

Krukenberg's Spindles Strongly Suggest Long Anterior Zonule Associated Pigment Dispersion Mechanism in Older Patients

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PURPOSE. The purpose of this study was to further investigate factors associated with Krukenberg's spindle (KS) presence in a primary eye care setting.

METHODS. As part of a larger investigation, several practitioners in an academic eye care facility in Chicago, IL, USA evaluated patients for the long anterior zonule (LAZ) trait during 2011 to 2018, and data were collected on ocular/systemic health, lifestyle, and demographic variables, including the presence of a KS. Multivariate regression was used to assess relationships to KS presence.

RESULTS. Analysis included 3501 subjects with mean age of 51 ± 15 years (18–98 years; 65% women; and 84% African American). Among the right eyes, 57 (1.6%) had a KS, with this group having a mean age of 62 ± 13 years (25–86 years; 75% women; and 82% African American). There were 120 subjects (3.4%) with right eye LAZ, with mean age of 64 ± 11 years (36–91 years; 77% women; and 92% African American). There were 19 of 57 (33.3%) KS eyes that also had LAZ. Controlling for other factors, variables with the strongest relationship to KS presence were the LAZ trait (odds ratio [OR] = 12.2, 95% confidence interval [CI] = 6.5 to 22.8, $P < 0.0001$) and advancing age (OR = 1.3 per decade, 95% CI = 1.3 to 1.9, $P < 0.0001$).

CONCLUSIONS. In the population studied, KS presence had its strongest relationship to the LAZ trait and advancing age. The KS-LAZ relationship may not be well-known, but these data strongly suggest that pigment dispersion signs, such as a KS, should prompt the clinician to consider the LAZ trait as a potential etiology, especially because LAZ is associated with higher IOP and possibly glaucoma.

Keywords: Krukenberg's spindle, long anterior zonules, pigmentary glaucoma, pigment dispersion syndrome, intraocular pressure

Krukenberg's spindle (KS) formation is well-known to occur in association with "classic" or primary pigment dispersion syndrome (PDS) and pigmentary glaucoma (PG), and there has been discussion of this important clinical finding over many decades.¹⁻⁸ Although the attention that KS formation has received in conjunction with classic PDS and PG is expected given this well-established association, it is clear that these conditions do not always explain KS presence, as KS is often described as idiopathic in nature.^{4,7-9} Through long-term investigation of the long anterior zonule (LAZ) trait, we have observed that KS formation can be explained frequently by the presence of LAZ, which may be overlooked unless there is careful examination for it.¹⁰⁻¹²

The LAZ trait is characterized by zonular fibers that extend more central than usual on the anterior lens capsule and are seen as radially oriented fine lines, which often become pigmented due to rubbing against the posterior iris

pigment epithelium (Fig. 1).¹³⁻¹⁶ Related pigment liberation may result in other pigment dispersal signs, including KS formation and trabecular meshwork pigmentation (i.e. LAZ-associated PDS). Population-based studies have not been done, but our group has determined the prevalence of LAZ to be 1 to 2% in our predominantly African American population.¹⁰ Although we had limited numbers of subjects from other groups, we also have detected a similar LAZ frequency among other racial groups (i.e. Asians, Hispanics, and non-Hispanic whites).¹⁰

At present, there seems to be at least two phenotypic varieties of LAZ, with one being very rare and resulting from a serine to arginine (S163R) substitution in the complement 1q tumor necrosis factor-related protein 5 (CIQTNF5, alternatively CTRP5) gene.^{17,18} The other variety, which has unknown etiology, most frequently occurs among hyperopic women with age > 50 years.^{10,19,20} In addition to

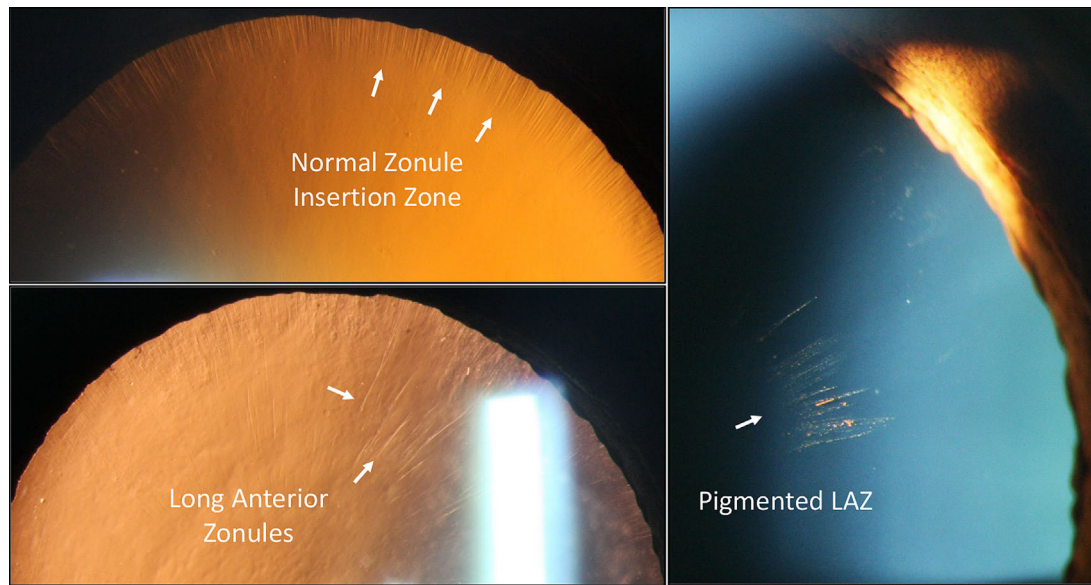


FIGURE 1. Example images showing: (1) a normal eye with a typical, well-delineated zonule insertion zone (*upper left*); (2) LAZ that are positioned well beyond the normal zonule insertion zone (*lower left*); and (3) pigmented LAZ in direct illumination (*right*).

LAZ's importance to cataract surgery due to anterior capsular zonule-free zones often being ≤ 3 mm,^{21–28} it has been shown that people with idiopathic LAZ have a higher IOP than people without the trait.²⁰ There is also the suggestion that LAZ could signal higher risk for narrow- and open-angle forms of glaucoma.^{17,20,29–33}

Given the importance of KS presence as a sign of pigment dispersion processes and its possible under-recognition as an indicator of LAZ-associated PDS, we further investigated this relationship among our patient population.

METHODS

For this study, we analyzed a dataset collected for an ongoing investigation, which has been described previously.²⁰ Data collection for the current analysis extended from October 2011 through November 2018, and the overall goal of the larger investigation has been to assess ocular and general health associations with the LAZ trait. Potential subjects for this investigation included consecutive patients who presented for regularly scheduled examination by one of nine attending doctors in the primary eye care service of an urban teaching facility in Chicago, Illinois, USA. Length and time period of each attending investigator's participation varied, with some contributing subject data over the entire study period and others contributing for shorter timeframes. Patients were included if they had their pupils adequately dilated (≥ 6 mm), were ≥ 18 years of age, provided informed consent, and completed a written questionnaire to supplement demographic and lifestyle information.

The examination included ocular/systemic medical history, Snellen acuity testing, pupil testing, motility/binocular testing, color vision screening, confrontation visual fields, pre-dilation subjective refraction, slit lamp evaluation, Goldmann applanation tonometry, and funduscopy examination that included binocular indirect ophthalmoscopy of the retinal periphery.

After initial work-up, student clinicians offered study participation prior to pupillary dilation and provided the questionnaires for completion without assistance. Faculty investigators learned of subject participation at the time of their final patient assessment, and they searched for the LAZ trait using direct and indirect, bright slit lamp illumination with 16 to 25 \times magnification. The criterion for existence of the LAZ trait was presence of radially oriented zonular fibers, pigmented or nonpigmented, with anterior tips that extended substantially (> 1.0 mm) beyond (central to) the normal anterior capsular zonular insertion zone located about 1.5 mm anterior to the lens equator.³⁴ Further detail on LAZ morphology and detection is presented elsewhere.^{11,20,26,35} To ensure definitive LAZ cases, we excluded subjects with < 5 LAZ fibers.^{20,26,35} To provide estimation of the number/density of LAZ, investigators used the following arbitrary scale based on countable LAZ fibers: grade trace = 0 to 4, grade 1+ = 5 to 9, grade 2+ = 10 to 19, grade 3+ = 20 to 49, and grade 4+ = ≥ 50 .

In addition to other ocular features, investigators examined subjects for KS formation.^{2,4,6,8} We considered a KS present when there was "fine pigment dusting" on the central aspect of the posterior cornea, and we considered "fine pigment dusting" present when individual pigment granules could not be "counted" because they were too fine, numerous, and coalesced (Fig. 2). Larger, coarse pigment flecks and pigment associated with guttata were not considered evidence of a KS, even when central.

Data for other variables (Tables 1, 2) relied on current history, the medical record, and the questionnaire. Race/ethnicity was classified as: (1) "Black/African American, (2) Asian, (3) Hispanic, black or white, (4) non-Hispanic white, and (5) other." Based on category frequencies, final analyses used groupings of "Black/African American" versus "not Black/African American."

Education level was determined by questionnaire: "What is your highest level of education? (1) Less than high school degree, (2) High school degree, (3) Vocational school or

TABLE 1. Unadjusted Relationships to KS – Categorical Variables

Variable	KS Present <i>N</i> = 57*	KS Absent <i>N</i> = 3430	<i>P</i> Value†
Long anterior zonule trait	33% (<i>N</i> = 19)	3% (<i>N</i> = 101)	<0.0001
Gender, Female	75%	65%	0.10
Race			
African American	82%	82%	0.98‡
Asian	0%	2%	
Hispanic	5%	7%	
White	8%	6%	
Other	3%	2%	
Education greater than high school	60%	62%	0.73
Diabetes	28%	22%	0.27
Hypertension	68%	48%	0.002
Body mass index			
Underweight, < 18.5	2%	4%	0.76‡
Normal weight, 18.5 to 24.9	23%	22%	
Overweight, 25.0 to 29.9	30%	29%	
Obese, ≥ 30	46%	45%	
Cancer history - any site	9%	4%	0.10
Cholesterol med – current (per record)	28%	16%	0.02
Cholesterol med – ever (per survey)	44%	29%	0.01
Alcohol use			
Current	46%	49%	0.57
Ever	60%	60%	0.93
Smoking			
Current	26%	30%	0.56
Ever	53%	47%	0.43
Smoking in home when child	47%	44%	0.65

KS, Krukenberg's spindle; N, number of subjects.

* Right eyes used in analysis.

‡ Statistical comparison is African American versus non-African American; overweight/obese versus underweight/normal weight.

† Bolded *P* values are significant at $\alpha = 0.05$ level.

TABLE 2. Unadjusted Relationships to KS - Continuous Variables

Variable	KS Present <i>N</i> = 57*	KS Absent <i>N</i> = 3430	<i>P</i> Value†
Age, y	61.5 ± 13.4	50.4 ± 15.4	<0.0001
Refractive error, SE, diopters	−0.96 ± 3.62	−0.90 ± 2.90	0.91
Body mass index, kg/m ²	30.0 ± 6.8	30.6 ± 7.8	0.53
Systolic blood pressure, mm Hg	136.7 ± 17.2	128.8 ± 18.1	0.001
Diastolic blood pressure, mm Hg	80.2 ± 9.7	79.2 ± 11.2	0.49
Pack years smoking	11.7 ± 21.8	10.1 ± 27.2	0.64

Kg/m², kilograms per meter-squared; KS, Krukenberg's spindle; mm Hg, millimeters of mercury; SE, spherical equivalent.

* