WHAT DO WE KNOW ABOUT MYOPIA

LIONEL KOWAL

ACBO 2009
It’s good to be a myope!

Are children with myopia more intelligent? A literature review.

Czepita D, Lodygowska E, Czepita M.

Katedra i Klinika Okulistyki Pomorskiej Akademii Medycznej w Szczecinie al. Powstańców Wlkp. 72, 70-111 Szczecin.

PURPOSE: Refractive errors are a serious worldwide problem. So far a few papers have described the relationship between refractive errors and intelligence. However, based on the growing interest into the relationship between refractive errors and intelligence quotient (IQ) we decided to present and discuss the latest results of the clinical studies on that subject.

MATERIAL AND METHODS: A review of the literature concerning the relationship between refractive errors and IQ was done. RESULTS: In 1958 Nadell and Hirsch found that children in America with myopia have a higher IQ. A similar relationship has been described by other researchers from the USA, the Czech Republic, Denmark, Israel, New Zealand, and Singapore. In other related studies, it was reported that myopic children regardless of their IQ gain better school achievements—table 1. It was also observed that schoolchildren with hyperopia have a lower IQ and gain worse school achievements—table 2. Several hypotheses explaining the relationship between refractive errors and intelligence have been published. Recently, Saw et al. concluded that higher IQ may be associated with myopia, independent of books read per week, in schoolchildren. According to them “the association between genetically driven IQ and myopia of hereditary predisposition could be forged because of a pleiotropic relationship between IQ and myopia in which the same causal factor is reflected in both genetic traits. There may be similar genes affecting eye size or growth (associated with myopia) and neocortical size (possibly associated with IQ).” CONCLUSIONS: The conducted clinical observations suggest that children with myopia may have a higher IQ. This relationship is most probably determined by genetic and environmental factors.

Does refractive surgery damage the IQ?
Types of myopia....

Alcohol myopia: Its prized and dangerous effects.
Steele, Claude M.; Josephs, Robert A.


This article explains how alcohol makes social responses more extreme, enhances important self-evaluations, and relieves anxiety and depression, effects that underlie both the social destructiveness of alcohol and the reinforcing effects that make it an addictive substance. The theories are based on alcohol's impairment of perception and thought—the myopia it causes—rather than on the ability of alcohol's pharmacology to directly cause specific reactions or on expectations associated with alcohol's use. Three conclusions are offered: (a) Alcohol makes social behaviors more extreme by blocking a form of response conflict. (b) The same process can inflate self-evaluations. (c) Alcohol myopia, in combination with distracting activity, can reliably reduce anxiety and depression in all drinkers by making it difficult to allocate attention to the thoughts that provoke these states. These theories are discussed in terms of their significance for the prevention and treatment of alcohol abuse.
How much Nature, how much Nurture

• Accommodation and myopia
Uncertain relationship**
• 3 recent studies* show increased outdoor activity protective against myopia
• Night lights
• Maternal smoking protective!

*Rose & Morgan 2008 [X2], Dirani 2009
Overview of stats

- <5% of infants born @ term, then declines
- Preschool: 2-3%
- 11-13yo: 5%
- **15% by age 15**
- US adults: 33%

F > M, younger > older, whites > African- or Mexican- Americans

- Prematurity: 25 - 50%

increased corneal curvature bigger factor than increased axial length
TERRY YOUNG
MYOPIA GENETICS
CURRENT OPINION OPHTHALMOLOGY 2009

• Jon Ruddle [Melbourne]:
gene on 5q for axial length

• Twin studies: increased concordance
  of refractive error & all of the
  refractive components in mono-
  c.f. di- zygotic twins
from TERRY YOUNG

