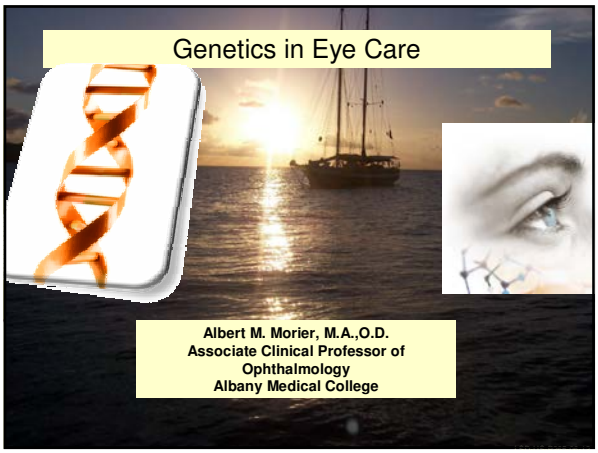
Genetics in Eye Care



Albert M. Morier, M.A.,O.D.
Associate Clinical Professor of Ophthalmology
Albany Medical College

Financial disclosure

- Genzyme Pharmaceuticals

Genetics- Gregor Mendel

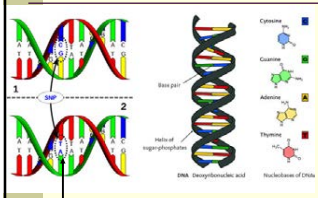
Discovered genetics, traits, dominant, recessive

Watson and Crick 1953

They walked into the Eagle Pub in Cambridge, Crick announced, "We have found the secret of life."

Nobel Prize in Physiology or medicine 1962

Watson and Crick 1953



DNA is packaged into chromosomes. We have 2 sets of 23 chromosomes that we inherit from our parents. Each chromosome has 2 strands that are held together by links (chemical bonds) between 4 chemical bases or "nucleotides". These bases fall into 2 groups.

C ↔ G A ↔ T

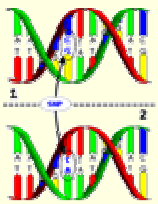
The **pyrimidines** (cytosine and thymine) and the **purines** (guanine and adenine). Cytosine on one strand and guanine on the other are always are bound to each other. Likewise, adenine and thymine bind to one another

Bases are switched

Single nucleotide polymorphisms

Inherited sites of sequence variability where the new base occurs over 1% of the time are referred to as "single nucleotide polymorphisms" **(SNPs)**

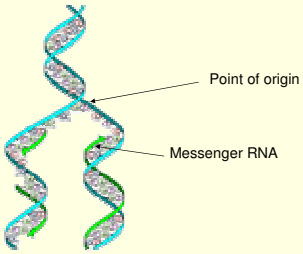
Associated SNPs on a chromosome are called a **Halotype**



- In human DNA, a portion (25%) is organized into approximately 30,000 functional units (genes), which code for the structure of different proteins. The order or sequence of the bases in a gene determines the composition of proteins. If an error during DNA replication occurs (a "mutation"), the "code" becomes altered and the composition and function of the proteins specified by the DNA sequence may be compromised.

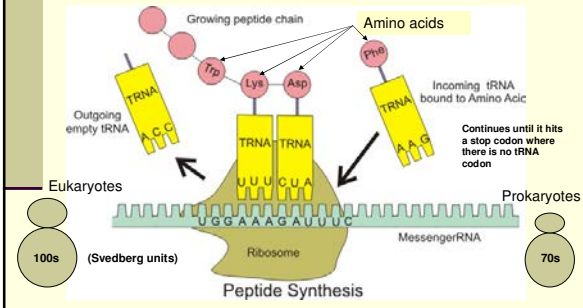
- These base changes ("polymorphisms") have been introduced into mankind's genes (the "gene pool") as "spelling mistakes". Some of these changes are deleterious and cause disease, others are neutral and have no discernable effect on human health and others may actually result in functional improvement in certain environments.

DNA Replication



Protein synthesis

The ribosome moves along the mRNA, "reading" its sequence and producing a corresponding chain of amino acids.



Human Genome Project

- **Human Genome Project**
  - HGP: Project completed 2003; human genome available online
    - 3 billion base pairs
      - Less than 2% of the genome codes for proteins
    - 20,000-30,0000 genes
      - Functions are unknown for many
    - > 200 mapped and cloned ocular disorders

State of the Genome

- Two unrelated people share 99.5% of their DNA sequences, the remaining % is unique → genetic variants that influence response to drug or disease.

New terms

- **Proteomics** - study of proteins encoded by the genome
  - Not only i.d., but determination of localization, interactions, activities → ultimately function
- **Pharmacogenetics**
  - Genes affected drug metabolism
- Personalized medicine
- Impact of medication on individual, based upon genetic make-up

How will this change patient care?

- Improve understanding of pathogenesis
- Mutations that make us *susceptible to particular conditions* will be identified
  - Ex: Glaucoma
- Understanding of disease processes will improve
  - Ex: Retinitis Pigmentosa

Why test?

- **Symptomatic patient:**
  - Establish or confirmation a diagnosis
- **Presymptomatic patients: predictive testing**
  - Allow clinician to determine if pt is **predisposed** to or affected with specific type of glaucoma, even before symptoms appear

Importance for Optometry

Being aware of the genetic aspects of common ocular and systemic diseases seen in clinical practice

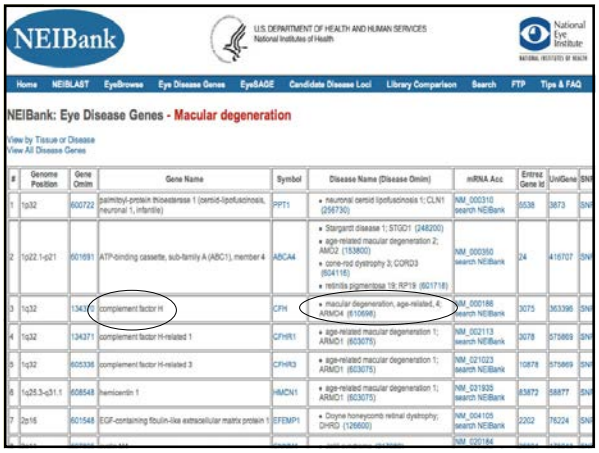
Direct marketing of genetic tests to consumers and potential patients

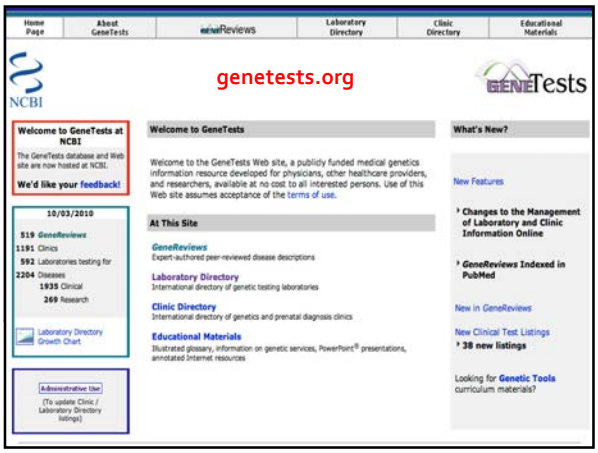
New diagnostic and treatment options are increasingly available and accessible

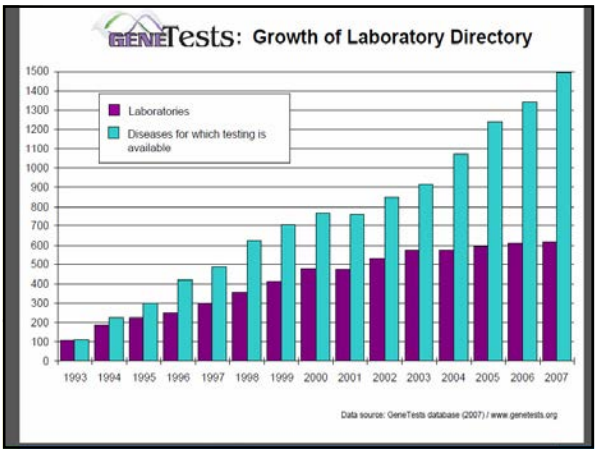
I want to know about them!

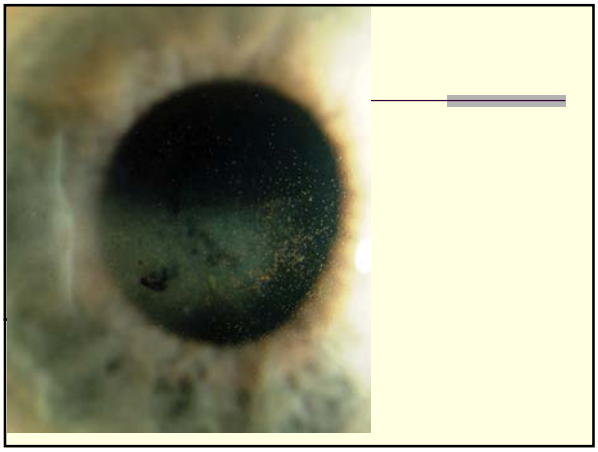
State of the Genome

- National Eye Institute (NEI) Bank: gathers and organize genomic resources for eye research
  - Current databases for human eye tissues
    - OMIM™ Online Mendelian Inheritance in Man
      - Catalogues all known genetic diseases & links them to genes in the human genome
    - RetNet™ Retinal Information Network
      - tables of genes and loci causing inherited retinal diseases

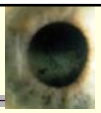






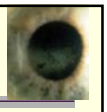


Fuch's Dystrophy



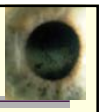
- Fuchs corneal dystrophy (FCD) accounts for the majority of corneal grafts in the United States.
- Corneal guttae, the hallmark of FCD, are present in approximately 5% of individuals over the age of 40 years.

