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Genetics and Eyecare

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Genetics and Eyecare

Description

Most, if not all, diseases have an underlying genetic contribution, therefore all clinicians, as health care providers, must have a basic understanding of genetics and competency to care and educate patients on their diseases, especially diseases with significant genetics basis. This report presents ten ophthalmic conditions that are known to be caused by mutations in single genes or combined defects in multiple genes. The main purpose is to introduce interns and clinicians in eye care to some ophthalmic genetics conditions, the core competency in genetics for all health care professionals, the resource available online for further reference, and answers to questions that patients may have about their ocular disorders.

Keywords

Ophthalmic genetics, Glaucoma, Diabetes, Macular degeneration, Coloboma, LCA, EBMD, Stickler, Usher, Lowes

Disciplines

Optometry

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Genetics and Eyecare

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PREFACE

Most, if not all, diseases have an underlying genetic contribution, therefore all clinicians, as health care providers, must have a basic understanding of genetics and competency to care and educate patients on their diseases, especially diseases with significant genetics basis. This report presents ten ophthalmic conditions that are known to be caused by mutations in single genes or combined defects in multiple genes. It was produced by five optometric interns as part of their requirement for an elective credit. The main purpose is to introduce interns and clinicians in eye care to some ophthalmic genetics conditions, the core competency in genetics for all health care professional established in 2007, the resource available online for further reference, and answers to questions that patients may have about their ocular disorders.

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Core Competencies for All Health Care Professionals (2007)

<http://www.nchpeg.org/>

BASELINE COMPETENCIES

- At a minimum, each health-care professional should be able to:
- a. examine one's competence of practice on a regular basis, identifying areas of strength and areas where professional development related to genetics and genomics would be beneficial.
- b. understand that health-related genetic information can have important social and psychological implications for individuals and families.
- c. know how and when to make a referral to a genetics professional.

1. KNOWLEDGE

Health professionals should understand

- 1.1 basic human genetics terminology.
- 1.2 the basic patterns of biological inheritance and variation, both within families and within populations.
- 1.3 how identification of disease-associated genetic variations facilitates development of prevention, diagnosis, and treatment options.
- 1.4 the importance of family history (minimum three generations) in assessing predisposition to disease.
- 1.5 the interaction of genetic, environmental, and behavioral factors in predisposition to disease, onset of disease, response to treatment, and maintenance of health.
- 1.6 the difference between clinical diagnosis of disease and identification of genetic predisposition to disease (genetic variation is not strictly correlated with disease manifestation).
- 1.7 the various factors that influence the client's ability to use genetic information and services, for example, ethnicity, culture, related health beliefs, ability to pay, and health literacy.
- 1.8 the potential physical and/or psychosocial benefits, limitations, and risks of genetic information for individuals, family members, and communities.
- 1.9 the resources available to assist clients seeking genetic information or services, including the types of genetics professionals available and their diverse responsibilities.
- 1.10 the ethical, legal and social issues related to genetic testing and recording of genetic information (e.g., privacy, the potential for genetic discrimination in health insurance and employment).
- 1.11 one's professional role in the referral to or provision of genetics services, and in follow-up for those services.

2. SKILLS

Health professionals should be able to

- 2.1 gather genetic family history information, including at minimum a three-generation history.

- 2.2 identify and refer clients who might benefit from genetic services or from consultation with other professionals for management of issues related to a genetic diagnosis.
- 2.3 explain effectively the reasons for and benefits of genetic services.
- 2.4 use information technology to obtain credible, current information about genetics.
- 2.5 assure that the informed-consent process for genetic testing includes appropriate information about the potential risks, benefits, and limitations of the test in question.

3. ATTITUDES

All health professionals should

- 3.1 appreciate the sensitivity of genetic information and the need for privacy and confidentiality.
- 3.2 seek coordination and collaboration with an interdisciplinary team of health professionals.

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WEB RESOURCES

➤ Genetic Eye Disorders

- <http://ghr.nlm.nih.gov/conditionCategory/eyes-and-vision>
- <http://www.nei.nih.gov/resources/eyegene.asp>
- <http://www.sph.uth.tmc.edu/retnet/>
- <http://www.ncbi.nlm.nih.gov/sites/GeneTests/>

➤ Genetics in Clinical Practice

- <http://iml.dartmouth.edu/education/cme/Genetics/>

➤ Genomics Overview & Genetic Primers

- <http://learn.genetics.utah.edu/units/basics/tour/>
- <http://www.learner.org/channel/courses/biology/units/genom/images.html>
- http://highered.mcgraw-hill.com/sites/0072835125/student_view0/animations.html#
- <http://www.chromodisorder.org/CDO/General/IntroToChromosomes.aspx>
- <http://www.ygyh.org/>

➤ Family History and Pedigree

- <http://www.marchofdimes.com/gyponline/> (do create an account for future reference)
- <http://familyhistory.hhs.gov/>
- <http://pa.nchpeg.org>

➤ Genetic Testing and Counseling

- <http://www.genetests.org/>
- <http://neibank.nei.nih.gov/cgi-bin/eyeDiseaseGenes.cgi>
- <http://www.sph.uth.tmc.edu/Retnet/>
- <https://www.carverlab.org/genetic-tests-offered-all-nonprofit>
- <http://www.nsgc.org>
- <http://www.acmg.net>
- <http://www3.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM> (Online Mendelian IM)
- <http://www.rarediseases.org/>

- <http://www.geneticalliance.org/> (International Coalition)
- <http://iml.dartmouth.edu/education/cme/Genetics/> (Genetic in Clinical Practice)
- **Gene Therapy**
 - <http://learn.genetics.utah.edu/units/genetherapy/>
- **Genomics and Common Disease**
 - <http://iml.dartmouth.edu/education/cme/Genetics/> (Medical genomics & the future)
 - <http://www.genome.gov/26525384> (Genome Wide Association Studies database)
- **Pharmacogenomics, Epigenetics, Nutrigenomics**
 - <http://learn.genetics.utah.edu/units/pharma/phfrogs/>
 - <http://www.prometheuslabs.com>
 - <http://www.pharmgkb.org> (Pharmacogenetics Research Network)
 - <http://www.pbs.org/wgbh/nova/sciencenow/3411/02.html> (Epigenetics)
 - <http://nutrigenomics.ucdavis.edu/>
- **Direct-to-consumers**
 - <http://www.navigenics.com/healthcompass/AboutHCVideo/>
 - <https://www.23andme.com/ourservice/tour/>
 - <http://www.decodediagnostics.com/index-flash.php>