<table>
<thead>
<tr>
<th>Locus</th>
<th>OMIM</th>
<th>Cytogenetic location</th>
<th>Reference study</th>
<th>Myopia severity: age of onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYP1</td>
<td>310460</td>
<td>Xq28</td>
<td>[14–16]</td>
<td>High: −6.75 to −11.25 D Early: 1.5–5 years</td>
</tr>
<tr>
<td>MYP2</td>
<td>160700</td>
<td>18p11.31</td>
<td>[17–19]</td>
<td>High: −6 to −21 D Early: 6.8 years (average)</td>
</tr>
<tr>
<td>MYP3</td>
<td>603221</td>
<td>12q21–q23</td>
<td>[20,21,22*]</td>
<td>High: −6.25 to −15 D Early: 5.9 years (average)</td>
</tr>
<tr>
<td>MYP4</td>
<td>608367</td>
<td>7q36</td>
<td>[24]</td>
<td>High: −13.05 D (average) Early: 8.9 years (average)</td>
</tr>
<tr>
<td>MYP5</td>
<td>608474</td>
<td>17q21–q22</td>
<td>[25]</td>
<td>High: −5.5 to −50 D Early: before school age</td>
</tr>
<tr>
<td>MYP6</td>
<td>608908</td>
<td>22q12</td>
<td>[26–28]</td>
<td>Mild-moderate: −1.00 D or lower</td>
</tr>
<tr>
<td>MYP7</td>
<td>609256</td>
<td>11p13</td>
<td>[29]</td>
<td>−12.12 to +7.25 D</td>
</tr>
<tr>
<td>MYP8</td>
<td>609257</td>
<td>3q26</td>
<td>[29]</td>
<td>−12.12 to +7.25 D</td>
</tr>
<tr>
<td>MYP9</td>
<td>609258</td>
<td>4q12</td>
<td>[29]</td>
<td>−12.12 to +7.25 D</td>
</tr>
<tr>
<td>MYP10</td>
<td>609259</td>
<td>8p23</td>
<td>[29,30]</td>
<td>High: −5 to −20 D Early: before school age</td>
</tr>
<tr>
<td>MYP11</td>
<td>609994</td>
<td>4q22–q27</td>
<td>[31]</td>
<td>High: −7.25 to −27 D Early: before 12 years</td>
</tr>
<tr>
<td>MYP12</td>
<td>609995</td>
<td>2q37.1</td>
<td>[32,33]</td>
<td>High: −6 to −20 D Early: before school age</td>
</tr>
<tr>
<td>MYP13</td>
<td>HGNC:32582</td>
<td>Xq23–q25</td>
<td>[34]</td>
<td></td>
</tr>
<tr>
<td>MYP14</td>
<td>610320</td>
<td>1p36</td>
<td>[35]</td>
<td>[11,36**–38**,39*,40,41*,42,43,44*]</td>
</tr>
</tbody>
</table>


Waardenburg’s textbook, Genetics and Ophthalmology of 1961-3 …… "axial myopia may be due to different genes, either by itself or as part of syndromes."
Does peripheral optical defocus cause myopia?

- Most myopic eyes are prolate
  
  Peripheral retina ~1DS less myopic. Literature ++ for 50+ years.

- ‘improved’ by laser refractive surgery

![Diagram of eye shapes](image-url)

Fig. 1. Shapes of the vitreous chamber forms in chick. The vitreous chamber shape can be predictably modified in chick by altering visual input, changing photoperiod or administering pharmaceutical agents. The vitreous chamber can become diffusely enlarged, selectively elongated along the visual axis or selectively widened in the equatorial dimension. Asymmetries or local bulges can be induced in the posterior eye wall by altering the visual experience in part of the visual field. Each pattern is illustrated, superimposed on a spherical representation of the eye.
‘CONGENITAL’ MYOPIA
Hiatt, Costenbader, Albert  1965

• ..@ birth or by 6y
• N= 177; 120 studied. C’s office 1936-64. M=F
• 1st exam 2m to 6y, av 3y4m. Myopia -0.4 to -17, av. -8
• Final exam 4-18y, av 10y7m.
Av -0.6 DS greater.
+ve FH: slightly greater increase -0.9 c.f. -0.2 [p=0.05]
43 showed decrease - range 0.25 to 4.5 DS.
• 46% FH of some type of myopia
• 13% prematurity ≈ ‘normals’
• 58%: typical fundus findings of myopia
• 50% strabismus. Most ET. Also XT, vertical, CN, SN

Selection bias: Costenbader was famous pediatric ophthalmologist and strabismus surgeon [First in USA].
Myopic infants in Cambridge
Ehrlich, Atkinson, Braddick... Vis Res 1995

• Changes in Cyclo Refraction from 8m to 38m
• Myopes ≤-3.5DS : trend to low+
• Low+ controls: little/ no change

Selection bias: population study
Medium to **high** grade myopia in infancy and early childhood.

Lavrich, Nelson,... Wills, Albany, 1993

- Bilateral myopia ≥ -3 by age 4  \(R: -3 \text{ to } -19.5\)
- N=45. M>F.
- 19/45: seen ≥2y later:
  - 12/38 eyes: progressed ≥ 1DS \([\text{range } -1 \text{ to } -7, \text{ median } -3]\)
  - 7/38: hyperopic shift ≥ 1DS \([1 \text{ to } 6 \text{ DS, median } 2.25]\)
- 40% strab, ET >> XT
- FH 51%

*Selection bias: pediatric ophthalmology offices*
Early / birth myopia

- Many change very little
- Many improve or get worse
- Some get better. Low myopes tend to emmetropise
- FH ~ 50%
- Strab ~ 50%
STABILITY OF REFRACTION IN CHILDHOOD ANISOMYOPIA
Caputo, Frosini, Strabismus 2001

- 46 anisomyopes age <10, followup ≥ 2y
- 14 ET, 11 XT, 3 nystag, 2 IOOA
- W -4 to -18 [-8 ±3 DS]
- B +4.5 to -6.5 [-1 ±2]
- W-B [aniso]: -7.5±3, end -6±4
- B: Myopic shift [p<0.001]74%, hyperopic shift 6%
- W: stable refraction [p=0.8]. Myopic shift 50%, hyperopic shift 40%

Worse eye - More myopic W
Better eye - Less Myopic  B
STABILITY OF REFRACTION IN ADULT MYOPIA
Nizam..Waring..PERK study group J Ref Corneal Surg 1992

• Manifest and cyclo refraction over 5y
• Unoperated eye [other had RK]
• Age 21 to 57y. 82 eyes
  37 non- CL wearers:
  • 13% progressed ≥ 1DS [max 2DS]
  • 3% [n=1] less myopic by 1DS
  45 CL users:
  • 38% progressed ≥ 1DS
  • MR > CR in 37% by 0.5 to 1.5 DS
STABILITY OF REFRACTION IN ADULT MYOPIA
Bullimore...OhioSU.. IOVS 2002

• Manifest refraction in 291 CL wearers age 20-40 over 5y
• Baseline -3.3 DS ±2, age 28 ± 5y
• 21% progressed by ≥ 1 DS over 5y
• ROMP decreased with increasing age p=0.006
• Progressors cf non-progressors: independent of h/d of reading/writing, computer use, education level, FH myopia, age onset myopia, age CL wear
Oculometry findings in high myopia at adult age: considerations based on oculometric follow-up data over 28 years in a cohort-based Danish high-myopia series. Fledelius HC, Goldschmidt E. ActaOphthalm 3/2009

...adults with high myopia followed between the ages of 26 and 54 years. Myopia increased in most, average 1.0 D [± 1.84]. Ultrasound measurements over the 28 y: correlation between axial eye elongation and myopia progression (r = 0.65). Many eyes with high myopia had steeper corneas than expected
ADULT MYOPES

Some / many have modest increases in their myopia
Rate Of Myopia Progression

• Number / complexity of proposed explanations of myopia progression proportional to the imagination and IQ of the investigators

• Number of trials to try and decrease the Rate Of Myopia Progression exceeded only by the persistence of the investigators
PREVENTING MYOPIA PROGRESSION: MECHANISM

Many Interesting Innovative and Credible Theories – no proof

1. disruption of emmetropisation
2. form deprivation
3. optical defocus – central, peripheral
4. excessive accommodation
5. incremental retinal defocus theory
   Hung & Ciuffreda ARVO 01
6. abnormal scleral collagen
MECHANISM

*Genetic aspects*
Many different genes
Will there be a phenotype / genotype correlation?

? Each genetic type of myopia has a UNIQUE MECHANISM / ROMP / RESPONSE TO DIFFERENT TREATMENTS

*Hong Kong*
? 90% incidence of myopia
Genetic influences less credible
MAINSTREAM TREATMENTS TO ARREST MYOPIA

OPTICAL
1. ↓duration of spectacle wear
2. planned under correction
2. Bifocals / PALs
3. contact lenses / orthoK

PHARMACOLOGICAL
4. atropine / pirenzipine
5. ocular hypotensives
6. 7-methylxanthine
NON- MAINSTREAM TREATMENTS TO ARREST MYOPIA

OFFICE BASED
1. HELMHOLTZ – trans-scleral laser with infrasound pneumatic massage and 2,5% phenylephrine drops
2. EnergieEyerelax – franchises available
3. NeuroVision - franchises available

SURGERIES
1. Scleral reinforcement   USSR, USA
2. Implantation of placenta& injections of extracts from whole eyes
IDEAL STUDY FOR Rx TO REDUCE ROMP

Prospective Randomised Double blind
?

