Exfoliation Syndrome: A look beyond *LOXL1*

Louis R. Pasquale, MD, FARVO
Director, Glaucoma Service
Massachusetts Eye and Ear Infirmary
Harvard Medical School

Current Concepts in Ophthalmology 2013; **REVEL** Atlantic City, NJ
OUTLINE

• **KNOWLEDGE:** Impact of the *LOXL1* gene discovery

• **SKILLS:** Strategies to minimize cataract surgery complications in exfoliation syndrome

• **ATTITUDE:** Appreciate the spectrum of ocular morbidity associated with exfoliation syndrome
KNOWLEDGE: Impact of the LOXL1 gene discovery
Landmark study in Exfoliation Syndrome:

99% of Nordic patients had changes in a gene called *LOXL1*, which codes for an enzyme involved in forming elastin, a protein that lines blood vessels.
RESEARCHERS WORLDWIDE CONFIRM THAT LOXL1 GENE VARIANTS ARE ASSOCIATED WITH EXFOLIATION SYNDROME / EXFOLIATION GLAUCOMA.
BUT....

80% of people without exfoliation syndrome also have the same changes in the *LOXL1* gene
Frequency of changes in the **LOXL1** gene in Exfoliation Syndrome patients and Controls

Adopted from Bao Jian Fan, PhD
Rate of Exfoliation Syndrome throughout Europe and Asia

- P = 23%
- P = 8% - 18%
- P = 11%
- P = 9%
- P = 6.5%
- P = 7.9 - 12%
- P = 3 - 6%
- P = 1.1%
- EQUATOR
HYPOTHESIS:

In the continental US, the risk of exfoliation syndrome is higher in the North vs. the South after accounting for age and other factors.

NORTHERN TIER: NORTH OF 41 – 42°

SOUTHERN TIER: SOUTH OF 37°

Relational healthcare database:
- Used by pharma to assess real market patterns

- Longitudinal database containing:
  a) Medical and pharmacy claims
  b) Lab test results
  c) Enrollment data

We needed to exclude CA because our database was de-identified.

Relation between most recent continental tier residence and multivariate risk of ES/EG in the i3 InVision cohort (N = 3,465 cases)

NORTHERN TIER: \( RR = 1.87 \ [1.69-2.08] \)

CENTRAL TIER (IN WHITE):
\( RR = 1.0 \) REFERENCE GROUP

SOUTHERN TIER: \( RR = 0.73 \ [0.65 – 0.82] \)

Stein JD, Pasquale LR et al.
Arch Ophth 2011.
Relation between most continental tier residence and multivariate risk of ES in the i3 InVision cohort among non-Caucasians (N = 244)

NORTHERN TIER: RR = 2.88 [1.80 - 4.61]

SOUTHERN TIER: RR = 1.15 [0.72 – 1.89]
Can we confirm the latitude effect in a 2\textsuperscript{nd} cohort?

Nurses Health Study (N = 121,700) and Health Professionals Follow-up Study (N = 51,529) are located throughout the continental US.
Study period: 1980 – 2008
Cohort size: 1.2 million person-yrs

NORTHERN TIER: NORTH OF 41 – 42°

SOUTHERN TIER: SOUTH OF 37°
Relation between continental tier residence throughout life and multivariate risk of ES/EG in NHS and HPFS (N = 348 cases).

NORTHERN TIER: REFERENCE RR = 1.0

CENTRAL TIER (IN WHITE): RR = 0.53 [95% CI: 0.40 - 0.71]

SOUTHERN TIER: RR = 0.25 [95% CI: 0.09 – 0.71]
Myth or reality?

• Scandinavian ancestry is a risk factor for exfoliation syndrome
The relation between race and exfoliation syndrome in the Nurses Health Study and Health Professionals Follow-up Study (1980-2008)

<table>
<thead>
<tr>
<th>RACE</th>
<th>Pooled odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other Caucasian</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>Southern European</td>
<td>0.98 (0.56, 1.72)</td>
</tr>
<tr>
<td>Scandinavian</td>
<td>0.75 (0.48, 1.17)</td>
</tr>
</tbody>
</table>

Based on 288 cases detected during 1.2 million person years of follow-up

Myth or reality?