Fuch's Dystrophy

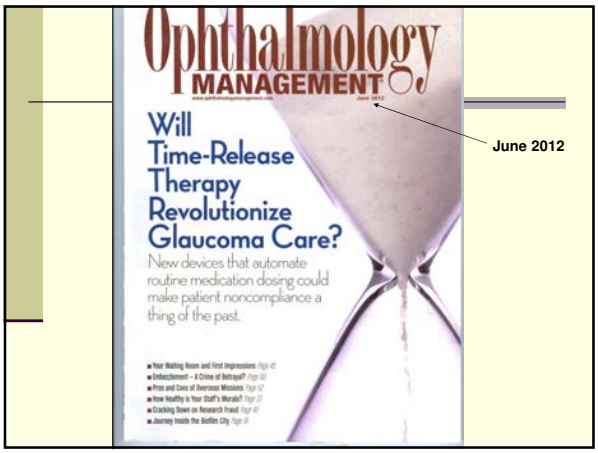


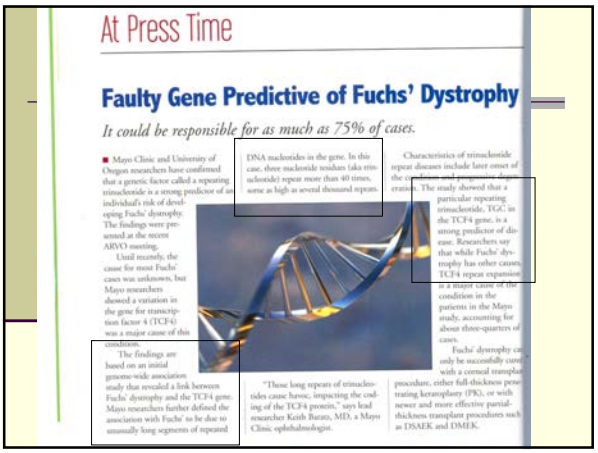
- Keith Baratz, MD and William Brown, O.D. of the Mayo Clinic Department of Ophthalmology and collaborators at the University of Oregon and University of Michigan, however, has discovered a strong association between the transcription factor 4 gene (TCF4) on **chromosome 18 and FCD**.

Fuch's Dystrophy



- A genome-wide association study (GWAS) compared 100 affected study participants with 200 controls. GWAS techniques identify genetic variation of individual alleles, or single nucleotide polymorphisms, at thousands of sites along the entire genome.
- This study allowed a simultaneous comparison of 330,000 alleles between the affected and unaffected subjects. The strength of the association between FCD and variation at the TCF4 gene was unprecedented. The TCF4 gene may be responsible for 75% of FCD
- They found repeating trinucleotides (40x's to several thousands x's) reeks havoc in the TCF4 gene.



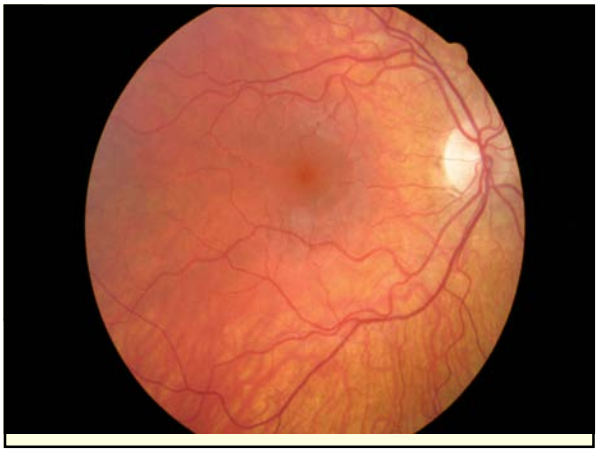


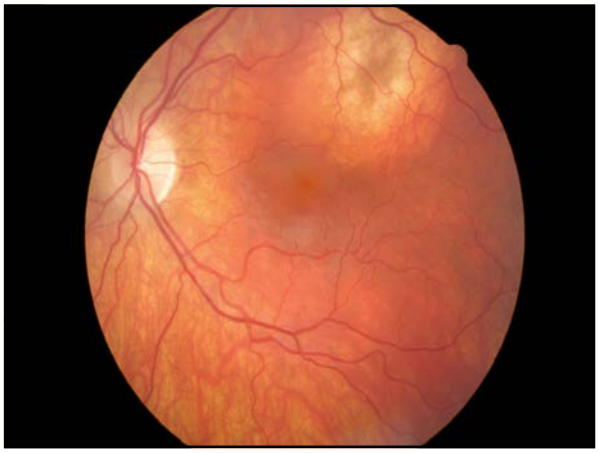
Case 1

- 1/29/2010- SV, a 29 y.o. female presents for a routine eye exam.
- Symptoms- slight DV blur
- Negative health hx.
- Vsc- 20/25 OU
- Vcc- 20/20
- .2 C/D OU, IOP 18 mmHg OU NCT

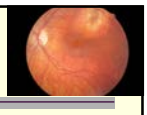
Case 1

- 3/27/2012- SV returns for a second visit as she feels a "pressure and blurred vision" in her left eye. Also, she has a different color perception OS
- Health hx- 9 month post partum
- Vcc -20/20 OD, 20/30 OS
- IOP- 21,20 mmHg applanation
- Dilated fundus reveals…



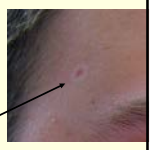


Case 1



- SV was referred to a retina specialist
- Lesion OS shows minimal elevation with OCT with significant edema
- Angiogram shows that it is not vascular
- Differential diagnosis

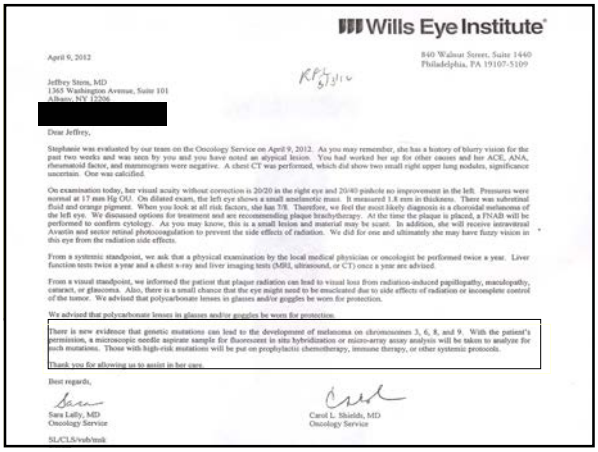
1. **amelanotic halo nevus with associated central serous retinopathy**
2. **a granulomatous lesion**
3. **a metastatic tumor**



White blood cells "attack" the nevus

Case 1

- Referred to Carol Shields, MD at Wills (4/9/12)
- ANA, ACE, rheumatoid factor and mammogram were negative
- Chest CT showed 2 small nodules (one calcified) on right upper lung. Significance is uncertain.
- Dx was <u>choroidal melannoma</u>
- Plaque therapy was performed
- Intravitreal Avastin was injected and sectoral photocoagulation to prevent effects of radiation (maculopathy, papillopathy, cataracts and glaucoma.



Wills Eye Institute

840 Walnut Street, Suite 1440
Philadelphia, PA 19107-5109

April 6, 2012

Jeffrey Stern, MD
1365 Washington Avenue, Suite 101
Albany, NY 12206

[redacted]

Dear Jeffrey,

Stephanie was evaluated by our team on the Oncology Service on April 9, 2012. As you may remember, she has a history of blurry vision for the past two weeks and was seen by you and you have noted an atypical lesion. You had worked her up for other causes and her ACE, ANA, rheumatoid factor, and mammogram were negative. A chest CT was performed, which did show two small right upper lung nodules, significance uncertain. One was calcified.

On examination today, her visual acuity without correction is 20/20 in the right eye and 20/40 pinhole no improvement in the left. Pressures were normal at 17 mm Hg OU. On dilated exam, the left eye shows a small amelanotic mass. It measured 1.8 mm in thickness. There was subretinal fluid and orange pigment. When you look at all risk factors, she has T/8. Therefore, we feel the most likely diagnosis is a choroidal melanoma of the left eye. We discussed options for treatment and are recommending plaque brachytherapy. At the time the plaque is placed, a FNAB will be performed to confirm cytology. As you may know, this is a small lesion and material may be scant. In addition, she will receive intravitreal Avastin and sector retinal photocoagulation to prevent the side effects of radiation. We did for one and ultimately she may have fuzzy vision in this eye from the radiation side effects.

From a systemic standpoint, we ask that a physical examination by the local medical physician or oncologist be performed twice a year. Liver function tests twice a year and a chest x-ray and liver imaging tests (MRI, ultrasound, or CT) once a year are advised.

From a visual standpoint, we informed the patient that plaque radiation can lead to visual loss from radiation-induced papillopathy, maculopathy, cataract, or glaucoma. Also, there is a small chance that the eye might need to be enucleated due to side effects of radiation or incomplete control of the tumor. We advised that polycarbonate lenses in glasses and/or goggles be worn for protection.

We advised that polycarbonate lenses in glasses and/or goggles be worn for protection.

There is new evidence that genetic mutations can lead to the development of melanoma on chromosomes 3, 6, 8, and 9. With the patient's permission, a microscopic needle aspirate sample for fluorescent in situ hybridization or micro-array assay analysis will be taken to analyze for such mutations. Those with high-risk mutations will be put on prophylactic chemotherapy, immune therapy, or other systemic protocols.

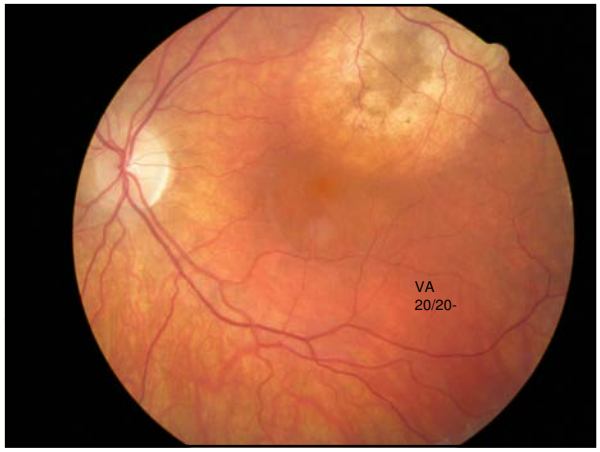
Thank you for allowing us to assist in her care.

Best regards,

Sara Lally, MD
Oncology Service

Carol L. Shields, MD
Oncology Service

SL/CLS/vnh/tmk

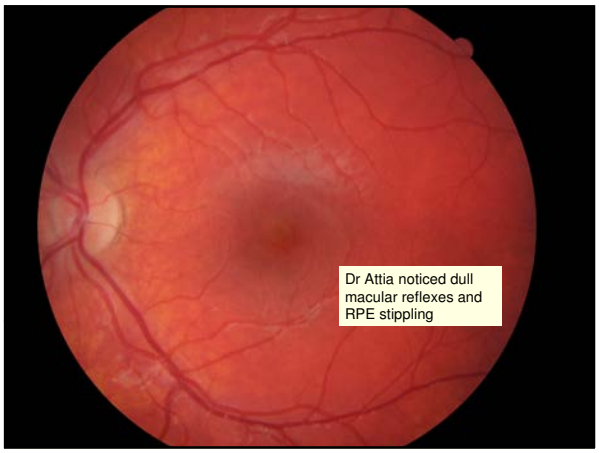


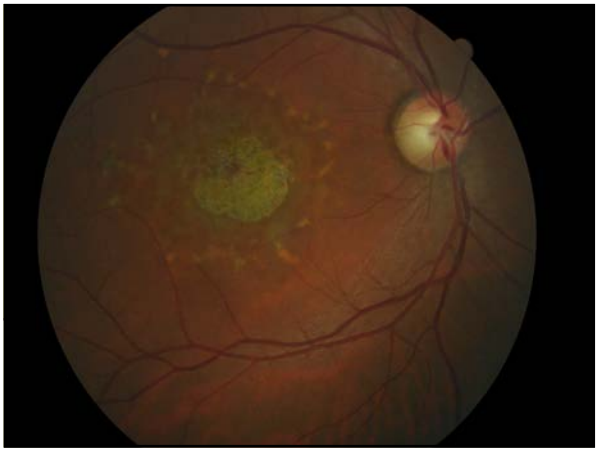
Case 1

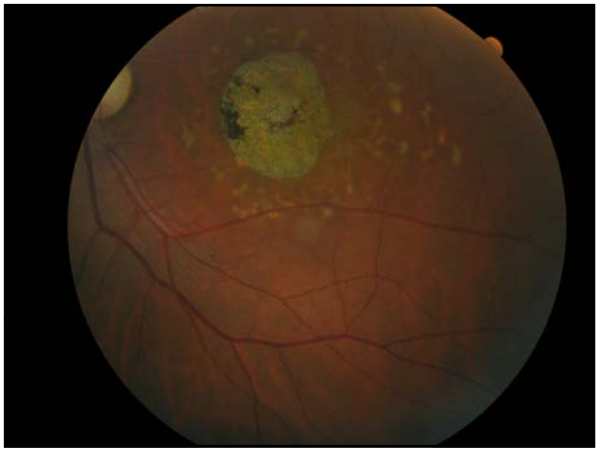
- A small amount of aspirate was taken to check for genetic mutations which lead to development of melenoma on chromosomes 3.6.8. and 9.
- Those with high risk will be put on chemotherapy, immune therapy, or other systemic treatments.
- 4/30/12- on chemotherapy. Vcc 20/200 OS

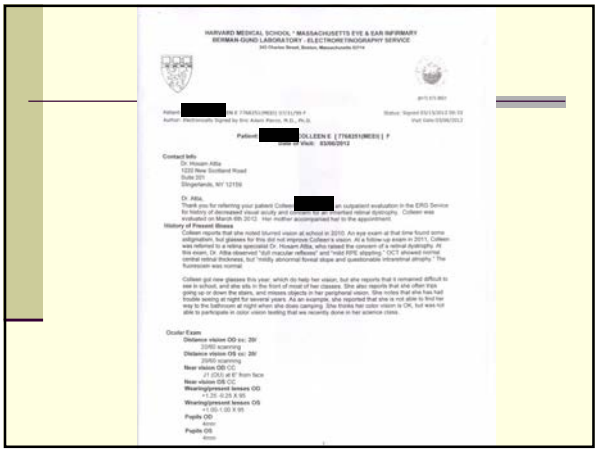
Case 2 Colleen T.

- 11 year old female is seen for a low vision evaluation
- Acuities are OD: 20/70- , OS: 20/80-
- Was suspected of malingering
- Was sent to Mass General for ERG testing








HARVARD MEDICAL SCHOOL * MASSACHUSETTS EYE & EAR INFIRMARY
BERMAN-GUND LABORATORY - ELECTRORETINOGRAPHY SERVICE

Patient [redacted] COLLEEN E [7768251/M/E3] | F
Visit: 03/06/2012

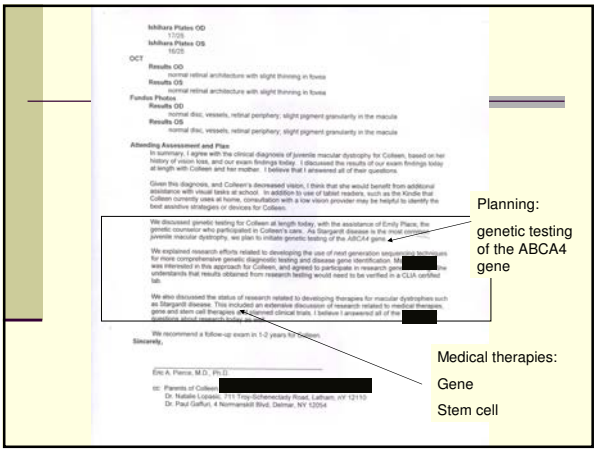
Contact Info
Dr. Hosam Attia
1233 New Scotland Road
Suite 201
Slingerlands, NY 12159

Dr. Attia,
Thank you for referring your patient Colleen [redacted] an outpatient evaluation in the ERG Service for history of decreased visual acuity and a diagnosis of an inherited retinal dystrophy. Colleen was evaluated on March 6th 2012. Her mother accompanied her to the appointment.

History of Present Illness
Colleen reports that she noted blurred vision at school in 2010. An eye exam at that time found some astigmatism, but glasses for this did not improve Colleen's vision. At a follow-up exam in 2011, Colleen was referred to a retina specialist Dr. Hosam Attia, who raised the concern of a retinal dystrophy. At this exam, Dr. Attia observed "dull macular reflexes" and "mild RPE stippling." OCT showed normal central retinal thickness, but "mildly abnormal foveal shape and questionable intraretinal atrophy." The fluorescein was normal.

Colleen got new glasses this year, which do help her vision, but she reports that it remained difficult to see in school, and she sits in the front of most of her classes. She also reports that she often trips going up or down the stairs, and misses objects in her peripheral vision. She notes that she has had trouble seeing at night for several years. As an example, she reported that she is not able to find her way to the bathroom at night when she does camping. She thinks her color vision is OK, but was not able to participate in color vision testing that we recently done in her science class.

Ocular Exam
Distance vision OD sc: 20/
20/60 scanning
Distance vision OS sc: 20/
20/60 scanning
Near vision OD CC
J1 (OU) at 6" from face
Near vision OS CC
Wearing/present lenses OD
+1.25 -0.25 X 95
Wearing/present lenses OS
+1.00-1.00 X 95
Pupils OD
4mm
Pupils OS
4mm


Ishihara Plates OD
17/25
Ishihara Plates OS
16/25
OCT
Results OD
normal retinal architecture with slight thinning in fovea
Results OS
normal retinal architecture with slight thinning in fovea
Fundus Photos
Results OD
normal disc, vessels, retinal periphery; slight pigment granularity in the macula
Results OS
normal disc, vessels, retinal periphery; slight pigment granularity in the macula

Attending Assessment and Plan:
In summary, I agree with the clinical diagnosis of juvenile macular dystrophy for Colleen, based on her history of vision loss, and our exam findings today. I discussed the results of our exam findings today at length with Colleen and her mother. I believe that I answered all of their questions.

Given this diagnosis, and Colleen's decreased vision, I think that she would benefit from additional assistance with visual tasks at school. In addition to use of tablet readers, such as the Kindle that Colleen currently uses at home, consultation with a low vision provider may be helpful to identify the best assistive strategies or devices for Colleen.

We discussed genetic testing for Colleen at length today, with the assistance of Emily Place, the genetic counselor who participated in Colleen's care. As Stargardt disease is the most common juvenile macular dystrophy, we plan to initiate genetic testing of the *ABCA4* gene.

We explained research efforts related to developing the use of next-generation sequencing techniques for more comprehensive genetic diagnostic testing and disease gene identification. [redacted] was interested in this approach for Colleen, and agreed to participate in research genetic testing. She understands that results obtained from research testing would need to be verified in a CLIA certified lab.

We also discussed the status of research related to developing therapies for macular dystrophies such as Stargardt disease. This included an extensive discussion of research related to medical therapies, gene and stem cell therapies. [redacted] planned clinical trials. I believe I answered all of the questions about research today as well.

We recommend a follow-up exam in 1-2 years for Colleen.

Sincerely,

Eric A. Pierce, M.D., Ph.D.

cc: Parents of Colleen [redacted]
Dr. Natalie Lopasic, 711 Troy-Schenectady Road, Latham, NY 12110
Dr. Paul Gaffuri, 4 Normanskill Blvd, Delmar, NY 12054

Planning:

genetic testing of the ABCA4 gene

Medical therapies:

Gene

Stem cell

HARVARD MEDICAL SCHOOL * MASSACHUSETTS EYE & EAR INFIRMARY
BERMAN-GUND LABORATORY - ELECTRORETINOGRAPHY SERVICE

July 2nd 2012

[redacted]

On March 8th 2012, your daughter Colleen [redacted] underwent a clinical evaluation in ERG Service at Massachusetts Eye and Ear Infirmary for [redacted] diagnosis of juvenile macular dystrophy. At this appointment, genetic testing for the *ABCA4* gene was initiated at Prevention Genetics Laboratory.

Gene sequencing of *ABCA4* identified one genetic variation. This genetic variation is a missense mutation defined as c.2588G>C which is predicted to result in the amino acid substitution p.Gly863Ala. This mutation has been documented to be a causative for Stargardt Disease. A second genetic variation or mutation was not identified. *ABCA4*-related Stargardt Disease is an autosomal recessive condition and thus two genetic changes must be identified to confirm *ABCA4*-related disease. Follow-up testing to assess for deletions and duplications within the *ABCA4* gene was recommended in order to determine if the second mutation was in fact due to a deletion or duplication within the gene.

Deletion and duplication screening of the *ABCA4* gene was negative; no deletions or duplications were identified.

In summary, one genetic mutation within the *ABCA4* gene was identified but a second mutation was not detected.

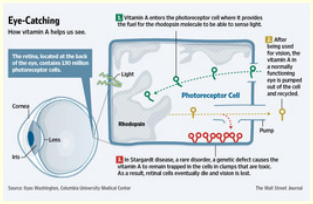
A negative result for genetic testing does not exclude the possibility that your vision problems could be due to genetic changes not tested by this assay. Additional testing options may be available based on your clinical diagnosis or family history. As we discussed at your evaluation, your willingness to participate in our research study allows us the ability to continue the genetic analysis on a research basis.

If you have any questions regarding this result or would like to discuss arranging further studies, please contact Emily Place, Genetic counselor at 617-573-6902.

Sincerely,

Eric Pierce, MD, PhD

Stargardt's Macular Degeneration



Leber Congenital Amaurosis

- Scientists have identified 14 genes with mutations that can each cause LCA. These genes account for approximately 75 percent of all cases of LCA. With this information, scientists are better equipped to develop preventions and treatments.
- Clinical trials of gene replacement therapy for LCA caused by mutations in the RPE65 are now beginning.
- These studies provide extraordinary promise for eradicating LCA caused by RPE65, and eventually, LCA caused by other genetic variations.

Leber Congenital Amaurosis

- Mutations in any of the genes associated with Leber congenital amaurosis disrupt the development and function of the retina, resulting in early vision loss. Mutations in the CEP290, CRB1, GUCY2D, and RPE65 genes are the most common causes of the disorder, while mutations in the other genes generally account for a smaller percentage of cases.
- 30% are unknown
- Frequency- 2 or 3 in 100,000 births[1]

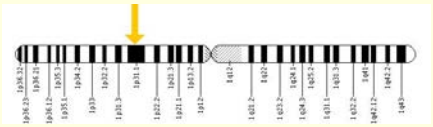
http://ghr.nlm.nih.gov/condition/leber-congenital-amaurosis[1]

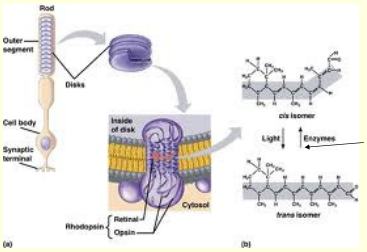
RPE65

- Retinal pigment epithelium-specific protein 65kDa
- The RPE65 gene provides instructions for making a protein that is essential for normal vision. The RPE65 protein is produced in the retinal pigment epithelium (RPE).
- The RPE65 protein is involved in a multi-step process called the visual cycle, which converts light entering the eye into electrical signals that are transmitted to the brain. When light hits photosensitive pigments in the retina, it changes a molecule called 11-cis retinal (a form of vitamin A) to another molecule called all-trans retinal. This conversion triggers a series of chemical reactions that create electrical signals. The RPE65 protein then helps convert all-trans retinal back to 11-cis retinal so the visual cycle can begin again.

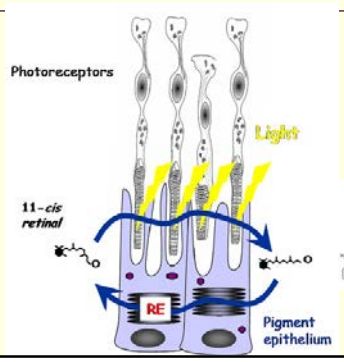
RPE65

- **Where is the RPE65 gene located?**
- Cytogenetic Location: 1p31
- Molecular Location on chromosome 1: base pairs 68,894,506 to 68,915,641
-

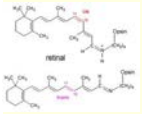




RPE65 gene

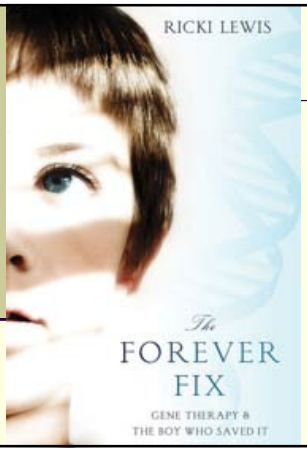


Chromophore



RPE65 gene

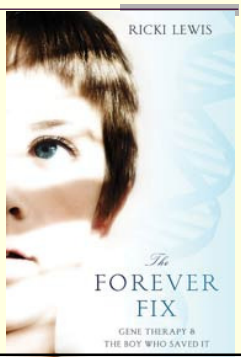
- The RPE65 gene mutations that cause retinitis pigmentosa disrupt RPE65 protein function, which leads to vision loss by impairing the visual cycle. Mutations in this gene appear to be an uncommon cause of retinitis pigmentosa; these genetic changes are responsible for only a small percentage of all cases.

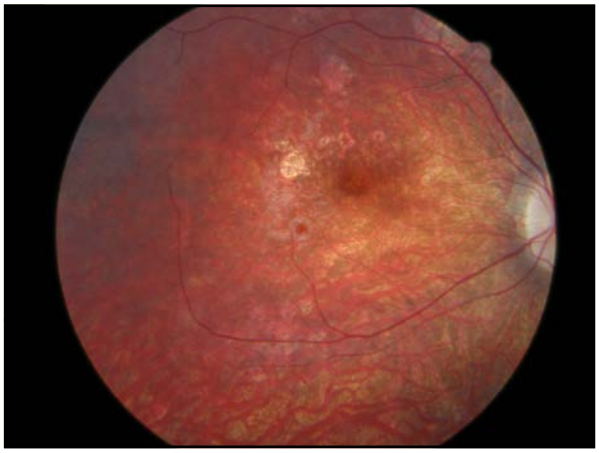


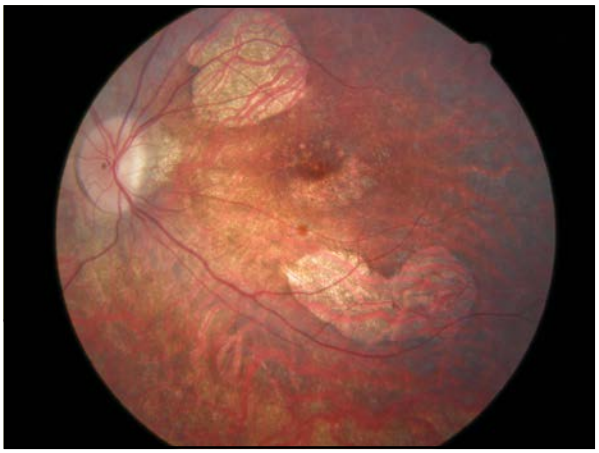
Leber Congenital Amaurosis

- Cory Haas
- DOB: 9/22/2000
- OD: 10/140
  OS: 10/100
- RX:

OD: -12.50 sph
OS: -14.00 -0.50 x 160



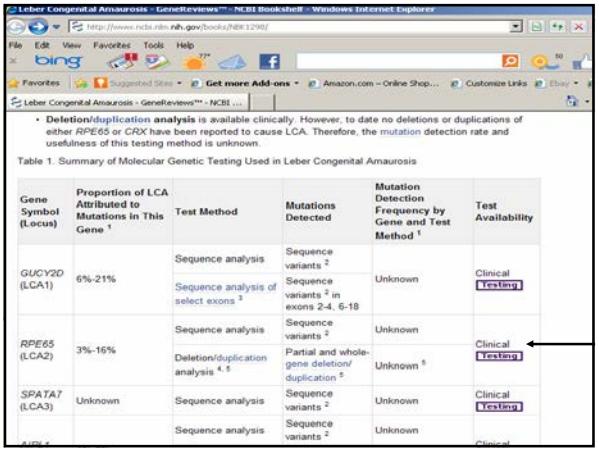




Gene Tests - DNA tests ordered by healthcare professionals

- These resources supplement the information in the Genetics Home Reference condition summary on Leber congenital amaurosis.
- Gene Tests: AIPL1-Related Leber Congenital Amaurosis
- Gene Tests: CEP290-Related Leber Congenital Amaurosis
- Gene Tests: CRB1-Related Leber Congenital Amaurosis
- Gene Tests: CRX-Related Leber Congenital Amaurosis
- Gene Tests: GUCY2D-Related Leber Congenital Amaurosis
- Gene Tests: IMPDH1-Related Leber Congenital Amaurosis
- Gene Tests: LCA5-Related Leber Congenital Amaurosis
- Gene Tests: Leber Congenital Amaurosis Multi-Gene Panels
- Gene Tests: LRAT-Related Leber Congenital Amaurosis
- Gene Tests: RD3-Related Leber Congenital Amaurosis
- Gene Tests: RDH12-Related Leber Congenital Amaurosis
- Gene Tests: RPE65-Related Leber Congenital Amaurosis
- Gene Tests: RPGRIP1-Related Leber Congenital Amaurosis
- Gene Tests: SPATA7-Related Leber Congenital Amaurosis
- Gene Tests: TULP1-Related Leber Congenital Amaurosis

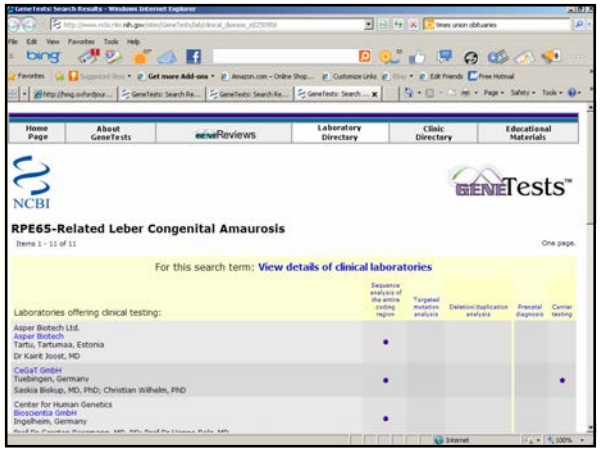
http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab/clinical_disease_id/250956



- **Deletion/duplication analysis** is available clinically. However, to date no deletions or duplications of either *RPE65* or *CRX* have been reported to cause LCA. Therefore, the mutation detection rate and usefulness of this testing method is unknown.

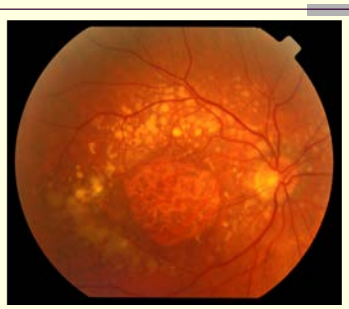
Table 1. Summary of Molecular Genetic Testing Used in Leber Congenital Amaurosis

Gene Symbol (Locus)	Proportion of LCA Attributed to Mutations in This Gene [1]	Test Method	Mutations Detected	Mutation Detection Frequency by Gene and Test Method [1]	Test Availability
GUCY2D (LCA1)	6%-21%	Sequence analysis	Sequence variants [2]	Unknown	Clinical Testing
		Sequence analysis of select exons [3]	Sequence variants [2] in exons 2-4, 6-18		
RPE65 (LCA2)	3%-16%	Sequence analysis	Sequence variants [2]	Unknown	Clinical Testing
		Deletion/duplication analysis [4, 5]	Partial and whole-gene deletion/duplication [5]	Unknown [6]	
SPATA7 (LCA3)	Unknown	Sequence analysis	Sequence variants [2]	Unknown	Clinical Testing
		Sequence analysis	Sequence variants [2]	Unknown	Clinical

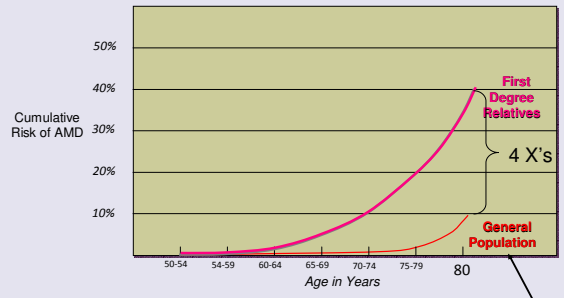


Is it only esoteric conditions which can be tested for genetic mutations?

Macular Degeneration



Is Age-related macular degeneration (AMD) in our DNA?



First degree relatives of people affected by AMD are at significantly increased risk of AMD

NOTE: the general population still has a ten percent chance of developing advanced AMD regardless of their family history

Genetic Risk for Progression of AMD (vision loss)

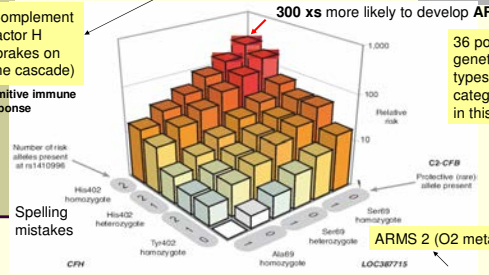
Proteins which start a cascade they form a complex which attacks the bacterial membrane and they die

Complement factor H (brakes on the cascade)

Primitive immune response

300 xs more likely to develop **ARMD**

36 possible genetic types categorized in this study



Spelling mistakes

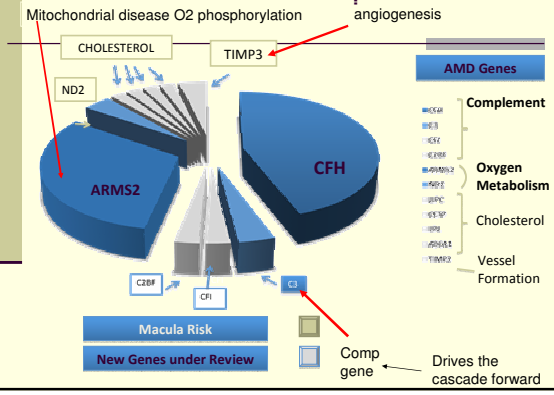
ARMS 2 (O2 metabolism)

J Maller / J Seddon: Nature Genetics; Vol 38, No 9, Sept 2006

2nd study May 2009, and 3rd Jan 2012

Makes an enzyme with traps free radicals

Macula Risk Development®



The Genetic Components of AMD

Naturally occurring variations conferring AMD risk

	Marker	Allele	Odds Ratio	Freq
Drusen Complement Protein	CFH	H1+H3 (risk haplotypes)	17.9x risk	0.202
		Average		0.495
		(H2+H4 low risk)	1.0	0.303
	C3 rs2230199	G (risk)	2.6	0.18
		C		0.83
VEGF Oxidative Stress	ARMS2 (indel)	(risk)	8.2	0.17
		(no-risk)		0.83
	Smoking	Current (risk)	3.14	0.17
		Never		0.55
	ND2 mt A4917G	G (risk)	2.2	0.09
		A		0.90

Mitochondrial gene

Having both CFH and ARMS2 is 147xs more likely to develop ARMD (8.2 x 17.9)

Clinical Assessments –
1446 Patients (AREDS 1)

- "Clearly, genetic factors play a major role…"

2009 - Validated combination of CFH, C3, ARMS2
2012 - more genes + Drusen size – 0.91 'C' statistic score

- "The predictive power of this composite of risk factors for progression to advanced AMD, with a C statistic score of **0.83** (propensity score), is comparable to the Framingham risk functions for CHD in which the C statistics were 0.79 for white men and 0.83 for white women"

(BP and Chol) ***J.M. Seddon, B Rosner et al; IOVS May 2009 / January 2012***

AMD – A Genetic Disease

Macula Risk

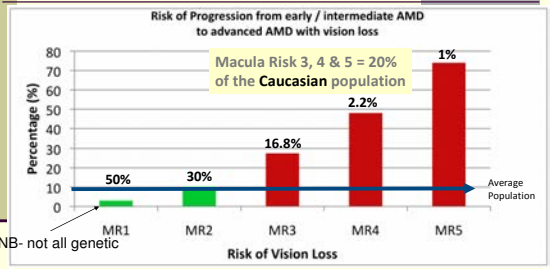
- A test that identifies AMD
- patients who will progress
- to vision loss

Cheek Swab

Macula Risk Score

If you live until 80 yrs old

Once the test has been performed, your genotype, along with smoking status, is combined into a risk calculation to place you into one of five different risk categories.



