Ocular Genetics:
What Every Ophthalmologist
Should Know
and What Opportunities Exist

Alex V. Levin, M.D., MHSc, FRCSC
Chief, Pediatric Ophthalmology and Ocular Genetics
Wills Eye Hospital
Thomas Jefferson University
Philadelphia
Objectives

After this activity the participant will
1. know the role of Ocular Genetics
2. know the importance of genetic counselling
3. recognize the difficulties in genetic testing
4. be able to respond to patient queries about gene therapy
Poll question #1

I see patients with ocular genetic disease in my practice

1. Every day
2. Once weekly
3. Once monthly
4. Rarely
Poll question #1

I see patients with ocular genetic disease in my practice

1. Every day
2. Once weekly
3. Once monthly
4. Rarely
Eye genetics rules!!!
Why??
Albinism = deficient ocular melanin
Ocular Albinism = normal skin

Oculocutaneous Albinism
= skin and eyes affected
Snowflake
Barcelona Zoo
Captured 1966, Guinea
38-40 y/o (live to 25 in wild)
Died of skin cancer
Ocular Albinism

X linked Recessive
Lyonization
Lyonization

XX

XX
The eye is the only organ we see inside easily
Albinism: Old Nosology

- tyrosinase negative OCA
- tyrosinase positive OCA
- ocular albinism
Albinism: Changing Nosology

OCA Type 1: tyrosinase related
OCA Type 2: p gene
OCA Type 3: TYRP1
OCA Type 4: MATP/SLC45A2
OA1: X linked

....Hermansky-Pudlak, Chediak-Higashi
....and many more
And it’s happening everywhere in ophthalmology!
# Cataract Genetics

<table>
<thead>
<tr>
<th>Volkmann</th>
<th>1p36</th>
<th>CCV</th>
<th>AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posterior polar</td>
<td>1pter</td>
<td>CAE1/MP70 connexin 50 (Cx50/CJA8)</td>
<td>AD</td>
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<tr>
<td>zonular pulverulent</td>
<td>1q21-25</td>
<td>PROX-1</td>
<td>AD</td>
</tr>
<tr>
<td>Nuclear</td>
<td>2p12</td>
<td>CRYGC (not pseudogene CRYGE)</td>
<td>AD</td>
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<tr>
<td>Coppock-like</td>
<td>2q33-35</td>
<td>CRYGD</td>
<td>AD</td>
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<tr>
<td>Acuelliform</td>
<td>2q33-35</td>
<td></td>
<td>AD</td>
</tr>
<tr>
<td>Cereulean</td>
<td>2q33-35</td>
<td></td>
<td>AD</td>
</tr>
<tr>
<td>Congen polymorphic</td>
<td>2q33-35</td>
<td></td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>2q36</td>
<td></td>
<td>AD</td>
</tr>
<tr>
<td>Variable</td>
<td>3q21.1-21.3</td>
<td>BFSP2/phakinin/ CP49 (cytoskeletal protein)</td>
<td>AD</td>
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<tr>
<td>Pulverulant</td>
<td>3q21.3-25.2</td>
<td></td>
<td>AR</td>
</tr>
<tr>
<td>PHPV</td>
<td>9q13-22</td>
<td></td>
<td>AR</td>
</tr>
<tr>
<td>with ASMD</td>
<td>10q11-21</td>
<td></td>
<td>AR</td>
</tr>
<tr>
<td>Posterior polar</td>
<td>11q22.3-23.1</td>
<td>CRYAB</td>
<td>AD</td>
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<tr>
<td>embryonal nuclei</td>
<td>12q13</td>
<td></td>
<td>AD</td>
</tr>
<tr>
<td>zonular pulverulent</td>
<td>13q11-cen</td>
<td></td>
<td>AD</td>
</tr>
<tr>
<td>Central pouchlike + sutural</td>
<td>15q21-22</td>
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</tr>
<tr>
<td>Marner</td>
<td>16q22.1</td>
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</tr>
<tr>
<td>Lamellar</td>
<td>16q22.1</td>
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<td>AD</td>
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<td>anterior polar</td>
<td>17p13</td>
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<td>AD</td>
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<tr>
<td>zonular sutural</td>
<td>17q11.2-12</td>
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<td>AD</td>
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<td>cerulean (blue dots)</td>
<td>17q24</td>
<td></td>
<td>AD</td>
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<td>Dominant cataract</td>
<td>19q13.3</td>
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<td>AD</td>
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<tr>
<td>Pulvurrulent + Y</td>
<td>19q13.3</td>
<td></td>
<td>AD</td>
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<td>Hyperferritinemia</td>
<td>19q13</td>
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<td>AD</td>
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<tr>
<td>nuclear (late cort/PSC)</td>
<td>21q22.3</td>
<td></td>
<td>AD</td>
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<tr>
<td>recessive cataract</td>
<td>21q22.3</td>
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<td>AD</td>
</tr>
<tr>
<td>cerulean (blue dots)</td>
<td>22q11.2</td>
<td></td>
<td>AD</td>
</tr>
<tr>
<td>Coppock-like</td>
<td>22q11.2</td>
<td></td>
<td>AD</td>
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# GLC1: Open Angle Glaucoma