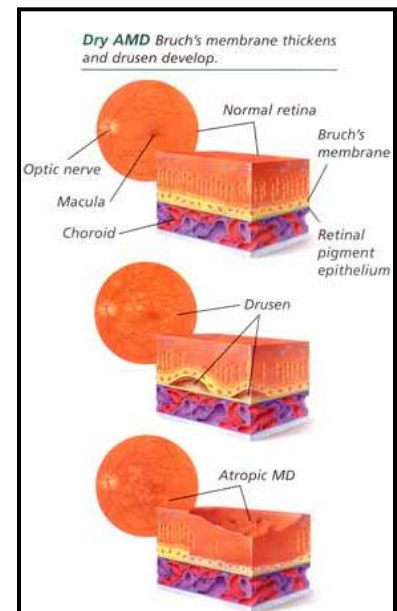
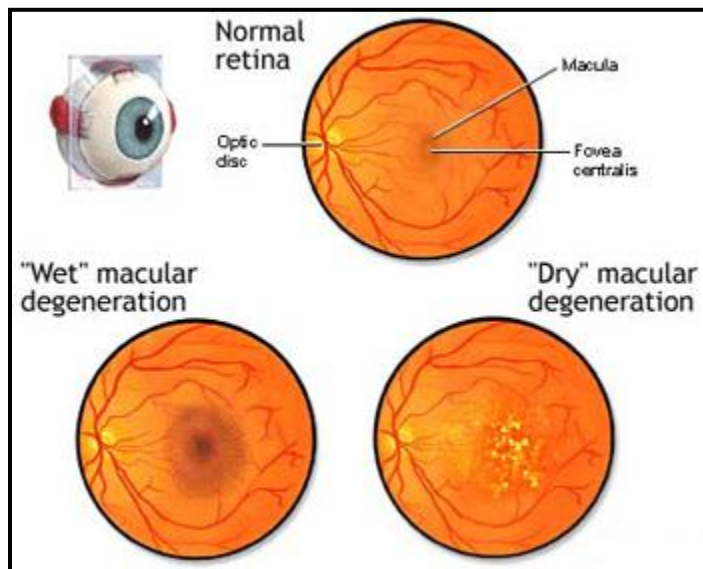
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Age Related Macular Degeneration

Caroline Slagle

Clinical Description:

- Macular Degeneration is the most common cause of vision loss in the U.S. for people over 60 years of age. Vision loss due to AMD is never restored, so any treatment just slows the progression
- Waste products, called drusen, build up in the RPE at the macula. In the wet form, fragile blood vessels grow under the normally avascular macula. These fragile blood vessels can leak and cause blurry, distorted central vision.
- Patients complain of central vision loss, night vision loss, and metamorphopsia
- The dry form of AMD accounts for 90% of AMD, yet the wet form is more devastating
- AMD risk factors include: women, Caucasians, smokers, overweight, and lightly pigmented individuals



Diagnosis and testing

- Amsler Grid for metamorphopsia, color vision tests, photostress tests, Central visual field, fluorescein angiography, OCT, PHP (preferential hyperacuity perimetry).
- Large, soft drusen is diagnostic for AMD.
- Hyperpigmentation of the retina, drusen, geographic atrophy, lipofuscin build up
- PED- pigmented epithelial detachment (serous detachment of the RPE), round oval elevation of the RPE/macula. This finding has a 30-50% chance of developing CNV!

Management (only prophylactic as there is no cure for AMD)

- AREDS II vitamins: copper, zinc, Vit ACE, zeaxanthin, leutin
- Antioxidants, sun protection
- Laser photocoagulation, Photodynamic therapy, VEGF inhibitors,
- Avastin or Lucentis injections or sustained delivery
- Stem cell therapy, implantable mini telescope
- PEDF gene (Pigmented Epithelial Derived Factor) injected into the eye. Inhibits neovascularization

Genetic Counseling

- There is a 2.5x risk of developing AMD if a family member is affected
- The Complement factor is a system that destroys foreign invaders by triggering inflammation. CFH puts a hold on the inflammatory response. CHF binds to CRP to stop inflammation. Variations in the SNP within CFH prevent this binding, thus the immune system is not suppressed and continues to damage tissue.
 - SNP is a single nucleotide letter change. Some have this riskier version of SNP on the CFH. Smoking can augment the devastation.
 - Having this high risk type of SNP increases the odds of developing AMD by 18 fold.
 - Smoking increases the risk by 2.4x, but if the patient also has the high risk CFH SNP, the risk is 34x.
- ARMS2/HTRA1 gene chromosome 10. Increases risk by 7.6 times.
C3 on chromosome 19
- CFB and C2 on chromosome 6.
- AREDS II vitamins: copper, zinc, Vit ACE, zeaxanthin, leutin
- Antioxidants, sun protection
- Laser photocoagulation, Photodynamic therapy, VEGF inhibitors,
- Avastin or Lucentis injections or sustained delivery
- Stem cell therapy, implantable mini telescope
- PEDF gene (Pigmented Epithelial Derived Factor) injected into the eye. Inhibits neovascularization

Genetic Tests

- Macular Risk (Arctic DX)
 - Calculates the risk of AMD based on genetics and history of smoking
 - A cheek swab is required in office and takes a few weeks to get a report back.
 - Clinical trials reveal it has an 83% predictability
 - MR is covered by most insurances including Medicare if an ICD-9 code for AMD is used, but if the patient does not have AMD yet, it costs %750
- AMD Risk Assessment Test (Asper Ophthalmics)
 - Analyses 3 SNPs in CFH and ARMS2. Also can detect CFB and C2
- RetinaGene AMD (Sequenom)
 - Tests for choroidal neovascularization AMD as of May 2011
 - First commercial evaluation validated on a large scale population (2,000 subjects) that targets CNV
 - Must be ordered through a retinal specialist and is covered by most insurances
- Other labs in the U.S.
 - UPenn: \$220 for testing 3 major AMD polymorphisms
 - Decode Me: all 47 tests \$1,100.
 - 23andMe: \$99 + \$9/mo 1 yr. commitment required. \$207

Future Treatments

1. Factor B polymorphism 32Q has a protective ability by dampening the complement factor pathway decreasing inflammation
2. CD59 inhibits MAC (membrane attack complex) and reduces CNV. Tufts University Medicine.
 - a. 62% less Neovascular growth.
3. PEDF (pigment epithelium derivative)

- a. Inhibits neovascularization in the retina and choroid
 - b. Can even reverse neo
 - c. Clinical trials show high dose treatment improved lesion size in 71% vs 50% in low dose treatments
4. Anti-VEGF
- a. Ranibizumab or Bevacizumab injections currently used
 - b. Long lasting effects with gene transfer.
 - c. Current clinical trials are recruiting to determine the maximum tolerable load in a single dose of an intravitreal injection.

Resources:

1. Wills Eye Manual. Lippincott Williams & Wilkins. Fifth Edition Edition. February 1, 2008.
2. Age-Related Macular Degeneration. National Eye Institute.
<http://www.nei.nih.gov/health/maculardegen/armd_facts.asp>. February 2011
3. Myvisiontest.com
4. 23andme.com
5. Handbook of Ocular Disease Management. EBMD.
<http://cms.revoptom.com/handbook/sect3i.htm>
6. PubMed. A subset of patients with epithelial basement membrane corneal dystrophy have mutations in TGFBI/BIGH3.

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Coloboma

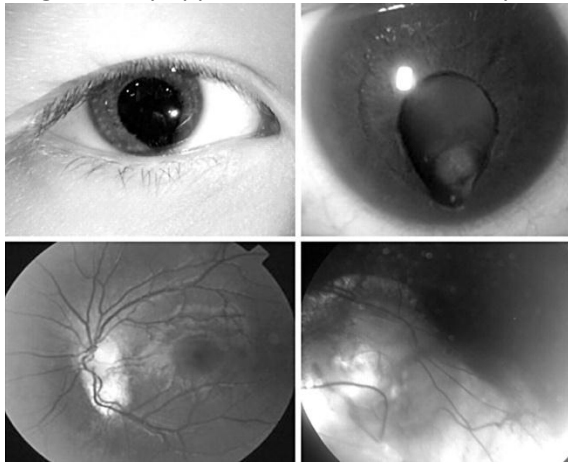
Bobby Champion

Clinical Description

- An incomplete closure of the optic fissure during the embryonic period of development can lead to colobomata to one or more areas of the eye including cornea, iris, ciliary body, lens, retina, choroid, and optic nerve. An eyelid coloboma can also occur, but this is unrelated etiologically and is not from failed closure of the optic fissure. (Gregory-Evans, Williams, Halford, & Gregory-Evans, 2004)
- Occurs in about 2.6 births per 10,000 in the USA (Porges, 1992)

Diagnosis/testing

- Diagnosed by appearance, most commonly inferonasal.



Clockwise from top-left: Iris coloboma, iris coloboma with cataract, small choroidal coloboma beneath optic nerve head, large chorioretinal coloboma affecting retina and optic nerve head. (Gregory-Evans, Williams, Halford, & Gregory-Evans, 2004)

- Iris coloboma can be associated with photophobia (Pagon, 1999)
- Chorioretinal defects are associated with superior visual field defects and decrease VAs (Pagon, 1999)
- Colobomata affecting the macula or optic nerve usually decrease VAs significantly (Pagon, 1999)
- Associated with microphthalmos, anophthalmia, craniofacial abnormalities, skeletal abnormalities, and genitourinary anomalies (Gregory-Evans, Williams, Halford, & Gregory-Evans, 2004)

Management

- Full refractive correction with possible tinting for photophobia or colored SCL for cosmetic purposes
- Patching for any amblyopia
- Monitor/treat any cataracts, retinal detachments, etc.
- Refer to PCP for medical examination to rule out syndromes

Genetic Counseling

- Many genes are involved in the closing of that optic fissure. These genes are also involved in many other developmental functions. This results in an extraordinary number of heritable

conditions with coloboma, at least 74 conditions (NCBI, 2011). 11 are chromosomal aberrations, 13 are autosomal dominant, 14 are autosomal recessive, 3 are X-linked, and more are undetermined (Gregory-Evans, Williams, Halford, & Gregory-Evans, 2004). The coloboma phenotype is definitely heterogenous and is mostly associated with systemic disease.

- A large proportion of sporadic, unilateral colobomata are due to non-genetic factors
- A family history should be obtained to determine any Mendelian Inheritance patterns. If a familial form is identified, counseling follows a conventional method based on the type of inheritance (Gregory-Evans, Williams, Halford, & Gregory-Evans, 2004).
- In cases where there is no family history, occurrence in a sibling with a coloboma is between 2.9% and 33% depending on presentation.
- When specific syndromes are suspected or considered, the appropriate genetic screens should be done.

Patients FAQs

Could you explain about the disease?

- A coloboma is when a part of the eye failed to fully form. It appears as a lack of tissue, usually in the bottom left part of the structure affected. It can occur with the iris (colored part of the eye), the retina/choroid (part of the eye that detects light), and/or the optic nerve (the part of the eye that sends the signal to the brain). Iris colobomata are the most cosmetically noticeable but least symptomatic. The retina, choroid, and optic nerve colobomata won't usually be noticed cosmetically, but can lead to very significant reductions in vision in the affected eye.

How is it diagnosed?

- Iris coloboma: External examination of the eye
- Retina/choroid/optic nerve coloboma: The doctor will use special tools to examine the back of the eye. Also, Visual Field testing and Visual Acuity testing will aid in diagnosis.

Why am I being offered genetic testing?

- Colobomata are often associated with syndromes or diseases that can affect our whole body. The main purpose of the tests are to help determine if you have the genes for any of these diseases.

What treatment exists and how effective is it?

- Iris colobomata can be fit with colored contact lenses to help with light sensitivity and for a cosmetic effect
- Regular eye exams will be required because they can put you at risk for retinal detachments or cataracts.

How will I be informed about results?

- We will arrange an appointment where we can review the results.

Who will care for me in the event of positive result?

- That depends on what you test positive for. Remember, colobomata are associated with many disorders, so if you tested positive for one of those, we would refer you to the appropriate specialist.

What if the test is negative, can I relax?

- A negative test result is great news and means that you do not have the genetics associated with the most common of the syndromes. It is not possible, however, to test for every possible disease associated with colobomata, so it would still be possible to have one of the rarer disorders.

How will my confidentiality and privacy be protected?

- We will only release these test results to you (or someone you authorize). The tests are performed by professionals and we will only forward them on to another doctor with your permission.

Who will have access to my results?

- See above

How much will the test cost?

- Between \$100 and \$1000

Will my insurance cover testing?

- Many companies will, we can check with your specific insurance provider.

What's involved?

- We will collect a sample by swabbing the inside of your mouth and then we'll send that sample to the lab.

How does genetic testing work?

- They take the DNA from your cheek swab and screen it for target genes associated with diseases using advanced technology

What's the next step?

- If positive for a disorder, we will refer you to a specialist who can educate you about the disorder and come up with a treatment plan.

Where can I get more information?

- Here's a link to a informative pdf file:
<http://www.nei.nih.gov/health/coloboma/factsaboutcoloboma.pdf>

Works Cited

- Gregory-Evans, C., Williams, M., Halford, S., & Gregory-Evans, K. (2004). Ocular coloboma: a reassessment in the age of molecular neuroscience. *Journal of Medical Genetics* , 881-891.
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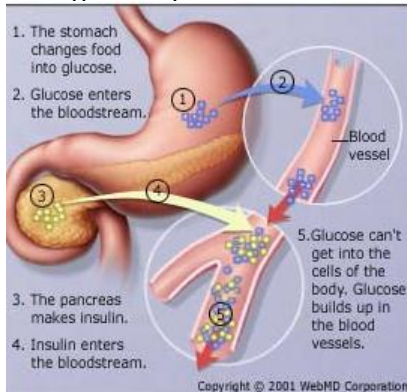
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Type 2 Diabetes

Collin Robillard

Type 2 diabetes is a condition in which there is a problem with insulin and your body's ability to use it properly. The purpose of insulin is to move sugars (glucose) from food into your body's cells in order for the cells to function properly. Insulin is made by the pancreas, which is an organ just above your stomach. A type 2 diabetic patient will have cells that are resistant to insulin and too much sugar will accumulate in their blood (hyperglycemia). If the sugar stays in the vessels, it can cause damage to them. Individuals can have diabetes at any age, but type 2 occurs more often in overweight adults, and has an increased incidence in individuals with family members who have diabetes. Diabetes mellitus is a lifelong condition.

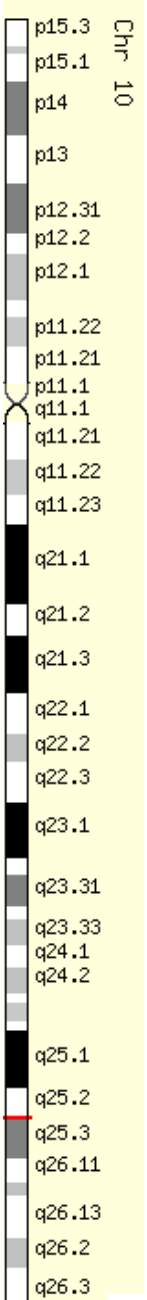
Recent evidence suggests that diabetes may have a genetic component that centers around the TCF7L2 gene located on the long arm of chromosome 10. The presence of this gene during genetic testing indicates a higher likelihood of type 2 diabetes. The TCF7L2 gene carries with it an increased risk of diagnosis by a factor of 55-70% within the patients lifetime.



Type 2 Diabetes is diagnosed by a doctor taking a careful medical history, a physical examination, and two blood tests each must be consistent with a fasting blood glucose level of 126mg/dl. There is a large genetic component associated with type 2 diabetes. Therefore genetic tests can be done to see if an individual carries the specific TCF7L2 gene. If so, there is an increased risk of ones development of type 2 diabetes.

Treatments for type 2 diabetes can vary depending on the severity of the condition it could be as simple as diet and exercise control. Avoiding high fat and sugar rich foods can help the body cope with the amount of sugar present in the blood. Exercise can help regulate the amount of fat in the body and improve the immune system. However some type 2 diabetic patients are better controlled with medications that aid in the bodies ability to use sugar.

Type 2 diabetes is a complex condition that has many factors that affect a patient's ability to manage the condition. Lifestyle modifications will need to be made, but results are promising. With proper genetic counseling some patients may be able to avoid the diagnosis if they take preventative measure against the disease. Remember to go to your doctor for a physical once a year as well as your optometric physician in order to indentify warning signs of type 2 diabetes.



How Is

- 2) Diagnosis/testing
- 3) Management
- 4) Genetic Counseling

Patient FAQs

Could you explain about the disease?

- Type 2 diabetes is a condition in which there is a problem with insulin and your body's ability to use it properly. The purpose of insulin is to move sugars (glucose) from food into your body's cells in order for the cells to function properly. Insulin is made by the pancreas, which is an organ just above your stomach. A diabetic patient will have cells that are resistant to insulin and too much sugar will accumulate in their blood (hyperglycemia). If the sugars stay in the vessels, it can cause damage to them. Individuals can have diabetes at any age, but type 2 occurs more often in overweight adults, and has an increased incidence in individuals with family members who have diabetes. Diabetes mellitus is a lifelong condition.

How is it diagnosed?

- Diabetes is diagnosed by a doctor taking a careful medical history, a physical examination, and two blood tests each must be consistent with a fasting blood glucose level of 126mg/dl.

Why am I being offered genetic testing?

- Diabetes has a strong genetic component, but also is influenced by environmental factors such as diet, exercise, stress, and smoking. There is a specific gene known as TCF7L2 that is associated with a high risk of developing Type 2 diabetes. In particular, an overweight individual with this gene shows a 50-77% increased risk of developing type 2 diabetes in their lifetime.

What treatment exists and how effective is it?

- Treatments for type 2 diabetes can vary. Depending on the severity of the condition it could be as simple as diet and exercise control. Avoiding high fat and sugar rich foods can help the body cope with the amount of sugar present in the blood. Exercise can help regulate the amount of fat in the body and improve the immune system. However some type 2 diabetic patients are better controlled with medications that aid in the body's ability to use sugar. If those pills don't work, the body can be given injections of insulin.

How will I be informed about results?

- The results will be mailed to you and when you receive them you can come in for a consult to explain the results and discuss any preventative treatments.

Who will care for me in the event of positive result?

Fortunately type 2 diabetics if well controlled can lead a healthy and happy lifestyle.

What if the test is negative, can I relax?

No you cannot relax. You should still take preventative measures to developing type 2 diabetes such as, proper diet and exercise. Reduce environmental factors that could lead to the diagnosis of type 2 diabetes such as, reduced alcohol consumption and smoking.

How will my confidentiality and privacy be protected?

Your genetic code may be used in a database, but without your name attached anywhere to it.

Who will have access to my results?

Your doctor and the company in which you asked to complete your testing. Again, your name will be erased from their file so that you're genetic code will not be able to be identified by anyone else.

How much will the test cost?

-Depending on how much you would like to test about your genetics it can range from \$299-\$2000.

Will my insurance cover testing?

Currently insurance will not cover genetic testing.

What's involved?

It can be as simple as a cheek swab or blood sample

How does genetic testing work?

- Your DNA goes through a series of lab processes to mark out specific codes in your DNA that are associated with particular genetic conditions. In your example the TCF7L2 gene could be found to be a part of your DNA.

What's the next step?

The next step is education about the results and how to prevent or treat the condition found.

Where can I get more information?

- You can do an Internet search of genetic testing and find sites like decomeme.com, genetests.com, etc...

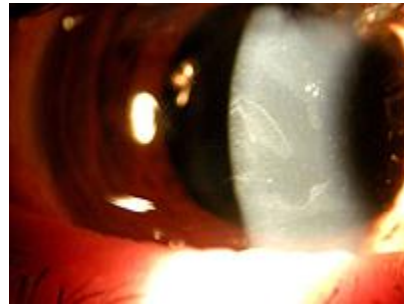
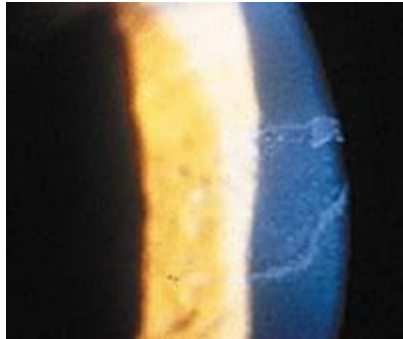
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Epithelial Basement Membrane Dystrophy

Caroline Slagle

Clinical Description

- a. EBMD is the most common anterior dystrophy
- b. Bilateral, grey epithelial patches (maps) and white cysts (dot) or fingerprint lines.
- c. Debris in the BM. Autosomal Dominant
- d. Spontaneous painful corneal erosions can develop especially upon waking/opening the eye



Diagnosis/testing

- e. Asymptomatic or RCE after age 30 seen on fluorescein dye.
- f. Decreased Vas, painful erosions, monocular diplopia, shadow images.

Management

- g. Hypertonic (Muro 128 5% NaCl)
- h. Bandage CL and topical antibiotic qid
- i. After initial healing, use artificial tears 4-8 times per day and ointment qhs for 3-6 mo
- j. Debridement if not healing
- k. PTK. Phototherapeutic keratectomy

Genetic Counseling.

- l. EBMD is not totally inherited
- m. TGFB1 on chromosome 5. Controls extracellular matrix proteins. Cell-collagen interactions, inhibits cell adhesion. Many corneal dystrophies occur if this gene is altered. (Lattice and Reis Buckler, many kinds of corneal dystrophies)
- n. Type 1,2,3 collagen affected. Also in cartilage bone formation.
- o. Up to 10% of patients with EBMD have this altered gene TGFB1

Resources:

1. Wills Eye Manual. Lippincott Williams & Wilkins. Fifth Edition Edition. February 1, 2008.
2. Handbook of Ocular Disease Management. EBMD.
<http://cms.revoptom.com/handbook/sect3i.htm>
3. PubMed. A subset of patients with epithelial basement membrane corneal dystrophy have mutations in TGFBI/BIGH3. [Back to CONTENTS](#)

Leber's Congenital Amaurosis (LCA)

Vivian Diep

Clinical Description:

Leber's Congenital Amaurosis is the most common genetic disorder that causes congenital blindness. Roughly 2 out of every 100,000 babies are born visually impaired or blind. This condition is typically stable but can progressively worsen with age and specifically targets the retinal photoreceptors causing abnormal photo-transduction process. There are many gene mutations that play a role in this loss of retinal function, but the most notably studied gene mutation occurs in the light-detecting RPE cells, specifically the RPE65 gene. This mutation impairs RPE cell production of Vitamin A, preventing the normal process of the retina to take place leading to the loss of vision occurring at birth.

An autosomal recessive pattern is most characteristically seen with the RPE65 mutation, but this condition can also have an autosomal dominant pattern due to other forms of mutations. Idiopathic causes due to completely new mutations that are not seen through any sign of inheritance have been found to occur as well.