NB- not all genetic

Catagories MR1 and MR2 have a 2.5% and 9.5% respectively of developing advanced AMD. Patients in catagories MR3-MR5 have a much greater chance of developing severe disease

Increased risk (Macula Risk® Level 3, 4 and 5) patients may benefit from:

- Increased frequency of eye examinations
- Disease education and possibly 'at-home' Amsler Grid or Home PHP testing
- Preventative eye vitamin therapy and possibly nutritional supplements
- Early diagnosis and treatment of wet AMD with effective therapies

Medical Utility

Macula Risk®

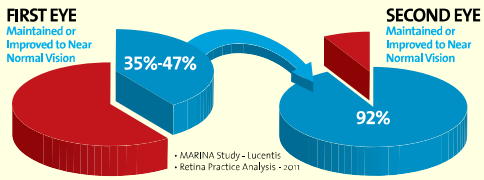
Why Should we test?

Early Detection and Early treatment = Improved Outcomes

- Early Detection
- CAPT Research Group:
  - **1052 participants at 22 centers**
  - **Examinations at 6 mo. Then annually for 5 – 6 yrs.**
- "monitoring of a population with bilateral large drusen, using annual fluorescein angiography, allowed neovascular lesions to be detected early, when most lesions were occult, small and outside the fovea."
  - *McGuire / Alexander et al Ophthalmology, Sept 2008*

- Early Treatment
- Lucentis (ranibizumab):
- "a sub group analysis of the MARINA trial showed that treatment benefit was greater with higher baseline visual acuity and smaller lesions"
  - *Boyer DS, Awh CC et al. Ophthalmology 2007; 114:246-252*

AMD Disease Management Gap



20/80 or worse

SAVE THE FIRST EYE

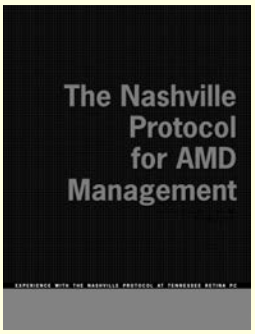
•MARINA Study – Lucentis
•Retina Practice Analysis - 2011

Recommendations

Retina – General Ophthalmology - Optometrists

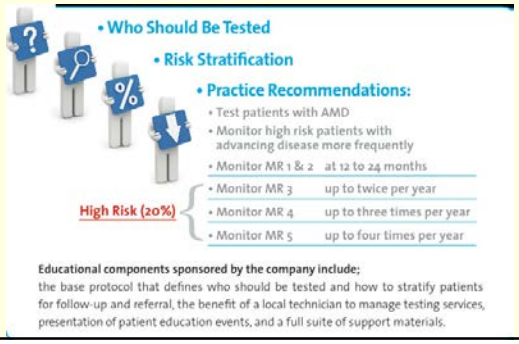
1. **All specialties Screen patients over 65 yrs with large drusen (over 125µ);**
2. **Refer 'high risk' to RS for a base-line exam and new medical record;**
3. **Monitor MR 1 & 2…… annually;**
4. **Monitor MR 3…… twice per annum;**
5. **Monitor MR 4…… three times per annum;**
6. **Monitor MR 5…… four times per annum;**
7. **Refer advanced cases to Retina Specialist.**

Protocol for Eye Care Professionals



Nashville Protocol

A Comprehensive Approach to the Management of AMD



Reimbursement

ICD-9 Codes

- 362.50 non-specific AMD
- 362.51 nonexudative senile macular degeneration
- 362.52 exudative senile macular degeneration
- 362.57 drusen

Medicare

BLUE CROSS®

CIGNA

KAISER PERMANENTE

HUMANA

New clinical trial wet ARMD- Phase 1

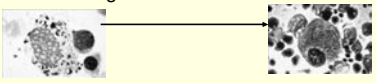
- The study drug is "AAV2-sFLT01"

  AVV- adeno associated virus
- This experimental study drug uses a virus to transfer a gene (genetic code) into cells within the eye. The gene codes for a protein that is intended to diminish the growth of abnormal blood vessels under the retina
- The duration of the gene's effect is currently unknown, but might last for years.
- Lead sponsor is Genzyme

http://inclinicaltrials.com

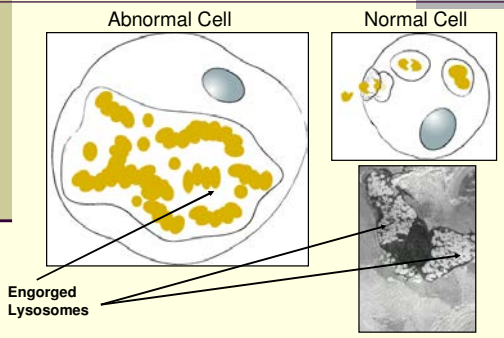
What are Lysosomal Storage Disorders (LSDs)?

- Family of > 40 disorders1
- Lysosomes with an internal pH of 4.5, digest cellular materials, food particles, bacteria and viruses
- Enzyme deficiency, acid hydrolases, causes lysosomes to become engorged1. Lipases, proteases, nucleases, amylases
- Each disease is a consequence of type of substrate and where it accumulates1
- Progressive accumulation of substrate may result in irreversible damage2



1. Meikle P et al. *JAMA*. 1999;281:249-254.
2. Wraith JE et al. *J Pediatr*. 2004;144:581-588.

Lysosomal Storage of GAGs



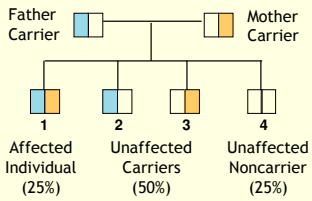
Incidence of LSDs[1]

- Individually rare but collectively more common
  - Individual incidence: 1:40,000 to 1:1,000,000 births
  - Collective incidence: 1:7,700 births
- Most are panethnic
- Some more prevalent in certain ethnic groups:
  - Ashkenazi Jewish descent—Gaucher, Niemann-Pick, Tay Sachs
  - African Americans—Infantile-onset Pompe disease
  - French Canadians- Tay-Sachs

1. Meikle P et al. *JAMA*. 1999;281:249-254.

Inheritance

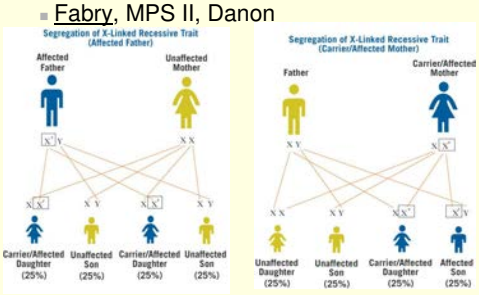
- Most are autosomal recessive[1]



1. Hirschhorn R et al. In: *The Metabolic and Molecular Bases of Inherited Disease*. 2001:3389-3420.

Inheritance

- Three are X-linked
  - Fabry, MPS II, Danon



Fabry Disease

83

Fabry Disease

- Fabry disease is a progressive, debilitating and eventually fatal disease first described by Johannes Fabry in Germany and William Anderson in England at the end of the nineteenth century.

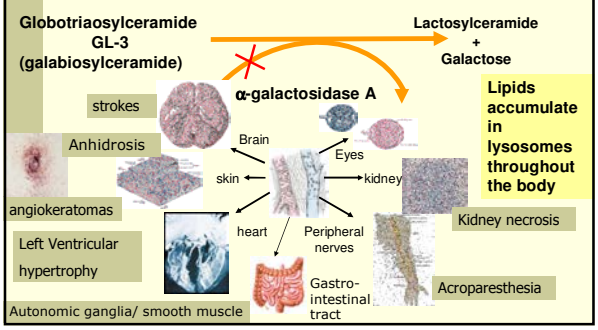
What is Fabry Disease?

- A Lysosomal Storage Disorder
- X-linked (like hemophilia)
  - **Females carriers are affected-** How much depends on the level of activation of the x-chromosome (0-100%) (Lyonization)
- Incidence is unknown ~1:40,000 males to ~1:117,000 individuals. Panethnic.
- Progressive, destructive, life threatening disorder which affects multiple organs
- Early identification of patients and their family members at risk is the key to treatment

Lyonization

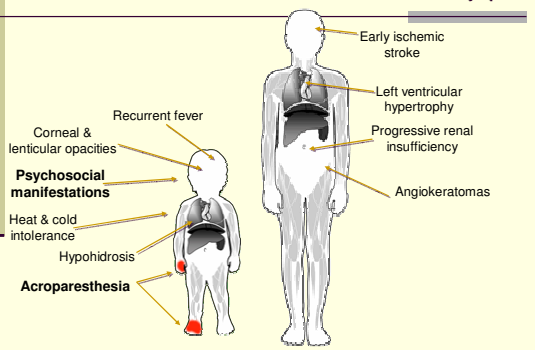
- **Lyonization** (also called **X-inactivation**) is a process by which one of the two copies of the X chromosome present in females is inactivated. The choice of which X chromosome will be inactivated is random but once an X chromosome is inactivated it will remain inactive throughout the lifetime of the cell and its descendants in the organism. Thus, the traits of the majority of the chromosome sets dictates the extent of the phenotypic presentation of the condition.

