Genetics in Eye Care: Confirm, Understand, Plan

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Abstract:
Medicine is becoming more targeted due to the understanding of genetics. This course will teach the basics of genetics, the historic and current use in medicine and eye care. We will also review targeted genetic treatments.

Learning objectives:

1. Understand the basics of genetics
2. Understand common modern and historical use
3. Discuss the application to eye care in specific disease states

Outline:

1. Genetics
    a. Inherited characteristics
        i. Geneotype = biochemical make-up
        ii. Phenotype = physical manifestation
    b. History
        i. 1990 - Human Genome Project
            1. Sequencing complete in 2003
2. Genetics basics
    a. Deoxyribonucleic Acid (DNA)
        i. Nucleotides
            1. Pyrimidines
                a. Cytosine and Thymine
            2. Purines
                a. Adenine and Guanine
    b. Ribonucleic Acid (RNA)
        i. Nucleotides
            1. Pyrimidines
                a. Cytosine and Uracil
            2. Purines
                a. Adenine and Guanine
        ii. Commonly studied variants
            1. mRNA
            2. tRNA
            3. rRNA
    c. Mutations in gene = cause of disease
    d. Monogenic
        i. Single gene mutation = disease
            1. Yes/No
    e. Polygenic

i. Multiple gene mutations correlated with disease
    1. Risk

3. Genetics in action
    a. Common Applications
        i. Carrier testing
            1. ID people with one copy of a gene mutation that, when present in two copies, causes a genetic disorder.
                a. Family history of a genetic disorder
                b. Certain ethnic groups with an increased genetic risk
                    i. Risk of having a child with a genetic condition.
        ii. Prenatal testing
            1. Fetal genes or chromosomes before birth
                a. During pregnancy
        iii. Preimplantation testing
            1. Detect genetic changes in in-vitro embryos
                a. Embryos without these changes are implanted in the uterus to initiate a pregnancy.
        iv. Newborn screening
            1. Phenylketonuria
            2. Congenital hypothyroidism
            3. Others
        v. Diagnostic testing
            1. ID or RO conditions
                a. Confirm a diagnosis when condition is suspected
                b. Any time during a person's life
                    i. Can influence a person's choices
        vi. Predictive and presymptomatic testing
            1. Detect gene mutations associated with disorders that appear after birth, often later in life.
                a. Use case
                    i. Family member with a genetic disorder
                        1. No disorder at the time of testing.
                    ii. Identify mutations that increase a person's risk
                        1. Types of cancer
                            a. Preemptive care and behavior change
        vii. Forensic testing
            1. DNA to ID individuals for legal purposes
4. Applications in Eyecare
    a. Diagnosis
        i. Retina
            1. Inherited retinal disease (IRD)

Benati D, Patrizi C, Recchia A. Gene editing prospects for treating inherited retinal diseases. J Med Genet. 2020

Jul;57(7):437-444. doi: 10.1136/jmedgenet-2019-106473. Epub 2019 Dec 19. PMID: 31857428.

2. Age related macular degeneration (AMD)
   Gorin MB, daSilva MJ. Predictive genetics for AMD: Hype and hopes for genetics-based strategies for treatment and prevention. Exp Eye Res. 2020 Feb;191:107894. doi: 10.1016/j.exer.2019.107894. Epub 2019 Dec 17. PMID: 31862397.
3. Stargardt disease
   Tanna P, Strauss RW, Fujinami K, Michaelides M. Stargardt disease: clinical features, molecular genetics, animal models and therapeutic options. Br J Ophthalmol. 2017 Jan;101(1):25-30. doi: 10.1136/bjophthalmol-2016-308823. Epub 2016 Aug 4. PMID: 27491360; PMCID: PMC5256119.
4. Retinitis pigmentosa
   Dias MF, Joo K, Kemp JA, Fialho SL, da Silva Cunha A Jr, Woo SJ, Kwon YJ. Molecular genetics and emerging therapies for retinitis pigmentosa: Basic research and clinical perspectives. Prog Retin Eye Res. 2018 Mar;63:107-131. doi: 10.1016/j.preteyeres.2017.10.004. Epub 2017 Oct 31. Erratum in: Prog Retin Eye Res. 2018 Sep;66:220-221. PMID: 29097191.
5. Leber congenital amaurosis
   Kumaran N, Moore AT, Weleber RG, Michaelides M. Leber congenital amaurosis/early-onset severe retinal dystrophy: clinical features, molecular genetics and therapeutic interventions. Br J Ophthalmol. 2017 Sep;101(9):1147-1154. doi: 10.1136/bjophthalmol-2016-309975. Epub 2017 Jul 8. Erratum in: Br J Ophthalmol. 2019 Jun;103(6):862. PMID: 28689169; PMCID: PMC5574398.

ii. Glaucoma
Zukerman R, Harris A, Vercellin AV, Siesky B, Pasquale LR, Ciulla TA. Molecular Genetics of Glaucoma: Subtype and Ethnicity Considerations. Genes (Basel). 2020 Dec 31;12(1):55. doi: 10.3390/genes12010055. PMID: 33396423; PMCID: PMC7823611.

iii. Cornea
1. Dystrophies
   a. Fabry disease
      Bernardes TP, Foresto RD, Kirsztajn GM. Fabry disease: genetics, pathology, and treatment. Rev

Assoc Med Bras (1992). 2020 Jan 13;66Suppl 1(Suppl 1):s10-s16. doi: 10.1590/1806-9282.66.S1.10. PMID: 31939530.

2. Primary Ectasia
    a. Keratoconus

Bykhovskaya Y, Rabinowitz YS. Update on the genetics of keratoconus. Exp Eye Res. 2021 Jan;202:108398. doi: 10.1016/j.exer.2020.108398. Epub 2020 Dec 13. PMID: 33316263.

Romero-Jiménez M, Santodomingo-Rubido J, Wolffsohn JS. Keratoconus: a review. Cont Lens Anterior Eye. 2010 Aug;33(4):157-66; quiz 205. doi: 10.1016/j.clae.2010.04.006. PMID: 20537579.

3. Neovascularization

Sharif Z, Sharif W. Corneal neovascularization: updates on pathophysiology, investigations & management. Rom J Ophthalmol. 2019 Jan-Mar;63(1):15-22. PMID: 31198893; PMCID: PMC6531773.

b. Necessities
    i. Genetic counseling
        1. Aid in interpretation of testing
    ii. Physical orders when suspected
        1. Targeted testing vs wide genomic testing
            a. Best practices
                i. Confirm
                ii. Understand
                iii. Plan

5. Genetic treatment
    a. CRISPR = Clustered regularly interspaced short palindromic repeats
        i. Cas9 = protein = molecular scalpel
            1. Disable or repair a mutation
                a. Targeted by using RNA with matches the location of the DNA to edit
                b. Biochemically cuts the mutated DNA sequence
                    i. Opportunity to insert the correct DNA sequence
        ii. Application in eyecare
            1. Leber congenital amaurosis
                a. Phase 1/2a trial ongoing