Figure 1. Retinal photo of a pt w/ LCA RPE65 antibody

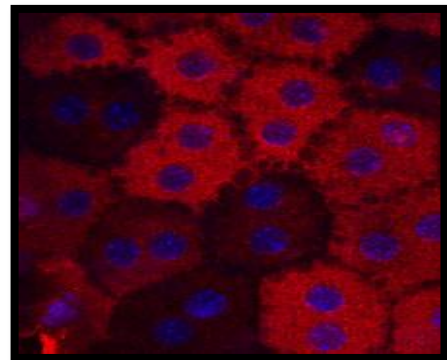


Figure 2. RPE cells stained red by RPE65 antibody

Diagnosis/testing

Diagnosis with Ocular Symptoms:

- Nystagmus
- Severe reduction of vision loss at birth; Hyperopia > 5 diopters
- Photophobia
- Impaired/Non-reactive pupil responses
- Self-limiting Keratoconus
- Franschetti's oculo-digital sign (diagnostic for LCA)
 - = newborns/infants are poking, rubbing, or pressing their eyes with either a knuckle or finger
- Varying fundus appearance (~RP)
- Impaired development & intellectual disability

Testing:

- Subnormal Photopic & Scotopic ERG findings
- Molecular test to examine 12 known gene mutations that account for 40-50% of all LCA

- | | |
|-------------------|--------------------|
| 1. GUCY2D (LCA1) | 7. CRX (LCA7) |
| 2. RPE65 (LCA2) | 8. CRB1 (LCA8) |
| 3. SPATA7 (LCA3) | 9. CEP290 (LCA10) |
| 4. AIPL1 (LCA4) | 10. IMPDH1 (LCA11) |
| 5. LCA5 | 11. RD3 (LCA12) |
| 6. RPGRIP1 (LCA6) | 12. RDH12 (LCA13) |

- Genetic testing:
 - Autosomal recessive
 - Autosomal dominant
 - Idiopathic mutations

Management

- Supportive – local support groups, LV aids, RE corrections, outreach for job opportunities\
- Preventive – watch the child & discourage them from poking/rubing their eye, genetic counseling
- Surveillance – continual RE correction, periodic examination of their eyes to screen for cataracts, amblyopia, glaucoma

Genetic Counseling

- Most often LCA is inherited in an autosomal recessive manner.
- 25% chance of each child becoming affected
- 50% chance of each child becoming an asymptomatic carrier
- 25% chance of being unaffected and not a carrier
- Carrier testing for at-risk family members and prenatal testing for pregnancies at increased risk may be possible if the disease-causing mutations in the family are known
- Rarely, LCA is inherited in an autosomal dominant manner as a result of mutations within *CRX*; the possibility of autosomal dominant inheritance resulting from a *de novo* *CRX* mutation should be considered in individuals with LCA and no family history of the disease

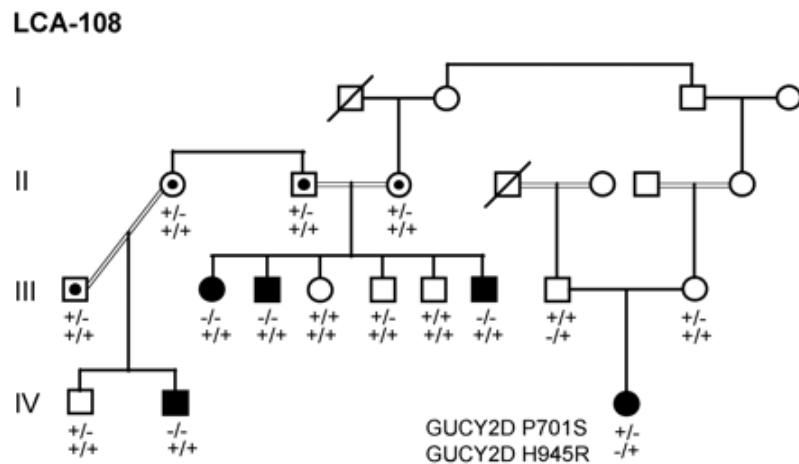


Figure 3. Example pedigree of a family segregating LCA with the LCA1

variant

Patient FAQs

Could you explain about the disease?

- Severe loss of vision or blindness present at birth
- Condition affects the part of the retina that detects light & color
- Specific cell in the retina is not producing Vitamin A, preventing normal process of retina to occur
- Non-fatal, but can impair development as well as intelligence

How is it diagnosed?

Not universal but most commonly seen:

- >20/400 VA
- < 6 months old are legally blind w/ this severe blindness/visual impairment
- Severely reduced ERG (Scotopic & Photopic conditions)
- Consistent w/ AR inheritance

Why am I being offered genetic testing?

- Risks:
 - Strong family history of eye blindness
 - Pregnancy after the age of 35
 - 2/more miscarriages
 - Ultrasounds/Screening tests that suggest a possible problems to unborn child
- Expands knowledge of the inherited condition
- Determines the overall health of each individual family member
- Determines chances of further passing on the disease to their children

What treatment exists and how effective is it?

- Major advances in treatment within the past decade for LCA
- Recent Clinical trial in 2009:
 - 5 known human trials ages ranging from 8-44
 - given single shot of gene therapy
 - Although have not fully recovered their eyesight, their vision has been improved enough to no longer be considered
- Clinical Trials are currently recruiting others with the disease to further study treatment outcomes
Legally blind.

How will I be informed about results? Who will care for me in the event of positive result?

- Genetics Counselor will be available for each client throughout the entire process to discuss the condition, inheritance pattern, outcome, and results from the tests
- Local support groups, LV aids, local optometrists/ophthalmologists referral, and outreach programs will be offered in the event of a positive result

What if the test is negative, can I relax?

- Although this disorder is primarily inherited from parent to child, there is chance that a new mutation can occur with at risk patients mentioned above

How will my confidentiality and privacy be protected?

- The Genetic Information Nondiscrimination Act, or GINA protects your privacy

Who will have access to my results?

- Independently paid counseling sessions will only be accessed by the client
- Insurance covered counseling sessions will be accessed by yourself as well as the insurance company

How much will the test cost?

- Testing costs vary between \$100.00-\$3,000.00

Will my insurance cover testing?

- Yes, insurance does cover testing

What's involved?

- Screening for most common genetic conditions
- If there is a family history, specific testing can be done
- Appointments for genetic testing may last from 2 hours to 2 days depending on the lab
- Tests involve:
 - Comprehensive eye exam with dilation to examine ocular health
 - Color vision screening
 - Visual field testing
 - Photography
 - Electrophysiology tests (ERG)
 - May involve blood tests
 - With a positive result, routine eye exams are required for monitoring the

progression

How does genetic testing work?

Genetic testing can be as simple as:

- Ordering a kit online
- Providing a saliva sample to an internet site or company
- Receiving results of a general screening of the most common genetically inherited conditions in 6-8 weeks.
- For a definitive diagnosis blood work up may be required
- Clinical trials of gene therapy are still available for individuals 6 years and older

What's the next step?

If positive for LCA, resources are offered to help manage the condition

1. Supportive – support groups, LV aids, RE corrections, outreach for job opportunities
2. Preventive – watch the child & discourage them from poking/rubbing their eye, genetic counseling
3. Surveillance – continual RE correction, periodic examination of their eyes to screen for cataracts, amblyopia, glaucoma

Where can I get more information?