Monocular control [systemic absorption]

*Determine optimal timing & duration of Rx

**Detect catch-up after stopping Rx
APPARENTLY EXCELLENT RESULT

\[
\begin{align*}
\text{Myopia} & \quad \text{DS} \\
\text{CONTROL} & \quad \text{TREATMENT} \\
\end{align*}
\]

\[
\begin{align*}
\text{AGE} \\
\end{align*}
\]
EXCELLENT RESULT

AFTER STOPPING Rx, ROMP @ ‘NEW’ [LOWER] RATE

Myopia DS

CONTROL

NEW RATE

TREATMENT STOPPED

AGE
SIMULATED EXCELLENT RESULT

CATCH UP ON STOPPING Rx

Myopia DS

AGE

CONTROL

STOP TREATMENT
AFTER STOPPING Rx, ROMP @ ‘OLD’ [control] RATE

SIMULATED EXCELLENT RESULT-2

Myopia DS

CONTROL

OLD RATE

TREATMENT STOPPED

AGE
SIMULATED EXCELLENT RESULT-3

Rx SLOWS ROMP. MYOPIA CATCHES UP DESPITE CONTINUING / AFTER STOPPING Rx
CONTROL

CATCH UP
SLOWS MYOPIC PROGRESSION

Myopia DS

AGE
APPARENTLY EXCELLENT RESULT: EASILY SIMULATED
MUST HAVE GOOD & LONG FOLLOWUP

Myopia
DS

AGE

CONTROL
TREATMENT
STUDY QUESTIONS

• 1. CONTROL GROUP
• 2. DURATION OF TREATMENT
• 3. DURATION OF FOLLOW UP
...ANY OTHER CRITERIA

• 4. DATA AFTER TREATMENT STOPPED
TREATMENTS TO ARREST MYOPIA

OPTICAL
1. ↓ duration of spectacle wear
2. planned under correction
2. Bifocals / PALs
3. contact lenses / orthoK

PHARMACOLOGICAL
4. atropine / pirenzipine
5. ocular hypotensives
OPTICAL Rxs
Saw : BJO, Ophthalmology 2002

1. < full time wear of full Rx
2. Under correction
3. B-F & PALs
< FULL TIME WEAR  #1
Saw, BJO  2002

NRCT    N= 43   3y
a. full time specs wear
b. wear for distance  ➔  full time
c. wear for distance
d. non wear
RESULT:  Non Significant differences
< Full time wear #2

NMRCT Finland n= 240  9-11y  f/u: 3y
a. SV, full correc, cont use
b. SV, full correc, distance only
c. Bifocals
RESULT: ROMP: Non Significant differences
Planned undercorrection

*Straub*: Fully corrected / Under corrected

ROMP: NS

*Tokoro and Kabe*:

Fully corrected $-0.83\text{D/y}$

Under corrected $-0.47\text{D/y}$

$p<0.01$
Planned undercorrection /2

CHILDREN UNDERCORRECTED BY -0.75

SMALL [STATS SIGN] INCREASE ROMP OVER 2y

0.25D GREATER THAN FULLY CORRECTED
BIFOCALS / PALs
Saw BJO 2002

3 well designed RCT

USA, DENMARK, FINLAND

Bifocals +1 to +2 adds

Sample sizes 32-240

Result : Non Significant differences
PALs - Non Significant differences

Leung and Brown  Hong Kong
36: +1.5 - +2 add. ROMP  -3.67 to -3.73D.
32: SV. ROMP -3.67D.

Shih and colleagues  Taiwan
227  6-12y
PALs -1.19D/y.  SV -1.40D/y.
CORRECTION OF MYOPIA
EVALUATION TRIAL (COMET)
PALs vs. SV

IOVS 2003
3 y. N= 469. age 6-11y
MULTICENTRE USA RANDOMISED
DOUBLE MASKED. SE –1.25 to –4.50

PALs
Slight ↓ ROMP, AL, # of Rx changes

RECOMMENDATIONS
Effects too small to change your current routine
CORRECTION OF MYOPIA
Multifocal CLs vs. glasses

Howell:
CLs retard ROMP more than glasses
The effectiveness of progressive addition lenses on the progression of myopia in Chinese children


178 Chinese juvenile-onset acquired myopes (aged 7-13 years, -0.50 to -3.00 D spherical refractive error), who did not have moderately or highly myopic parents.

149 (75 in SV and 74 in PAL) completed the 2-year study.

The myopia progression (mean +/- S.D.) in the SV and PAL groups was -1.50 +/- 0.67 and -1.24 +/- 0.56 D, respectively.

This difference of 0.26 D over 2 years was statistically significant (p = 0.01).

The lens type (p = 0.02) and baseline spherical equivalent refraction (p = 0.05) were significant contributing factors to myopia progression.

Mean increase in the depth of vitreous chamber * was 0.70 +/- 0.40 and 0.59 +/- 0.24 mm, respectively. This difference of 0.11 mm was statistically significant (p = 0.04).

Age (p< 0.01) was the only contributing factor to the elongation of vitreous chamber.

Different near phoria (p< 0.01) and gender (p = 0.02) caused different treatment effects when wearing SV lenses. However, there were no factors found to influence the treatment effect of wearing PALs.

CONCLUSIONS:

ROMP was found to be retarded by PALs to some extent in Chinese children without moderately or highly myopic parents, especially for subjects with near esophoria or females.

* reported by Neville McBrienActaOphthalmologica 1987
Myopia Progression in Children Wearing Spectacles vs. Switching to Contact Lenses.

- Optom Vis Sci. 2009

- **Marsh-Tootle WL, ...Gwiazda J**, [COMET]

- No clinically significant difference in ROMP
SUMMARY

< Full time wear / undercorrection

>5 STUDIES

MOST NOT SIGNIFICANT

2 SIGNIFICANT:

1 ROMP WORSE!
SUMMARY

*BIFOCALS & PALs*

>9 studies: NS

~2-3 PAL studies: Stats Significant

All clinically insignificant
ATROPINE

**EASILY UNDERSTOOD EFFECT:**
Muscarinic antagonist \(\rightarrow\) blocks accommodation
If Xs accom\(\rightarrow\)↑轴ial length, Atropine may block this

*Non–AccommEffects [McBrien]:*
  * Affects dopamine release  ?influence retinal signals  ?control eye growth
  * Suppresses GH
ATROPINE STUDIES

BEDROSSIAN

Ophthalmology 1979 n = 62

1% Atropine hs ONE eye for 12 mo.
Fellow eye treated in Y2 [previously Rx’d eye now control].

Atropine: ↓ ROMP

Post Atropine: ROMP @‘new’ [lesser] rate
ATROPINE STUDIES

KENNEDY ..... MAYO
Transactions AOS  1995
Olmsted county study

Excellent review of older literature on ROMP
Mayo Clinic study

KENNEDY .....MAYO
Transactions AOS 1995
Olmsted county study
N=214. Median age 11y, R6-15
Duration 3.5y [18w to 11.5y]
Follow up 11y

ROMP Atropine: 0.05DS/Y,
Control 0.36 DS/Y  [p<0.001]
ATROPINE STUDIES

RCT X3     TAIWAN

At 0.1 to 1%

Result: ROMP significantly ↓

Lower % better tolerated
ATROPINE & B-F       BRODSTEIN
OPHTHALMOLOGY 1984

n = 253.  1% Atropine  od.
9y f/up.

↓ ROMP during Rx

ROMP after Rx = Control group

ROMP fastest age 8 -12
15 Myopes / 15 control

Atropine 1% OU mean 29m [3-96]

ROMP:

Atropine: 0.05D Controls: 0.84D

p = 0.00021!!

Using same pair of glasses [months]:

Atropine: 25.1 (+/-19.3)
Control: 13.5 (+/-10.3) p = 0.049
ATROPINE & B-F   WILMER

CASE SERIES    RETRO / INTER / NON COM
n = 706        age 6-16 y
B-F : full cyclo / +2.25 add
Atropine  1%  1/w.    3w - 10 y
Result:  496  Fully  Compliant.  210 Partly

ROMP:
F/ Compliant  0.08D / y.   Partly  0.23D / y

p< 0.001 !!
ATOM STUDY

ARVO 2003  CHUA [SINGAPORE]
RANDOMIZED / DOUBLE MASKED / PLACEBO CONTROLLED
n=400  -1D to -6D  6-12 y
1% Atropine  Control: Isoptotears  1/d
F/U: 4 monthly for 2 y. 90% @ 12mo, 80+% @ 2y
Cyclo ref / axial length  CR / AL
12 mo: CR C: $-0.76 \text{D}$. Atropine: $+0.3 \text{D}!$

AL: C: $+0.2 \text{ mm}$. Atropine *reduction* 0.14 mm

2yrs: CR / AL

C: $-1.20 \text{D} / +0.38 \text{ mm}$

At $-0.25 \text{D} / \text{AL unchanged from baseline}$

$p < 0.0001$ @ 12 mo & 2 y
Subjects were followed up for 12 mo after stopping treatment [either 1% atropine or vehicle eyedrops once nightly for 2 y]. Only 1 eye of each subject was chosen through randomization for treatment.

RESULTS: After cessation of atropine drops, the mean progression in the atropine-treated group was -1.14+/-0.80 D over 1 year, whereas the progression in placebo-treated eyes was -0.38+/-0.39 D (P<0.0001).

After 3 y of participation in the trial (with 2 years on atropine treatment), eyes randomized to atropine have less severe myopia than other eyes. Spherical equivalent was -4.29+/-1.67 D in the atropine-treated eyes compared with -5.22+/-1.38 D in the placebo-treated eyes (P<0.0001).

Spherical equivalents in atropine-untreated and placebo-untreated eyes were -5.00+/-1.62 D and -5.28+/-1.43 D, respectively.

Over the 3 years, the increase in axial length of the atropine-treated eyes was 0.29+/-0.37 mm compared with 0.52+/-0.45 mm in the placebo-treated eyes (P<0.0001)
PIRENZEPINE

Selective M1 subtype muscarinic antagonist

Animal studies:
blocks ↑AL 2° to form deprivation
PIRENZEPINE #1

ARVO  2003 SIATKOWASKI
MULTICENTRE RCT  n=13  USA

N = 174   8-12 y   Rx / C : 2:1
BD for 12 mo
ENTRY : BCVA 20/25 or better
REF ERROR –0.75 to –4.00D SE
CYL ≤1D
PIRENZEPINE #1  RESULTS
OUTCOME :  CYCLO A/REF @ 12 mo
Entry Ref Error:  PIR -2.10;  C -1.93
ROMP:  PIR –0.26D;  C -0.53D  p<0.001
2% PIR >1D Myopic progression @ 12 mo
20% C > 1D Myopic Progression @ 12 mo
p<0.001
PIR 11% withdrew;  C: 0%. 
PIRENZEPINE : STUDY #2

1yr Asian Trial
353 children  6-12 y
a. PIR bd
b. Placebo morning+ PIR Evening
c. Placebo  bd           Ref error / AL
PIRENZEPINE – ASIA /2

ROMP @ 12 mo
a. -0.40D (PIR bd)
b. -0.70D (PIR 1/d)
c. -0.80D (C)

a / b : p < 0.001
a / c : p < 0.001
b / c : NS
PIRENZEPINE – ASIA /3

AXIAL LENGTH

a. +0.21mm (PIR bd)
b. +0.30mm (PIR 1/d)
c. +0.33mm (C)

All comparisons NS
OCULAR HYPOTENSIVES

↑ IOP → stretch sclera ↑axial length ↑myopia

Labetolol / Timolol

Several studies : no Controls, not randomised

Danish study 150 child. 0.25% timolol [2y]

ROMP: Timolol -0.59D/y
Single vision -0.57D/y
SUMMARY

PHARMACOLOGICAL STUDIES

1. ATROPINE  many studies
   Most : Stats significant
   One study : post Rx ROMP @ reduced ‘new’ rate

2. PIRENZEPINE  2% GEL  2 studies  Sig

3. OCULAR HYPOTENSIVES  NS
MYOPIA

• 1. Major personal / societal problem
• 2. Convincing data on ↓ ROMP with At / Pir. Need longer f/up.
• 3. No convincing evidence on optical treatments
• 4. ? Genetic segregation first & repeat optical and drug studies