Age-related maculopathy: What it is, what we know, what we need to learn

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The Eye
Macular Degeneration is a great example of eye research

- Condition affects millions of people
- Cause and cure are unknown
- Research has made incredible advances, especially due to the Human Genome Project
- New diagnostics and treatments are having a major impact on patient care
- We face a number of challenges that require additional research
What is macular degeneration?

- The eye uses the cornea and lens to focus light on the back surface of the eye (retina).

- The central portion of the retina (macula) is essential for reading vision and recognizing faces.

- **Macular degeneration** refers to a collection of conditions that cause progressive damage to the macular portion of the retina.

- **Not all** conditions that damage the macula are considered macular degeneration.
What the doctor sees in your eye

- A Normal Retina
- Optic nerve
- Retinal blood vessels
- The macula
- Fovea - the center of vision
The Retina

RPE: a single cell layer beneath the retina, maintains the retina

Choroid: a vascular meshwork that provides crucial blood flow
What is Age-Related Macular Degeneration?

- Age-related maculopathy (ARM) refers to changes in the retina and adjoining pigment epithelium with or without vision loss.

- Age-related macular degeneration (ARMD, also known as AMD or SMD) is included within age-related maculopathy but has the requirement that there is vision loss resulting from the changes in the back of the eye.
Features of Age-Related Macular Degeneration

- DRY ARM or AMD
  - Drusen - deposits of material under the retina
  - Pigment disturbances - changes in the retinal pigment epithelial (RPE) cells under the retina from chronic injury
  - Pigment epithelial detachments - blisters that form under the retina and pigment epithelium
  - Geographic atrophy - areas in which the pigment cells become unable to function properly and the retina can no longer see in those locations
Age-related Macular Degeneration

**DRY FORM:**
- Drusen - soft / hard
- Pigment epithelial detachment
- Geographic atrophy
Features of Age-Related Macular Degeneration

- **WET AMD**
  - Choroidal neovascular membranes - blood vessels that grow from the vascular meshwork under the retina and spread under the pigment epithelium and/or retina leading to leakage and bleeding and scarring (Disciform scars). These vessels are not tumors.
Treatments for dry ARM

- NEI-funded AREDS I study - successful
- The AREDS II study - just starting
- Laser of drusen - disproven
- Rheophoresis - unproven, under study

- We have a long way to go....
Age-related Macular Degeneration

WET FORM:
Choroidal neovascular membrane
Disciform scarring
Treatments for wet AMD

**Old therapies**
- Laser to cauterize the vessels,
- "cold" laser with a dye to chemically close the vessels

**New therapies (within the past 5 years)**
- Anti-VEGF therapies - have revolutionized therapy
  - Dramatically slows or halts the vessels
  - Actually can restore vision in many cases
  - Requires multiple treatments, sometimes monthly for years
  - Doesn’t necessarily stop the progression of the underlying disease
Diagnostics for AMD

- **Traditional**
  - Fluorescein angiography
  - Indocyanine green angiography

- **New developments (in the past 5 years)**
  - **Optical coherence tomography**
    - noninvasive method for detecting leakage in the wet form of AMD -
    - 3 D systems with better sensitivity and resolution are being introduced this year by several companies
  - **Retinal autofluorescence** (Heidelberg retinal tomography)
    - (to distinguish types of ARM) - more research is needed
OCT - optical coherence tomography

From the Macula Foundation, Inc.
High-resolution OCT - from Schmidt-Erfurth et al. (2005) IOVS; 46:3393-3402
HRT- Retinal Autofluorescence
Risk Factors

- Smoking - 2.5 fold increased risk
- Family History - 6 to 12 fold increased risk
- Controversial evidence for increased risk:
  - Light exposure
  - Diet
  - Hypertension
  - Cataract surgery
Genetic Evidence for AMD

- **Epidemiologic studies**
  - Consistently have shown family history as a risk factor
  - There is genetic heterogeneity of familial risk

- **Twin studies**
  - Nearly 100% concordance of disease in monozygotic twins

- **Family history of AMD patients**
  - Gass reported that 20% of AMD patients had a positive family history, confirmed for 10%.

- **Linkage studies of ARM families**
  - Replication of several loci by multiple studies

- **Genome-wide and candidate specific association studies**
  - CFH, LOC387715/HTRA1, C2, BF, C3, others
What’s so great about a genetics approach to AMD

- Genetic strategies allow us to approach susceptibility genes with or without a biological hypothesis.

- We can estimate the extent to which heredity contributes to disease susceptibility.

- Genetics provides a means of testing both the extent to which a gene and its variant(s) are associated with a disease state, as well as the attributable risk of that variant to the disease as a whole.
Publications - AMD genetics

- We started collecting our ARM families
- 1st genome-wide linkage study
- Complement factor H
- LOC387715
- C2 & BF
- Htra1
- C3
What ARM genetics has meant to the scientific community

- The study of the genetics of ARM has been the most outstanding success story for the application of modern molecular genetics to the study of a common chronic late-onset disease.

- It has been a model for studies of diabetes, obesity, atherosclerosis, dementia, mental health disorders, and other conditions.
Risk of age-related macular degeneration (AMD) as a function of the risk variants. Odds ratios based on the logistic regression model by Maller et al are calculated relative to a reference group (R), which has a post-test AMD risk equal to the population risk of AMD in persons aged 65 years or older (3%).

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What limits the value of predictive models

- The costs, risks, effectiveness of preventive therapies
- The relevance of the preventive therapy to general health and appropriateness for the total population.
- Compliance issues among an asymptomatic population
- Fears of social, insurance or employment discrimination
- The age at which a person is likely to adopt a preventive program and its relative effectiveness and cost as a function of years of adherence.
- The costs of therapy and rehabilitation for individuals who go on to advanced disease.
Evidence for additional genes

- Low prevalence of CFH risk alleles in Asian population (though the LOC387715 alleles do confer risk)
- There are several genes which have been reported to have variants that have not yet been replicated
- Many people with these “risk” alleles do not develop ARM.
- We still don’t know what makes the condition specific to the eye
- The next set of ARM-related genes are going to be more difficult to find
Proof

- You can only “prove” that a gene and its variants are causative of a complex disorder when you have exhausted every means at your disposal to prove that it is not a causative gene.

- Even when you are done, the final proof may simply be a statistical argument until there is a sufficient understanding of the biology to unite a set of contributory genes.
How might we use genetic testing for ARM

- Identify high-risk individuals to test preventive therapies more cost effectively and quickly.
- Identify high-risk individuals who might benefit from preventive therapy (particularly if the therapy has significant risks and/or costs).
- Use genetic testing to identify which individuals are more or less likely to respond to current therapies so that one might modify the treatment plans accordingly.
How do we use this knowledge of genetics now?

Consider the use of vitamin and nutrient supplements in individuals with mild ARM, but with a positive family history. Keep in mind that the efficacy of these nutrients is not established for these individuals.

Recent studies have shown that, given the high cost of treating wet macular degeneration, there is a cost-benefit for implementing preventive nutritional therapies even if they cause only a modest reduction in the incidence of advanced ARM.
How do we use this information for the benefit of patients in the future

We need to do a better job of distinguishing AMD from other causes of macular degeneration such as post-infectious or other hereditary dystrophies.

Can we develop better diagnostic tools for distinguishing ARM from similar conditions that may require different treatment or have a different prognosis?
How do we use this information for the benefit of patients in the future

- We need to know if the treatment of endstage disease (CNV) should be the same for people with different genetic risk factors.

- There was a report at ARVO 2007 that patients homozygous for the high risk CFH alleles had poorer outcomes in the treatment for CNV. However this would not necessarily dictate a different course of treatment for these individuals (based on their genetics alone).
How do we use this information for the benefit of patients in the future

• For a person with a high genetic risk (either family history or genetic variants) and no clinical evidence of disease
  • Should we counsel them to take preventive therapies?
  • There is no current evidence for efficacy
  • We need to understand the impact of other factors: risks, costs, patient’s anxiety, general health

• We need to know if the risk of progression of mild disease could be very different depending on the genetic background.
  • Some ARM preventive therapies may not be as effective for some genetic subsets of patients. Would this be a rationale for not offering them these therapies?
• We need to pay greater attention to the mitigation of the underlying disease processes of ARM, rather than attempting to control endstage complications (such as CNV and/or GA).

• A single therapeutic approach for prevention may not be feasible and there may be unanticipated consequences of any specific approach.
Should we be doing genetic testing now?

**NO  NO  NO**

- At the current time, we lack the information to properly counsel someone as to their risk of developing ARM based on having a specific genetic variant.

- A negative test result doesn’t mean that the person is not at risk for ARM and we lack the information to interpret negative results properly.

- Genetic testing might be appropriate if we had a definite therapy to prevent or retard ARM. It may be unnecessary if the therapy has minimal risks/costs and would be beneficial to the general public.
Testing without counseling can cause needless anxiety and stress for patients (and unnecessary medical costs). We may find that some of the risk factors for ARM are also risk factors for conditions that pose even more serious personal and social problems (such as Alzheimer disease).

Encourage patients with family histories of ARM to participate in clinical trials for preventive therapies. High risk cohorts can allow these studies to be done rapidly and in a cost efficient manner.
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