- Online resources:
<http://www.nei.nih.gov/lca/>

<http://ghr.nlm.nih.gov/condition/leber-congenital-amaurosis>
<http://www.ncbi.nlm.nih.gov/books/NBK1298/>
<http://www.ohsu.edu/xd/health/services/casey-eye/clinical-services/specialty-services/genetics/clinical-trials.cfm>
<https://www.23andme.com/howitworks/>
<http://www.nlm.nih.gov/medlineplus/genesandgenetherapy.html>
http://www.nfb.org/nfb/legally_blind_definition.asp?snid=2

- Video link:
http://www.biotechweblog.com/50226711/gene_therapy_for_lebers_congenital_amaurosis_lca.php

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Lowes Syndrome

Collin Robillard

Lowes Syndrome or Oculocerebrorenal syndrome of Lowe is a multisystem disease involving the eyes, central nervous system, and the kidneys. These patients typically do not live past the third decade of life. Lowes syndrome is an X-linked recessive disorder that affects 1:200,000-500,000 births. This rare disorder affects mostly males, whom are more likely to have severe symptoms compared to females. Females are only affected by lens opacities, but suffer not other side effects of the condition. Lowes syndrome in males is characterized by congenital cataracts, glaucoma, motor retardation, intellectual impairment, muscular hypotonia, seizures, renal tubular dysfunction also known as Fanconi's syndrome, metabolic acidosis, proteinuria, and aminaciduria. These patients also suffer from facial deformities such as enophthalmos, full cheeks, and frontal bossing or a bulging of the forehead outwards.



The metabolic portion of Lowes syndrome has to do with the bodies inability to remove certain components from the blood such as acids, proteins, and amino acids via the renal or kidney system. Because of this lack of removal from the renal system, the concentrations of these products increase causing the body to function inappropriately. However, these renal conditions are not present at birth and are more likely to develop later in life.

The eyes as mentioned previously suffer from glaucoma, and enophthalmos. Enophthalmos is when the eyes are pushed further back into their sockets. As a result, glaucoma may be present in up to 50% of males, although not at birth. Glaucoma is also a multi-factorial condition involving increased pressures in the globe that may lead to blindness. The cataracts associated with Lowes syndrome are posterior subcapsular and are a critical identifier in the diagnosis process.

As mentioned previously, muscular hypotonia is a component of Lowes syndrome. This is present at birth and results in low muscle mass and the inability for normal mobility. These patients also have reduced reflexes at birth. Because of this CNS defect and muscular abnormalities, these patients may suffer from mobility complications.



The genetic component to Lowes syndrome has to do with the OCRL 1 gene that has been

mapped to Xq25-26. This particular gene helps regulate certain levels of phospholipids. When these levels get too high, they impair intracellular function causing many of the developmental, muscular, facial, eye, and renal abnormalities present in Lowe's syndrome.

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Primary Open Angle Glaucoma (POAG)

Vivian Diep

Clinical Description

Primary open angle glaucoma, POAG, is the most common type of glaucoma affecting 1-2% of the population. POAG is described as a chronic condition having no symptoms with slowly increasing intraocular pressures. Glaucoma is generally known for causing damage due to high intraocular pressures from the blockage of aqueous at the filtration sites, such as the trabecular meshwork, attributed largely to small anterior chamber angles. In this case, patients with POAG have normal working trabecular meshwork and their angles are seen as open, yet still create an increase in intraocular pressures.

Damages from high pressures primarily involve the optic nerve head and destruction to the optic nerve cells causing visual field loss. Peripheral blind spots are initially observed with central vision loss occurring in later disease stages if it is not treated or properly maintained. The disease may go undetected and once damage has occurred, vision loss is irreversible. Once these cells are dead there is nothing that can be done to restore them. There is no cure for POAG but with treatment, it can slow the onset of vision loss if treatment is implemented with an early diagnosis.

It is not certain to what exactly may be the cause of this form of glaucoma but genetics have recently found specific gene mutations that can play a large role in the age of onset and severity of the disease.

One gene in particular, MYOC gene, has been found to play a key role in one of many causes of POAG. With the myocilin mutation Pro370Leu, an earlier onset form of POAG, also known as Juvenile open angle glaucoma (JOAG), can present more aggressively with higher elevations in IOPs. The only other myocilin mutation of Gln368STOP6 has been described as adult onset POAG with a lesser degree of aggressiveness and lower IOPs than JOAG.

This Myocilin gene (MYOC), initially named Trabecular Meshwork-Inducible Glucocorticoid Response Protein gene (TIGR), is expressed in the trabecular meshwork, ciliary body, retina as well as other tissues in the body. The pathophysiology of this MYOC mutation is still unclear, but studies have suggested accumulation of this myocilin mutated protein can damage the trabecular meshwork cells within the iridocorneal angle causing a reduction in the aqueous outflow leading to the increase in intraocular pressures and eventually glaucoma. Approximately 4% of the POAG adult population has this mutation. Other genes have been found to cause different glaucoma forms such as CYP1B1 for congenital glaucoma and Optineurin (OPTN) for normatensive or high tension glaucoma.

Diagnosis/testing

POAG has varying characteristics to the disease and many factors must be accounted for diagnosis:

- Optic nerve atrophy
- Visual field loss
- Increase intraocular pressures (without signs of angle closure)
- High risk patients:
 - Strong family history of glaucoma

- Early onset of disease
- Increased IOP's

Testing:

- Pachymetry
- Gonioscopy
- Tonometry
- Visual field tests
- Fundus exams w/ photo-documentation
- Genetic testing for presence of MYOC/TIGR mutation if warranted by high risk individuals

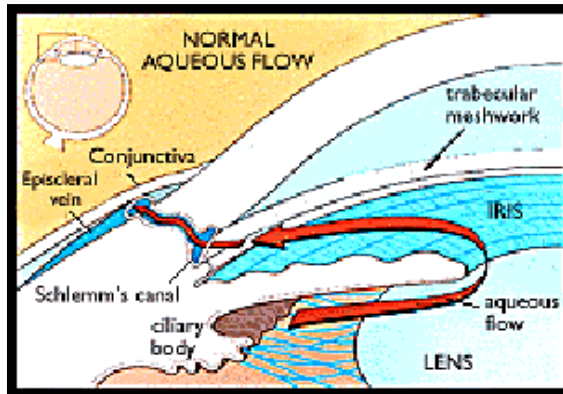
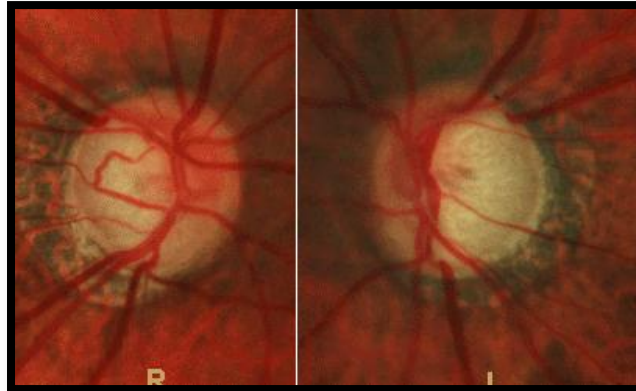


Figure 1. Characteristic notching of neural retinal tissue of the optic disc aqueous production

Figure 2. Rate of outflow through meshwork determined by

Management

Less aggressive POAG:

- Pharmaceutical medication
 - Singly or in combination with others
 - Ophthalmic ointments or solutions
 - Systemic oral medication
 - Advantages: Reduction of aqueous production and/or allow for other filtration passageways
 - Disadvantages: many different side effects
- Surgeries for more aggressive forms (i.e. JOAG or when medication is ineffective)