What is Fabry disease



Fabry Disease

Signs & Symptoms



Diagnosis

- **Confirmatory diagnosis**
- Enzyme assay
  - Blood test to evaluate enzyme levels
  - Males with classical Fabry disease usually have **less than 1%** of normal enzyme levels
  - Females can have **0-100%** of normal enzyme levels
    - Normal enzyme levels in females does NOT preclude affected/carrier status
- Genetic testing to identify females (expensive)
  - Mutation analysis when family mutation is known
  - Sequence analysis when the family mutation is not known

Fabry Disease

Disease-at-a-Glance

Pathology
α-Galactosidase A (α-GAL) deficiency[1]
Accumulation of globotriaosylceramide (GL-3)[1]

Inheritance
X-linked recessive

Onset
May present in childhood or adolescence

Incidence
~1:40,000 males[1]
~1:117,000 individuals[2]

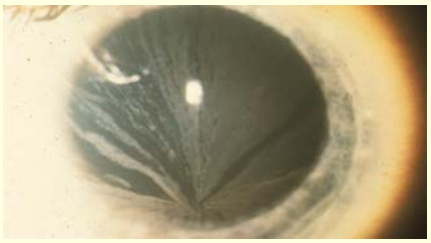
-Progressive
-Life threatening
-Death often due to renal, cardiac, or cerebrovascular complications
-Average life expectancy ~ 50 years[3]
-Without intervention, i.e. kidney transplants life expectancy was 29 yrs

1. Desnick RJ et al. In: *The Metabolic and Molecular Bases of Inherited Disease.* 2001:3733-3774.
2. Meikle P et al. *JAMA.* 1999;281:249-254.
3. MacDermot KD et al. *J Med Genet.* 2001;38:750-760.

Ocular manifestations of Fabry disease

- Corneal verticilatta (Corneal whorling)
- "Propeller" cataracts
- Fabry cataracts
- Conjunctival blood vessel tortuosity
- Retinal blood vessel tortuosity

Corneal Whorling in Fabry Disease

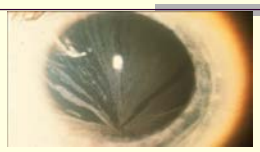


Typically do not impair vision, but are unique and diagnostic

Courtesy of Roscoe Brady, MD

What are we actually looking at?

Vortex Keratopathy / Cornea Verticillata



Clinical features:

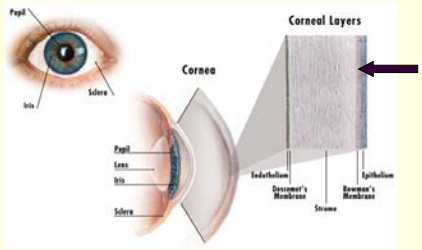
Symptoms: *the corneal changes are rarely of any visual significance*.

Signs:

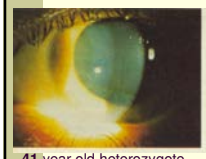
Symmetric, bilateral, whorl-like pattern of powdery, white, yellow or brown corneal epithelial deposits
Appears in a vortex fashion in the inferocentral cornea and swirls outwards sparing the limbus

Vortex Keratopathy / Cornea Verticillata

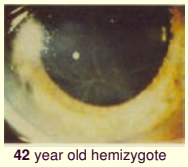
Light microscopy reveals a **0.3- to 0.5-microm** thick layer between the epithelial and Bowman's layers



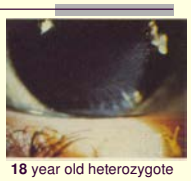
Whorl-like corneal Opacities
Subepithelial layer at or near the level of Bowman's Membrane



41 year old heterozygote

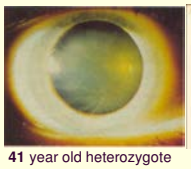


42 year old hemizygote



18 year old heterozygote

27 year old heterozygote



41 year old heterozygote

27 year old heterozygote

Corneal Involvement is the most prominent ocular finding

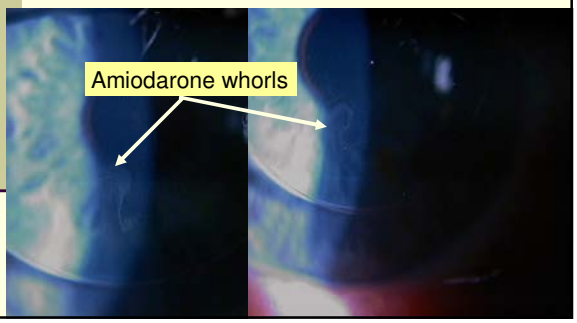
- Whorl-like corneal opacities are seen in the majority of Fabry Patients (90% of patients)
- Whorl-like opacities are usually inferior and typically cream colored; but can range from white to golden brown or appear faint
- More pronounced in heterozygotes
- Can be seen through slit lamp exam in 4 to 5 year olds (it has been reported as early as 6 months)
- In children, corneal involvement maybe a more diffuse epithelial haze.
- Corneal endothelium is not involved
- Present in almost all males by age 4
- Present in most females by age 10

Medications causing Cornea Verticillata

Corneal deposits in Fabry similar to:

- Amiodarone* (Cordarone) – antiarrhythmic
  **Most studies suggest that all or nearly all patients taking amiodarone will develop verticillata. What is the differential diagnosis????*
- Chloroquine (Aralen) – liver disease, malaria
- Chlorpromazine (Thorazine) - psychotic disorders
- Indomethacin (Indocin) – NSAID
- Meperidine (Demerol) - pain
- Tamoxifen (Nolvadex) – breast cancer

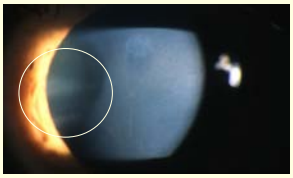
Amiodarone corneal effects



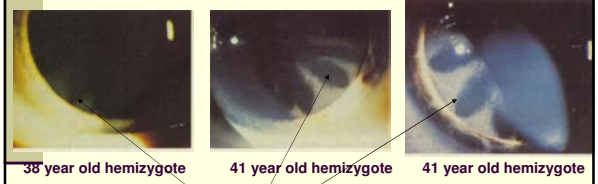
Same patient 1 year off Amiodarone

Two Types of Lenticular Changes

- First type- a granular anterior capsular or subcapsular deposit:
  - Typically are inferior in position
  - Frequently appear to be wedge-shape with there base near the lenticular equator
  - Can have a propeller distribution



A Granular (Cream-color) Anterior Capsular or Sub-capsular Deposits

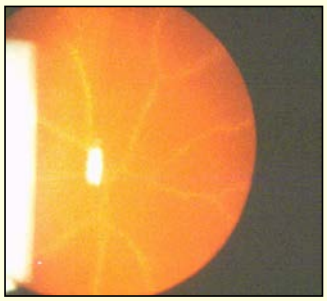


"propeller distribution"

Second Type of Lenticular Changes

- Fabry Cataract; posterior lens opacity
  - Linear and appear as a whitish translucent deposit on the posterior lens capsule
  - Maybe the first ocular manifestation
  - Best seen by retro-illumination
  - Found in 35% of hemizygotes and 15% of heterozygotes
  - First described by George Spaeth, MD

Fabry Cataract



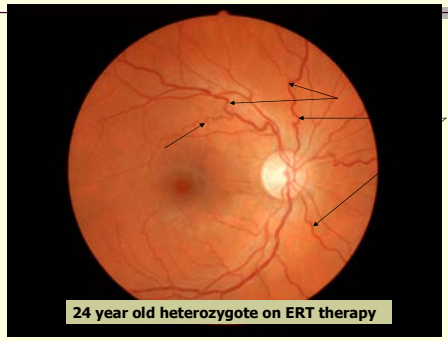
Retinal Changes in Fabrys

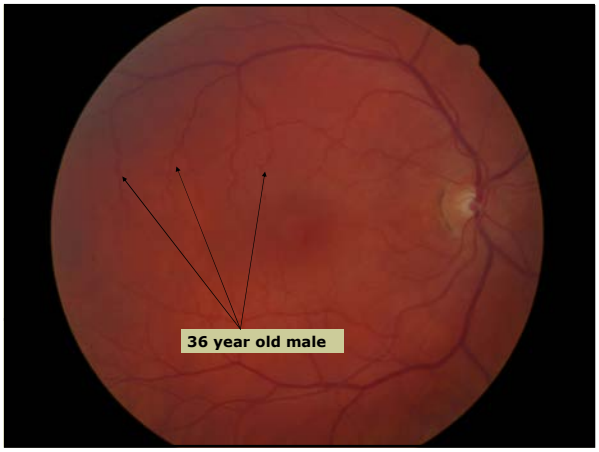
- More Prevalent in hemizygotes

(affected males)

- 70% vs 25% in heterozygous females
- Vascular changes may present as segmental sausage-like dilation of the veins or corkscrew-like diffuse tortuosity.