• Exfoliation syndrome is rare in people of color
Prevalence of Exfoliation Syndrome in various African-derived people

<table>
<thead>
<tr>
<th>POPULATION</th>
<th>PREVALENCE</th>
<th>STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>African Americans</td>
<td>0.4%</td>
<td>Ball et al. 1988</td>
</tr>
<tr>
<td>South Africans</td>
<td>7.7%</td>
<td>Rotchford et al. 2003</td>
</tr>
<tr>
<td>Zimbabweans</td>
<td>7.4%</td>
<td>Masanganise et al. 1997</td>
</tr>
</tbody>
</table>

Why is the prevalence of ES so much higher in people who live in S. Africa?
A look beyond \textit{LOXL1}

A 70 YO WM s/p TRX OU for Exfoliation Glaucoma

Bad Latitude!

- POH: Pseudo-uveitis episode.
- PMH:
- SH: Roofer, always worked in New England; always has a pack of cigarettes in his front pocket; always has a cup of coffee in hand at AM appts; “social drinker”
**LOXL1 knockout mice**

These mice get cataract

These mice have a disrupted blood-aqueous barrier

Wiggs et al. LOXL1 deficiency causes disruption of the BAB and cataract.
SKILLS: Strategies to minimize cataract surgery complications in exfoliation syndrome
Cataracts are more common in eyes with Exfoliation Syndrome than age matched controls. Cataract surgery is more difficult in Exfoliation Syndrome due, in part, to poor pupil dilation.
The support system for the lens is inherently weak in Exfoliation Syndrome, making it difficult to place a lens implant.
Gross and histopathologic correlates of a weak zonule
Tips for cataract extraction in Exfoliation Syndrome: Pre Operative plans

- Advocate for early extraction
- Preop assessment of phacodenesis
- Assess pupil size
- Look for anterior lenticonus
Tips for cataract extraction in Exfoliation Syndrome: Pupil management

Pupil plan: break synechiae; copious dilation; viscodilation

Mechanical dilation: 1) bimanual stretch with K hooks, 2) Sphincterototomies, 3) dilating forceps, 4) iris retractors, 5) Malyugin ring.
Tips for cataract extraction in Exfoliation Syndrome: CCC

- Watch out for crenation
- Capsular staining often helpful
- Keep CC ~5 mm if possible
Hydrodissection/
Delineation/Phaco

• Hydrodissection – minimize lens torsion
• Phaco: do what works for you; some recommend chop as all forces are directed to the center of the lens
• IOL: surgeons choice
Coexistent cataract and glaucoma

• Shingleton B et al. PhacoTRX may be better than phaco alone in lowering IOP in these patients.
J Cataract Refract Surg 2011
ATTITUDE: Appreciate the spectrum of ocular morbidity associated with exfoliation syndrome
Ocular burden of exfoliation syndrome

- Premature cataract
- More cataract surgery complications
- Late onset PBK / IOL subluxation
- Secondary open angle glaucoma with high IOP
- Propensity to vein occlusion
- Pseudouveitis
- Propensity to AMD
Ocular burden of disease:

- Most common form of secondary open-angle glaucoma
- IOP higher than POAG
- Responds very well to ALT
- Sometimes patients will present with painless, acutely recognized loss of vision.
From: A Ring on the Retina

CONCLUSION

• **KNOWLEDGE:** A look beyond *LOXL1* may point to environmental risk factors for ES.

• **SKILLS:** Don’t enter the OR without a plan for the small pupil and unstable zonule in ES

• **ATTITUDE:** There is more to ES than glaucoma. In fact, there is nothing pseudo about any of it!
Collaborators:

Janey L. Wiggs, MD., PhD
Cynthia Grosskreutz, MD, PhD
Douglas Rhee, MD
Teresa Chen, MD
Stacey Brauner, MD
Stephanie Loomis, MPH
Wael Abdrabou
Beth Delbono, MPH
Gil Feke, Ph.D.

Jae Hee Kang, Ph.D.
Susan Hankinson, ScD
Bernard Rosner, PhD
Walter Willett, MD

Joshua D. Stein, MD
Julia E. Richards, PhD
Nidhi Talwar, MS
Denise S. Kim, MD
David M. Reed, PhD
Bin Nan, PhD