- Cycloablation surgery: reduces aqueous production by destroying part of the ciliary body
- Argon Laser Trabeculoplasty (ALT): increases drainage outflow
- Selective Laser Trabeculoplasty (SLT): increases drainage outflow
 - Safer procedure due to its low energy lasers
 - Selectively treats portions of trabecular meshwork leaving other parts intact
- Can be repeated
- Preferred surgery: ALT followed by SLT treatment

Genetic Counseling

- Mutations in genes can be inherited as a Mendelian trait and contribute to development of glaucoma
- Mutation in a single gene can overwhelm other factors and can have a higher risk for the disease
- Vast majority of mutation carriers develop the disease

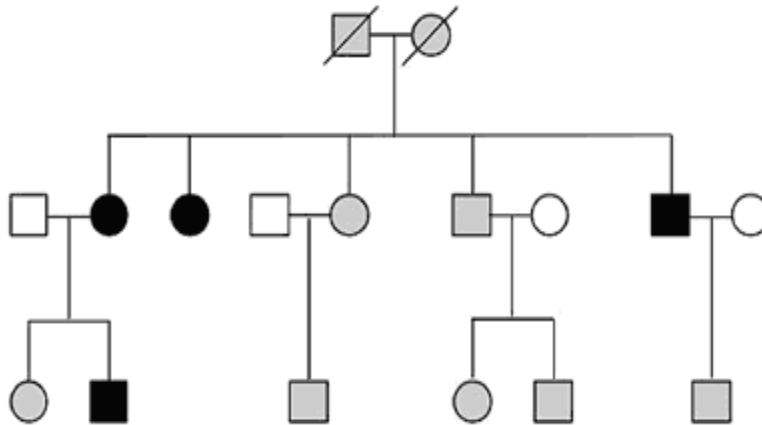


Figure 3. Pattern of inheritance of POAG pedigree

Patient FAQs

Could you explain about the disease?

- POAG is a form of glaucoma that causes an increase in the eye's pressure through a different process than the general blockage of the filtration system in the eye
- In this condition, the eye's filtration system is not blocked but rather the cells in the system are not functioning normally and cause an increase in pressures.

How is it diagnosed?

- POAG typically can go undetected due to the asymptomatic nature of the disease
- Genetic testing will rule out whether it is due to a mutation or environmental causes
- Other diagnostic tests include:
 - Checking pressures
 - Factors that account for the outflow of aqueous within the eye
 - Thickness of the cornea

- Visual field testing
- Dilation of the eye to assess possible defects of the optic nerve and the nerve fiber layer

Why am I being offered genetic testing?

- POAG has a hereditary component with common familial traits
- Screen for the specific genetic mutation in what is known as the MYOC gene
- Can help define the disease condition:
 - Age of onset
 - Severity
 - Prognosis
 - Effectiveness of available treatment

What treatment exists and how effective is it?

- Pharmaceutical medications prescribed to maintain and/or reduce intraocular pressures
 - Topical, solutions, and oral medication
 - Can be prescribed singly or in combination
- Filtration and Laser surgery is implemented for severe aggressive forms of POAG and when medication is no longer effective or causing too many side effects

How will I be informed about results? Who will care for me in the event of positive result?

- Genetics Counselor will be available for each client throughout the entire process to discuss the condition, inheritance pattern, outcome, and results from the tests
- Local support groups, local optometrists/ophthalmologists referral, and outreach programs will be offered in the event of a positive result

What if the test is negative, can I relax?

- There is a greater risk if you have a family history of glaucoma in the family
- A negative result does not indicate that you will not have the disease due to other causes.

How will my confidentiality and privacy be protected?

- The Genetic Information Nondiscrimination Act, or GINA protects your privacy

Who will have access to my results?

- Independently paid counseling sessions will only be accessed by the client
- Insurance covered counseling sessions will be accessed by yourself as well as the insurance company

How much will the test cost?

- Testing costs vary between \$100.00-\$3,000.00

Will my insurance cover testing?

- Yes, insurance does cover testing

What's involved?

- A general eye exam is required for diagnosis and management of this condition

- Routinely monitoring intraocular pressures as well as setting target/goal pressures
- Visual acuity assessment
- Optic nerve examination
- Corneal thickness readings with Pachymetry
- Visual field tests
- Examining the anterior chamber angles with Gonioscopy
- Fundus photos for documentation

How does genetic testing work?

Genetic testing can be as simple as:

- Ordering a kit online
- Providing a saliva sample to an internet site or company
- Receiving results of a general screening of the most common genetically inherited conditions in 6-8 weeks.
- For a definitive diagnosis blood work up may be required
- Clinical trials of gene therapy are still available for individuals 6 years and older

What's the next step?

Knowing the specific mutation will guide:

- Follow-up frequency
- Initiation of treatment
- Type of treatment that would be most beneficial
- The Chronic nature of the disease may require lifelong treatment & may be required even without symptoms noticeable to the patient
- Genetic therapy has not yet been implemented but promise of future trials may be beneficial in the prevention of vision loss and of an earlier diagnosis

Where can I get more information?

Online resources:

- http://www.emedicinehealth.com/primary_open-angle_glaucoma/page6_em.htm
- http://www.glaucomafoundation.org/treating_glaucoma.htm
- <http://ghr.nlm.nih.gov/condition/early-onset-glaucoma>

Articles:

- http://www.revophth.com/content/d/glaucoma_management/i/1341/c/25685/
- http://bmctoday.net/glaucomatoday/2009/06/article.asp?f=GT0509_02.php

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Retinoblastoma

Bobby Champion

Clinical Description

- Most common primary ocular tumor in childhood (Medscape, 2011)

Diagnosis/testing

- 95% of patients with retinoblastoma have no family history (Medscape, 2011)

- **Presenting Signs or Symptoms with Retinoblastoma:**

Sign or Symptom	Percentage (%)
White reflex or “cat’s eye” reflex	56.0
Strabismus	20.0
Red, painful eye with glaucoma	7.0
Poor vision	5.0
Routine Examination	3.0

(Medscape, 2011)

-
- Blood samples should be taken of patient as well as parents and siblings for genetic testing. Aqueous humor assays can also be helpful in diagnosis. (Medscape, 2011)
- Test for mutations/deletions of *RB1* gene on Chromosome 13 (U.S. National Library of Medicine, 2011)
- *RB1* is a tumor suppressing gene so when it’s function is altered, cell growth can continue uninhibited (U.S. National Library of Medicine, 2011)
- Testing can be done even prenatally (U.S. National Library of Medicine, 2011)
- Imaging studies, especially CTs, can confirm diagnosis (Medscape, 2011)
- Testing should also be done to screen for cancer that has spread (Medscape, 2011)

Management

- Survival rate between 86 and 92% with decreased survival rate in germinal mutations (Medscape, 2011)
- 5 Types of Treatment
 - a. Enucleation
 - b. Radiation therapy
 - c. Cryotherapy
 - d. Thermotherapy
 - e. Chemotherapy(National Cancer Institute, 2011)
- Clinical trials are available (National Cancer Institute, 2011)
- Orbital recurrence/relapse rate is approximately 2.5% (Hungerford, Kingston, & Plowman, 1987)

Genetic Counseling

- 2 types: germinal and non-germinal (somatic)
- Germinal can be inherited and when it is, it is autosomal dominant. The *RB1* mutation is inherited on one chromosome, and eventually (usually in childhood) the

other chromosome becomes mutated and a retinoblastoma forms. (U.S. National Library of Medicine, 2011)

- Non-germinal do not have a family history, are only in one eye, and are not passed on to future generations. (U.S. National Library of Medicine, 2011)
- If someone is identified as a carrier of a germinal mutation, 50% of children will inherit the gene. There is 90% inheritance. $0.50 \times 0.90 = 0.45$ so each of that carrier's children will have a 45% chance of developing a retinoblastoma. (Medscape, 2011)

Germinal	Non-Germinal (Somatic)
Less Common	More common
Passed on to children (Autosomal dominant)	Not passed on to children
Frequently bilateral	Unilateral
Often family history	No family history
Decreased survival rate	~90% survival rate

Patient FAQs

Could you explain about the disease?