<table>
<thead>
<tr>
<th>GLC1A</th>
<th>JOAG</th>
<th>1q23-25</th>
<th>MYOC (myocillin) / TIGR</th>
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<tbody>
<tr>
<td>GLC1B</td>
<td>POAG</td>
<td>2cen-q13</td>
<td>nl IOP, does well</td>
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<tr>
<td>GLC1C</td>
<td>POAG</td>
<td>3q21-24</td>
<td>high IOP</td>
</tr>
<tr>
<td>GLC1D</td>
<td>POAG</td>
<td>8q23</td>
<td>high IOP</td>
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<tr>
<td>GLC1E</td>
<td>POAG</td>
<td>10p14-15</td>
<td>Optineurin, nl IOP</td>
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<tr>
<td>GLC1F</td>
<td>POAG</td>
<td>7q35-36</td>
<td></td>
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<tr>
<td>GLC1G</td>
<td>POAG</td>
<td>5q22</td>
<td>WDR36</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19q13.33</td>
<td>NTF4</td>
</tr>
</tbody>
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What do I call it?
Why bother with gene diagnosis?
Gene=Diagnosis/Counseling
Gene=Etiology=?Cure
Gene Therapy: The Eye

immune privilege (AC, subret)
accessible
target cells can be visualized
blood/eye/brain barriers
RPE phagocytic
Gene Therapy: Routes

injections
peribulbar
anterior chamber
vitreous
subretinal
Metalloproteinase gene [increased] transcription in human ciliary muscle cells with latanaprost
Weinred RN, Lindsey JD, IOVS 2002;43:716-722

= Gene Therapy!!
obstacle course in kids dramatic improvements
2018 FDA approval

Luxturna
RPE65 disease
Other trials...

Other LCA genes
Retinitis pigmentosa genes
Stargardt disease
Choroideremia
JXLR
Usher
Bardet-Biedl
Achromatopsia
Other treatments for retinal dystrophies

medical (oral)

(QLT091001 = synthetic 11-cis retinal)

stem cell/retinal transplant

if no cells

bionic chips
Need to “know your gene”

For gene therapy
For stem cell?
CRISPR/cas9
vs natural history
So let’s start doing gene tests!
Poll question 2

Who can order a DNA test?
1. Only geneticists
2. Only ocular geneticists
3. Any ophthalmologist/optometrist
4. Genetic counsellors
Poll question 2

Who can order a DNA test?

1. Only geneticists
2. Only ocular geneticists
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Poll question 2

Who SHOULD order a DNA test?
1. Only geneticists
2. Only ocular geneticists
3. Any ophthalmologist/optometrist
4. Genetic counsellors
Poll question 3

A patient has a 2 base pair deletion in an RP gene just downstream from intron 4 donor site. This means...

1. This is the cause of the patient’s RP
2. This is not the cause of the patient’s RP
3. The patient doesn’t have RP
4. I don’t know!
A patient has a 2 base pair deletion in an RP gene just downstream from intron 4 donor site. This means…

1. This is the cause of the patient’s RP
2. This is not the cause of the patient’s RP
3. The patient doesn’t have RP
4. I don’t know!
What gene?
What phenotype?
Previously reported? Believable?
Normal variant?
Biologic prediction?
Evolutionary conservation?
In silico prediction?

Segregation?

......and more!
And it may not matter what the lab says!
It’s not so easy...
To get to a treatment...

diagnosis

pattern recognition

diagnostic testing

DNA
It’s not just a gene test!!

chose a test
  define phenotype/subtypes
examine family
which test to order?
payment
interpret the test result
  polymorphism vs mutation?
explains the phenotype?
segregation?
It’s not just a gene test!!

Genetic counselling is essential!

pre-test
  cost, risks, turn around, expectations
  ...and more

post-test
  interpretation, implications, next steps
  ...and more
Ethical issues

prenatal testing for eye disease
presymptomatic testing
confidentiality
what to disclose
whole exome/genome sequencing
Eugenics??

Photo credit: José Luis Riechman and Elliot Meyerowitz
Eugenics?

Mancuso K et al:  
Gene therapy for red-green colour blindness in adult primates  
Nature 2009
Gene therapy ethical issues

ethical issues

who, what, when, where
Is Luxturna a success?

n = 163
Not everyone improves
does it last?

$425,000 per eye!

one eye or two ($850,000)?
Help!!
Who ya’ gonna call?

Who will mange this exciting explosion?
The Ocular Geneticist...

...a new specialty
Ocular Genetics Program

Ocular Geneticist
Genetic counselor
Research and Teaching
Diagnostic Testing
Ophthalmologists (Wills >225!)
funneling rare pathology
Ocular Genetics Programs

- clinical and surgical care (adults and children)
- primary genetic eye disease
- consultant for systemic genetic disease
Ocular Genetics Program

collaborations

support groups

PGCFA (www.pgcfa.org)
Sturge-Weber Foundation
Cornelia de Lange syndrome
and many more.....
What does this mean for the patient?
No more...

I’m not sure...see you later
He/she will go blind...see you later
Nothing we can do...see you later
I don’t know what it is...
What we can do

- make a diagnosis!
- = knowledge
- = support
- = some feeling of control
- = genetic counseling
- = identification of those at risk
- = some idea of future
What we can do

identify treatable entities
  gyrate atrophy
  abetalipoproteinemia
  Refsum disease
  and others…

what to look for
  BBS, Alstrom etc : systemic issues

clinical trials
Clinical trials

www.clinicaltrials.gov

but be careful!

Inclusion/exclusion

age, vision, travel expenses etc

can you recommend?
You will be cured!
Can you do this all yourself?
We must train future ocular geneticists!
(and ocular genetics counsellors)

Fellowships
Ocular Geneticists

Mich Lingao and Jay Ibanez – Philippines
Yu-Hung Lai - Taiwan
Mario Zanolli - Chile
Vikas Khetan - India
Wadakaran Wuthisiri and Nutsuchar Wangtiraumnuay – Thailand
Sadagopan Karthikeyan - China
Anuradha Ganesh – Oman
Thales de Guimares – Brazil
Kristof van Schelvergem – Belgium
Amani Albakri – Saudi Arabia
Our world is changing…

…the future is here!