

Macular Degeneration, Age-Related

TO DETERMINE GENETIC RISK FOR DISEASE

Disease Overview

- Age-related macular degeneration (AMD) is a retinal degenerative disease resulting in progressive central vision loss most commonly developing after age 60. The central vision loss is caused by degeneration of the photo receptor cells in the macula (central portion of the retina).
- There are two types of AMD: dry and wet.
 - Dry AMD represents 90 percent of cases. This type occurs when drusen (fatty waste products of photoreceptor cells) accumulates within the retinal pigment beneath the macula. Dry AMD occurs gradually over many years; there is no known effective treatment.
 - Wet AMD accounts for 10 percent of cases. In this type of AMD, abnormal vessels grow beneath the macula, leaking blood and fluid into the macula. If diagnosed early, laser surgery may prevent extensive central vision loss.
- AMD is the main cause of blindness and severe visual impairment among the elderly in developed countries, and is a significant economic burden to the United States Medicare system.
- Known risk factors include: smoking duration, a body mass index (BMI) of 25 or more, sunlight exposure, female gender, increased age, Caucasian ethnicity, low socioeconomic status or educational level, and cardiovascular disease.
- Specific gene variants have been associated with predisposition to or protection against disease.
- Symptoms begin with central vision blurring, progressing to blind spots. If one eye is affected, the other is likely to develop the same symptoms.

Epidemiology

- AMD prevalence in individuals over 40 years of age: Caucasians, 9.3 percent; African-Americans, 7.4 percent; and Hispanics, 7.1 percent.
- AMD prevalence increases from 1.6 percent at 52–64 years to 11 percent at 65–74 years and 28 percent at greater than 74 years of age.

Genetics

- Inheritance of AMD is largely multifactorial.
- Two single nucleotide polymorphisms (SNP), Y402H and A69S, are independent risk factors for the development or progression of AMD. Together, they comprise approximately 70 percent of the risk for AMD
- Y402H (c.1277T>C) is in the complement H factor (*CHF*) gene, where histidine is substituted for lysine.

- A69S (c.205G>T) is located in the age-related maculopathy susceptibility 2 (*ARMS2*) gene, which is also known as LOC387715.
- Heterozygosity for either A69S or Y402H predicts a 2.8-fold (95 percent CI: 2.5–3.3) and 2-fold (95 percent CI: 2.0–2.6) increased risk for AMD, respectively.
- Heterozygosity for both Y402H and A69S is reported to cause a 5.8-fold (95 percent CI: 4.4–7.7) increased risk for AMD.
- Homozygosity for either A69S or Y402H increases the risk for AMD by 8.1 fold (95 percent CI: 6.0–10.9) and 7.1-fold (95 percent CI: 5.3–9.5), respectively.
- Homozygosity for both Y402H and A69S predicts a 57-fold (95 percent CI: 37.2–89.0) increased risk for AMD.

Indications for Ordering

- To predict likelihood of disease progression in individuals affected with early stage AMD.
- To provide incentive for lifestyle modification in individuals with high-risk genotypes.
- To determine risk for AMD in individuals with a positive family history.

Contraindication

- This test is not recommended for asymptomatic minors.

Interpretation

- Homozygous, heterozygous, and negative genotypes are reported.
- If neither Y402H nor A69S is detected, a low genetic risk for AMD development or progression is predicted.
- Heterozygosity for A69S or Y402H is associated with a mildly increased genetic risk for AMD development or progression.
- Homozygosity for A69S or Y402H, or compound heterozygosity at both loci (A69S/Y402H), is consistent with a moderately increased genetic risk for AMD development or progression.
- Homozygosity for both A69S and Y402H is consistent with a high genetic risk for AMD development or progression.

Methodology

- Polymerase chain reaction and fluorescence monitoring to detect p.Y402H (c.1277T>C) in *CHF* and p.A69S (c.205G>T) in *ARMS2*.
- Clinical sensitivity and specificity are unknown.
- Analytical sensitivity and specificity are 99 percent.

Limitations

- Detects only the two most common genetic variants associated with AMD.
- The variants tested are associated with risk for AMD, but may not be causal for the disorder.
- Analytical sensitivity may be compromised by rare primer- or probe-site mutations.

References

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2. Foundation Fighting Blindness. www.blindness.org (accessed on July 11, 2007).
3. Seddon JM, et al. Association of CFH Y402H and LOC387715 A69S with progression of age-related macular degeneration. *JAMA* 2007;297;16:1793–1800.
4. Yu J, et al. Biochemical analysis of a common human polymorphism associated with age-related macular degeneration. *Biochemistry* 2007;46(28):8451–61.
5. DeWan A, Liu M, et al. HTRA1 promoter polymorphism in wet age related macular degeneration. *Science* 2006;314:989–92.
6. Rivera A, et al. Hypothetical LOC387715 is a second major susceptibility gene for age-related macular degeneration, contributing independently of complement factor H to disease risk. *Hum Mol Gene* 2005,14:3227–36.

Test Information

0051674

Macular Degeneration, Age-Related, DNA Variants

For specific collection, transport, and testing information, refer to the ARUP Web site at www.aruplab.com.

For information on test selection, ordering, and interpretation, refer to ARUP Consult® at www.arupconsult.com.