- It is a tumor in the back of the eye that affects infants and young children

How is it diagnosed?

- The most common way is by identifying a white reflection in the back of the eye. It's similar to "red eye" in photographs, but instead of red, it appears white.

Why am I being offered genetic testing?

- There are two types of retinoblastomas: those that can be passed down to future children, and those that are highly unlikely to be passed down to children. The type that is unlikely to be passed down involves only the eye. The other type has a genetic component that may or may not be passed down. Genetic testing will help us determine which type your child has.

What treatment exists and how effective is it?

- Depending on the size and severity of the tumor, different treatments are available. Fortunately, the treatment is relatively successful with only 2.5% recurrence. Unfortunately, much of the time the tumor needs to be treated aggressively which can result in blindness of the affected eye and often loss of that eye.

How will I be informed about results?

- We will arrange an appointment where we can review the results.

Who will care for me in the event of positive result?

- There is a Ocular Oncology team at the Casey Eye Institute in Portland that we will refer you to.

What if the test is negative, can I relax?

- No. The test result will help us determine if your child can potentially pass it on to future generations or not. Also, the blood test only detects the most common retinoblastoma genes, so it is important to test the tumor DNA as well. If tumor DNA is not tested, it is possible that your child has a less common retinoblastoma gene. (Raizis A, 2002)
- Regardless, your child must be treated for this serious illness.

How will my confidentiality and privacy be protected?

- We will only release these test results to you (or someone you authorize). The tests are performed by professionals and we will only forward them on to another doctor with your permission.

Who will have access to my results?

- See above

How much will the test cost?

- Most likely between \$152 and \$536 (Joseph, Shanmugam, Srinivasan, & Kumaramanickavel, 2004)

Will my insurance cover testing?

- Many companies will, we can check with your specific insurance provider.

What's involved?

- It works best if tumor tissue is available, so often they will run the tests immediately following tumor extraction. Blood DNA is also be tested, but the test only checks for the most common retinoblastoma genes, so it can easily miss a less common gene if it is the sole method used (i.e. no tumor DNA).

How does genetic testing work?

- They collect a sample (blood, tumor, etc.) and use special techniques to examine it on a molecular level for specific genes.

What's the next step?

- Visit the Ocular Oncologist for an assessment and treatment plan.

Where can I get more information?

<http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002025/>

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Stickler Syndrome

Cayla Picklyk

Clinical Description:

Stickler syndrome has been categorized into four types, each with its own genotype and phenotype.

Three of these types include varying degrees of eye anomalies.

Manifestations include:

- Hearing problems
- Joint problems: arthritis, scoliosis (abnormal curve of the spine)
- Eye abnormalities due to collagen failure:
 - Cataracts
 - High myopia
 - High pressures/ glaucoma
 - Vitreous changes leading to a retinal detachments
 - Stickler's is the most common cause of childhood retinal detachments
 - Choriorretinal degeneration – lattice, holes, tears
 - Blindness in some cases
- Distinct facial appearance: named the “Robin sequence”
 - Cleft palate - opening in the roof of the mouth)
 - Macroglossia - large tongue
 - Micrognathia - small lower jaw



Diagnosis/testing:

- Eye Testing: refraction, slit lamp, pressures, Gdx, fundus exam
- Hearing tests: audiogram
- X-Rays: joints and spine damage
- Genetic testing to confirm diagnosis or prenatal testing. The genes currently known to be involved in this syndrome include:
 - *COL2A1*, *COL9A1*, *COL11A2*
 - Mutations impair collagen production, processing, and assembly which disrupts connective tissues throughout the body

Management:

- Prophylactic cryotherapy recommended in infants, since most experience a significant retinal tear by age 18 mo
- Monitor for cataract removal, glaucoma, and refractive error

Genetic Counselling:

One in eight newborns are affected with Stickler Syndrome. Mutations can be spontaneous or they may be inherited from affected parents in an autosomal dominant (genes *COL11A1*, *COL11A1*, *COL11A2*) or recessive pattern (gene *COL9A1*). There may be incomplete penetrance and variable expression, producing different types and degrees of severity. Prenatal testing can be performed for the genes that have been identified by research this far.

Support group: <http://www.sticklers.org/sip2/>

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Usher Syndrome

Cayla Picklyk

Clinical Description

More than four people per 100 000 living in the USA have Usher Syndrome. It accounts for 50% of the people who are both blind and deaf, as well as under 20% of those with retinitis pigmentosa.

Manifestations:

- Symmetric, progressive bone spicule retinal pigmentation (retinitis pigmentosa (RP))
 - Results in nyctalopia and loss of peripheral vision
- Posterior subcapsular cataract in the third decade
- Sensorineural deafness
- Vestibular dysfunction

There are three clinical phenotypes identified, each can be caused by multiple allele mutations (genetically heterogeneous). The mutations cause neuroepithelial cells of the body to be defective, thus affecting the inner ear hair cells, photoreceptors, and spermatozoa.

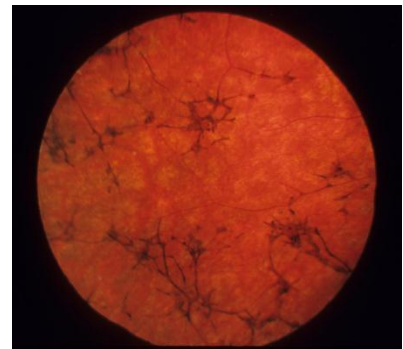
- Type 1 is the most severe and the most common. Deafness is congenital, contributing to speech impairment. Detectable signs of retinitis pigmentosa begin in childhood progressing until age 30-40. Typically, their field of vision will be restricted to 5-10 degrees. Vestibular system impairment leads to delayed walking and motor development
- Type 2 has a later onset of and only partial deafness. The retinopathy is milder and presents at variable times. This type is most likely to maintain visual acuity.
- Type 3 is the least common. Deafness is progressive and retinopathy is adult onset. Vestibular dysfunction is a possibility but not certain.

Diagnosis/testing:

- Funduscopy
- Visual field
- ERG – abnormal, sometimes undetectable

Management:

- Refer for cochlear implants immediately and speech therapy
- Training in tactile signing
 - Low vision devices and training as retinopathy progresses
 - Monitor regularly for cataracts and other treatable complications
- avoid swimming due to vestibular defects



Genetic Counselling:

Since Type I is the most common, it has been studied the most extensively. Not all of the mutations causing this condition have been identified yet.

- Type 1 is autosomal recessive, having a minimum of 7 loci affected. *MYO7A*: a protein in the cilia of vestibular inner ear cells as well as photoreceptors of the retina. This impairs protein transport between inner & outer segments of the photoreceptors

Ethnicity studies show that 40% of patients with Usher Syndrome are Finnish or Ashkenazi Jewish.

Prenatal tests are available if the gene has been identified from an affected family member. A patient with Usher Syndrome has a ~1 in 500 chance of having a child with the same condition if their partner has no positive family history of the syndrome.

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Usher Syndrome photo: <http://disorders.eyes.arizona.edu/disorders/usher-syndrome-type-i>

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