Even with monogenic disorders, such as retinitis pigmentosa, there can be incomplete penetrance, in which persons have the mutation and never develop the disease. In variable expressivity, individuals with the same disease-causing mutation experience a range of severity of ocular findings. In addition, interactions

(continued on page 2)

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MOLECULAR GENETICS

(continued from page 1)

between genes and the environment, and among genes and other genes, can play a role in whether a person develops a disease and how severe it becomes.

Thorough Family History, Recognition of Risk Factors

Integrating genetics into practice starts with recognizing the genetic contributions of the diseases the ophthalmologist observes, including both the genetic risk factors and the potential interactions of genetics and non-genetic factors.

"We know, for example, that people with Marfan syndrome have very weak lens zonules and only a subset of these individuals have readily apparent dislocated lenses," says Dr. Gorin. "If you were to do cataract surgery on an asymptomatic individual and not recognize that the person had Marfan syndrome, it could lead to a poor surgical outcome."

Simply asking the patient whether he or she knows of anyone in the family with an eye problem is often insufficient, due to a lack of systematic recall and knowledge about the health of other family members. Even if the pedigree is incomplete, Dr. Gorin says, the ophthalmologist should consider all of the possibilities and understand how the information that does exist affects the probabilities of genetic risk; know which key people within a family would provide the most useful additional information; and engage the patient in getting that additional family history data. It's also important to look beyond the ocular findings.

"A lot of eye conditions are associated with other diseases," Dr. Gorin says. "We may be worried about the eye, but we also don't want our patient to suffer a stroke."

In some cases, the existence of good treatments or preventive measures renders early recognition of genetic risk factors particularly critical. These include amblyopia, strabismus, vaso-occlusive disease (MTHR and Factor V-Leiden mutation) and glaucoma. A positive family history can be sufficient to lead to earlier and more careful screening. "For example, if a 75-year-old patient has macular degeneration and a family history, it would be worthwhile to look at the patient's asymptomatic adult children for evidence of high-risk features of the disease in their retina and, if found, consider placing them on preventive therapy," Dr. Gorin says.

Similarly, patients diagnosed with glaucoma should be encouraged to alert their siblings to the possibility that they may be at increased risk and could benefit from testing and closer monitoring.

Full Implications of Seeking DNA Tests Must Be Appreciated

The list of available diagnostic DNA tests is constantly growing. Dr. Gorin asserts that the clinician should carefully assess the pros and cons of testing and discuss these concerns with the patient or enlist the assistance of a genetic counselor or ophthalmic geneticist. In some cases, genetic tests can be very helpful to either clarify a diagnosis in a symptomatic patient or to identify individuals who may need life-long medical surveillance for disease-related problems.

Molecular diagnostic screening for Von Hippel-Lindau syndrome in at-risk family members can be life-saving and highly cost-effective: DNA testing can eliminate half of the potential individuals who may require life-long imaging and diagnostic studies for brain lesions and renal cancer. For families with a history of retinoblastoma, molecular diagnostic testing can identify whether children who have not yet developed the disease might be at increased risk; children shown to not carry the familial mutation in the retinoblastoma gene can avoid the need for multiple examinations under anesthesia.

DNA testing can also play a role in rare genetic conditions that are treatable, Dr. Gorin notes. Refsum's disease and gyrate atrophy, for example, are often confused with more common retinal degenerations; establishing the molecular diagnosis can lead to therapy that preserves vision.

However, many issues should be considered before ordering a test. "These tests can have enormous implications," Dr. Gorin says. "It's very important to be aware of the psychological consequences of a positive test result, including guilt, anger and depression. Often people won't raise the questions before being tested, or they don't know what to ask. Genetic counseling needs to take place both before and after the tests, and a great deal of consideration needs to go into whether getting tested is the right thing to do." Most molecular diagnostic testing is not definitive, Dr. Gorin adds.

Further, molecular testing has implications for more than just the patient; a positive result means that family members may also be at risk. Ophthalmologists must remain sensitive to the implications of genetic test results for these other individuals. Despite legislation that is intended to prevent genetic discrimination, there remain concerns that employers and insurers may use molecular test results to affect hiring and coverage practices, even if the individuals have no evidence of current manifestation of the disease.

(continued on page 4)

New Faculty

It is a great pleasure to announce the appointment of three full-time faculty members to Jules Stein Eye Institute's clinical divisions. The new appointments were effective July 1, 2007.

Sophie X. Deng, M.D., Ph.D., has been appointed Assistant Professor in the Cornea and Uveitis Division. Dr. Deng received a joint M.D. and Ph.D. through the University of Rochester's rigorous Medical Scientist Training Program. She studied immunology during her doctoral dissertation research. Dr. Deng completed her residency at the Illinois Eye and Ear Infirmary in Chicago, where she conducted a study on the use of intravitreal methotrexate in the treatment of inflammatory eye diseases that won the 2005 Beem Fisher Award, First Place, from the Chicago Ophthalmologic Society. She was awarded the prestigious Heed Fellowship in 2005. Upon completing fellowship training in corneal and external ocular diseases and refractive surgery at Jules Stein Eye Institute, she became a staff physician in its Cornea and Uveitis Division. In her new faculty position, she will continue patient care and her research in ocular surface reconstruction using regenerative medicine.

Referrals: (310) 206-7202

JoAnn A. Giaconi, M.D., has been appointed Assistant Clinical Professor of Ophthalmology in the Glaucoma Division. Dr. Giaconi received her medical degree from Columbia University in New York and completed a residency in ophthalmology at Stanford University Hospital. After completing a fellowship in Cornea and Refractive Surgery at the Bascom Palmer Eye Institute, University of Miami, she came to Jules Stein Eye Institute, where she completed a second fellowship in glaucoma. Dr. Giaconi has provided medical and surgical care to patients as an Associate Physician in both the Institute's University Ophthalmology Associates and Glaucoma Division for the past three years, while concurrently participating in the Institute's medical student education and residency programs at Harbor-UCLA Medical Center and the Department of Veterans Affairs Greater Los Angeles Healthcare System in West Los Angeles. As a full-time faculty member of the Glaucoma Division, she will continue her activities in patient care, teaching and research into the effect of glaucoma surgery on the corneal endothelium.

Referrals: (310) 794-9442

David Sarraf, M.D., has been appointed Associate Clinical Professor of Ophthalmology in the Retina Division. Dr. Sarraf received his medical degree from the University of Toronto in Canada. He completed an ophthalmology research fellowship at Jules Stein Eye Institute, followed by residency training in ophthalmology at the University of Chicago's Pritzker School of Medicine. He completed a fellowship in Medical Retina and Uveitis at Moorfields Eye Hospital at the University College London, returning to Los Angeles in 1998 as Assistant Professor of Ophthalmology at Martin Luther King Medical Center, Charles Drew University School of Medicine, and as clinical staff at Jules Stein Eye Institute. During the past nine years, Dr. Sarraf has provided medical retina services in the Institute's University Ophthalmology Associates, and has participated in its medical education and residency training programs, for which he received the JSEI Faculty Teaching Award in 2006. He will continue his patient care, research and teaching activities as a full-time member in the Retina Division.

Referrals: (310) 825-5000

MOLECULAR GENETICS

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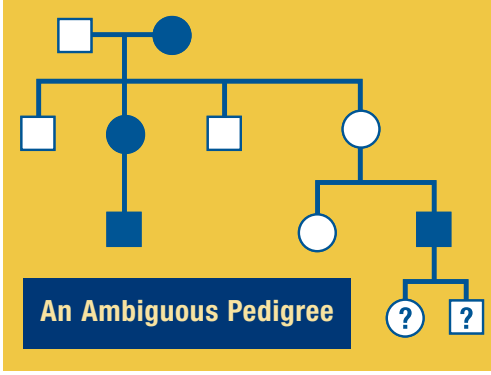

This could be an autosomal dominant inheritance pattern, but there are no cases of male-to-male transmission. If the females have milder disease than the males, then they could be symptomatic carriers of an X-linked condition. This would greatly change the risk assessment for the two unknown "?" children. If autosomal dominant, then they would each have a 50-50 chance of having the condition. If X-linked, the boy (square) would be unaffected and the girl (circle) would be an obligate carrier of the disorder.

"We encourage families to participate in genetics research at the JSEI and we make sure that our studies have Certificates of Confidentiality from the NIH in order to provide an extra layer of privacy protection for our participants," Dr. Gorin says. He also recommends that private practitioners establish their own "research registry" for patients with genetic diseases. Simple to set up and in compliance with HIPAA regulations, such a registry enables the practitioner to contact patients whenever new information on their disease becomes available, or opportunities arise to become involved in research.

Dr. Gorin believes that ophthalmologists should use genetics to help patients and their families maximize the quality of their lives and minimize the impact of disease.

"We want to make genetic diagnoses not to 'label' people," he concludes, "but to better determine prognosis and optimal treatment, and to recognize other potential life-threatening and/or treatable complications for patients and their family members."

Recent Publications

Gorin MB. A clinician's view of the molecular genetics of age-related maculopathy. *Arch Ophthalmol* 2007;125(1):21-9.

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