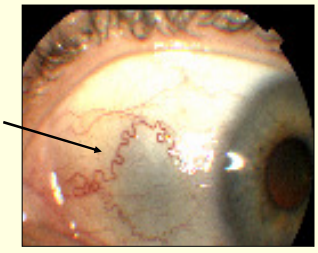
Retinal tortuosity in Fabry patient

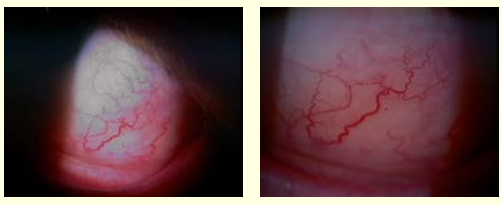




Conjunctival blood vessel tortuosity

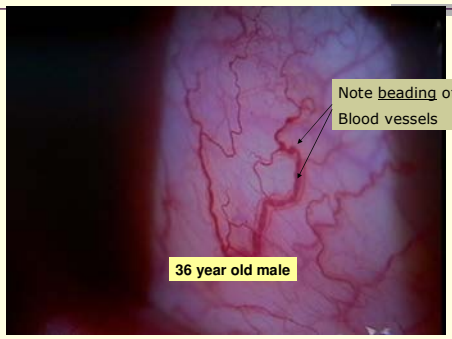
Vascular tortuosity



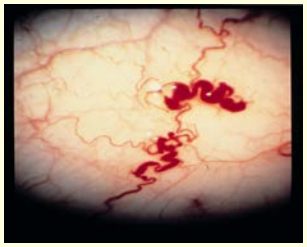


36 year old male

Tortuosity and kinking



26 year old hemizygote



Small vessels of the conjunctiva often show aneurysmal dilatations, tortuosity and kinking.

Discussion

- Conjunctival blood vessel manifestations have been clearly shown to present in two fashions: tortuosity and aneurysmal dilations. Accumulation of glycosphingolipids within the vessel walls results in the disruption of the vessel architecture. While tortuosity may be common in the general population, aneurysmal dilations are not. The presence of the aneurysmal dilations may well be predictive of end-organ pathology in the heart, brain, and/or kidneys.

Discussion

- Corneal verticillata does not have any effect on visual acuity. This is precisely what makes this finding so insidious. A practitioner who is not familiar with corneal verticillata as a marker for Fabry disease would not be alarmed at their presence

Fabry Disease: Importance of Family Screening

- In this extended family, 41 out of 99 members have been diagnosed with Fabry disease

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Ocular manifestations of Fabry disease within a single kindred

- This study looked at 23 members of a single family for the presence or absence of these ocular signs.
- **Methods:** Twenty three patients of a single family were seen on a single day at a private office. Patients were given comprehensive ophthalmic examinations which included visual acuities, pupillary responses, slit-lamp examinations, ocular motilities and muscle balance, intra-ocular pressure, pachymetry (corneal thickness), dilated retinal exams, anterior and retinal photography. Analysis of the nerve fiber layer and macula were also performed using the Stratus OCT™ from Carl Zeiss Meditec.

Morier, A. et al. Optometry. Journal of the American Optometric Association. 2000. Volume 81. P. 237-249

Effect of ERT on Corneal Verticillatta

Joshua Mali, M.D./ Albert M.Morier, M.A., O.D.

- **Purpose:** To evaluate the effect of enzyme replacement therapy (agalsidase beta) on corneal verticillata in patients with Fabry disease.
  Methods: Six Fabry patients with documented corneal verticillata on examination and being treated at that time with enzyme replacement therapy (agalsidase beta) participated in the study. On follow-up, careful slit lamp examinations were performed to analyze the anterior segment for the presence or resolution of corneal verticillata.
  Results: Three out of the six patients (50%) had complete resolution of corneal verticillata in both eyes.
  Conclusions: Corneal verticillata in patients with Fabry disease appear to resolve in about half of the patients when treated with enzyme replacement therapy.

Morier A. et al. Poster. Albany Ophthalmological Update. June 2012.

Previous patient	ERT Status	Corneal Verticillata
EH	yes-nine yrs	yes
JH	yes- four yrs	yes
SS	yes- six yrs	no
EK	yes-seven yrs	yes (trace)
JH1	yes-eleven yrs	no
DS	yes-four yrs	no
KK	no	yes

Conclusions

- As ocular findings are often the earliest presentation of the disease, it is the eye care provider who is in the perfect position to spot the ocular manifestation and make a timely referral to a geneticist or metabolic specialist for diagnosis.

Disease Progression Mucopolysaccharidosis I

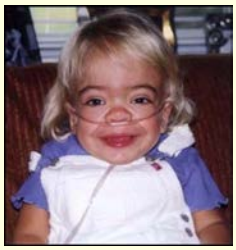
Patient with severe MPS I


10 months


12 months


22 months


34 months


39 months

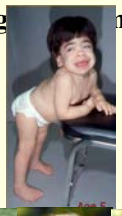
Photos courtesy of the MPS Society.

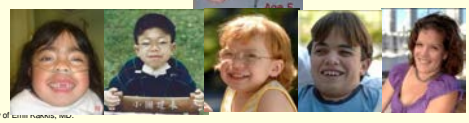
Importance of Early Diagnosis

- Progressive, debilitating, often life threatening
- Treatments exist for some LSDs
- Early diagnosis and intervention may make a significant difference
- ***Unusual*** signs and symptoms and ***clusters*** of common signs and symptoms aid recognition
- Timely referral to a ***geneticist*** or ***metabolic specialist*** is crucial

Mucopolysaccharidosis I (MPS I)

(g n)





Courtesy of Emil Kakkis, MD.

MPS I

Disease-at-a-Glance

Pathology
α-L-iduronidase enzyme deficiency
Accumulation of glycosaminoglycans (GAGs)

Onset
Severe form (Hurler): first 6 months after birth
Attenuated form (Hurler-Scheie and Scheie): 3 to 8 years of age

Progression
Often life threatening
Severe cases life span < 10 years
Attenuated cases life span ≈ normal

Inheritance
Autosomal Recessive

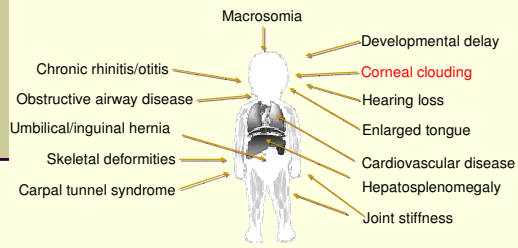
Incidence
≈1:100,000[1]

1. Meikle P et al. *JAMA.* 1999;281:249-254.

MPS I

Signs & Symptoms

Look for ***unusual*** symptoms or ***clusters*** of more common symptoms



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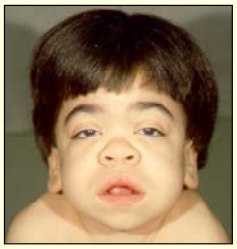
Neufeld EF, Muenzer J. In: Scriver C, Beaudet A, Sly W, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease.* New York, NY: McGraw-Hill; 2001:3421-3452.

Physical Appearance



- Facial dysmorphism
- Short nose
- Flat face
- Prominent forehead
- Large head
  - scaphocephaly

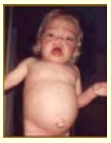
MPS I

Signs & Symptoms

Skeletal deformities (Gibbus)[1]

Carpal tunnel syndrome[2]

Short stature[2]



Hepatosplenomegaly[2]

Umbilical/inguinal hernia[3]

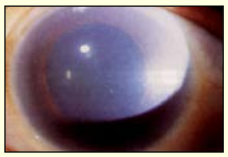
Corneal clouding[3]

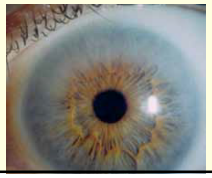
1. Courtesy of Emil Kakkis, MD.
2. Courtesy of MPS Society.
3. Nyhan & Ozand, 1998. Photo reproduced by permission of Hodder/Arnold Publishers.

Ocular Manifestations

- **Corneal clouding**
  - **can begin in first year of life**
  - **"ground-glass" appearance**
  - **Typically more pronounced in the periphery of the cornea**
  - **may lead to blindness**
- **Treated with:**
  - **Corneal transplant**

or risk amblyopia





MPS I: Ocular Manifestations

Corneal Clouding

- Can be unilateral or bilateral
- Extent of clouding may differ in each eye
- One of the earliest signs of MPS I

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Ocular Manifestations

- Retinal degeneration
  - decreased peripheral vision
  - night blindness
- Glaucoma
- Photophobia
- Optic nerve disease
  - may lead to blindness
  - Papilloedema
  - Optic atrophy
- Treated with:
  - sunglassess, brimmed hats
  - ophthalmic drops (beta-blockers, steroids)

MPS I

Treatment Strategies

- Supportive care
  - Eg, physical therapy, CPAP, hearing aids, surgery
  - Does not address enzyme deficiency
- Hematopoietic stem cell transplantation

  Bone marrow, umbilical cord, or peripheral blood
  - Best outcomes are in severe MPS I (<2 y)[1-4]
  - High morbidity and mortality
  - *Enzyme replacement therapy* (ERT) Aldurazyme

ERT does not seem to prevent progression of corneal or optic disc changes and, thus, the related worsening of visual function. [1]

1. Pitz, S et.al. Arch Ophthal 2007 Oct;125(10):1353-6.

1. Vellodi A et al. *Arch Dis Child.* 1997;76:92.
2. Whitley C et al. *Am J Med Genet.* 1993;46:209-218.
3. Neufeld EF, Muenzer J. In: Scriver C, Beaudet A, Sly W, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease.* New York, NY: McGraw-Hill; 2001:3421-3452.
4. Peters C et al. *Blood.* 1998;91:2601-2608.