Genetics in Eye Care

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

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

Finance disclosure

- Genzyme Pharmaceuticals
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

DNA Replication

Protein synthesis

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

Eukaryotes

100s (Svedberg units)

Prokaryotes

70s

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

20,000-30,000 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

State of the Genome

- National Eye Institute (NEI) Bank: gathers and organizes 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

I want to know about them!
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

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 choroidal melanoma
- Plaque therapy was performed
- Intravitreal Avastin was injected and sectoral photocoagulation to prevent effects of radiation (maculopathy, papillopathy, cataracts and glaucoma.)

Case 1

- A small amount of aspirate was taken to check for genetic mutations which lead to development of melanoma 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
Dr. Attia noticed dull macular reflexes and RPE stippling.

Planning:
- Genetic testing of the ABCA4 gene

Medical therapies:
- Gene
- Stem cell
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.

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.

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


RPE65

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

- Gene Tests: CRB1-Related Leber Congenital Amaurosis
- Gene Tests: LCA5-Related Leber Congenital Amaurosis
- Gene Tests: SPATA7-Related Leber Congenital Amaurosis


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

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

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

Spelling mistakes

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

The Genetic Components of AMD

Naturally occurring variations conferring AMD risk

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Having both CFH and ARMS2 is 147x 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

“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”


AMD – A Genetic Disease

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

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

Why Should we test?

Medical Utility

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.”

- 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”

AMD Disease Management Gap

FIRST EYE
Maintained or
improved in Near
Normal Vision

SECOND EYE
Maintained or
improved in Near
Normal Vision

20/80 or worse

RECOMMENDATIONS

- Treat First Eye
- Save the Second Eye

Recommendations

Retina – General Ophthalmology – Optometrists
1. All specialties SCREEN patients over 65 yrs with large drusen (over 125 μμ); 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 and 4 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

The Nashville Protocol for AMD Management

Nashville Protocol
A Comprehensive Approach to the Management of AMD

Who Should Be Tested
- Age 50 or older
- History of AMD
- Family history of AMD

Risk Stratification
- High Risk (30%)
- Moderate Risk (15%)
- Low Risk (5%)

Practice Recommendations:
- Monitor high-risk patients more frequently
- Monitor MFE 1 at 6 months
- Monitor MFE 2 at 12 to 24 months
- Monitor MFE 3 up to once per year
- Monitor MFE 4 up to three times per year
- Monitor MFE 5 up to four times per year

Educational components included:
- The core protocol that defines who should be tested and how to stratify patients
- The benefit of a local technician to manage testing
- The presentation of patient education materials
- A full suite of support materials

Reimbursement
ICD-9 Codes
- 362.50 non-specific AMD
- 362.51 nonexudative senile macular degeneration
- 362.52 exudative senile macular degeneration
- 362.57 drusen

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://inc clinical trials.com

What are Lysosomal Storage Disorders (LSDs)?
- Family of > 40 disorders
- Lysosomes with an internal pH of 4.5, digest cellular materials, food particles, bacteria and viruses
- Enzyme deficiency, acid hydrolases, causes lysosomes to become engorged. Lipases, proteases, nucleases, amylases
- Each disease is a consequence of type of substrate and where it accumulates
- Progressive accumulation of substrate may result in irreversible damage


Your DNA tests revealed that you are, in fact, a 93 year-old Chinese woman. I'm sorry, but since this job involves heavy lifting we cannot hire women or seniors.
Lysosomal Storage of GAGs

Normal Cell

Abnormal Cell

Engorged Lysosomes

Incidence of LSDs

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

Most are autosomal recessive

Inheritance

Father

Carrier

Mother

Carrier

Unaffected

(50%)

2

Unaffected

(50%)

3

Affected Individual

(25%)

2

Unaffected Noncarrier

(25%)

4

Three are X-linked

Fabry, MPS II, Danon

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

Globotriaosylceramide (GL-3) + Lactosylceramide + Galactose

α-galactosidase A

Lipids accumulate in lysosomes throughout the body

Strokes

Anhidrosis

Angiokeratomas

Left Ventricular Hypertrophy

Autonomic ganglia/ smooth muscle

Fabry Disease

Signs & Symptoms

- Early ischemic stroke
- Recurrent fever
- Heat & cold intolerance
- Hypohidrosis
- Acroparesthesia
- Progressive renal insufficiency
- Angiokeratomas
- Kidney necrosis
- Gastro-intestinal tract
- Autonomic ganglia/skeletal muscle

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/carry 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

Pathology

- α-Galactosidase A (α-GAL) deficiency
  - Accumulation of globotriaosylceramide (GL-3)

Onset

- May present in childhood or adolescence
- -Progressive
  - -Life threatening
  - -Death often due to renal, cardiac, or cerebrovascular complications
- -Average life expectancy ~ 50 years

Incidence

- 1:40,000 males
- 1:117,000 individuals

Without intervention, i.e. kidney transplants life expectancy was 29 yrs


Ocular manifestations of Fabry disease

- Corneal verticillata (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

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

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

- Amiodarone* (Cordarone) – antiarrhythmic
  *Most studies suggest that all or nearly all patients taking amiodarone will develop verticillata.
- 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 their base near the lenticular equator
  - Can have a propeller distribution

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

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 Fabry

- 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
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.

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.

Discussion

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

Fabry Disease: Importance of Family Screening

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.

Effect of ERT on Corneal Verticillata
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.


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<tr>
<th>Previous patient</th>
<th>ERT Status</th>
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<tr>
<td>EH</td>
<td>yes-nine yrs</td>
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<tr>
<td>JH</td>
<td>yes-four yrs</td>
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<tr>
<td>KK</td>
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</tbody>
</table>

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.

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

Thank you!!

Questions?

Disease Progression
Mucopolysaccharidosis I

Patient with severe MPS I

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<td>39 months</td>
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Photos courtesy of the MPS Society.
Mucopolysaccharidosis I (MPS I) (gargoylism)

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

Inheritance
- Autosomal Recessive

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

Incidence
- ≈ 1:100,000

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

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

Signs & Symptoms
- Look for unusual symptoms or clusters of more common symptoms

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

### Ocular Manifestations
- Retinal degeneration
  - Decreased peripheral vision
  - Night blindness
- Glaucoma
- Photophobia
- Optic nerve disease
  - May lead to blindness
  - Papilloedema
  - Optic atrophy
- Treated with:
  - Sunglasses, 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)\(^\text{1-4}\)
  - 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.\(^\text{1}\)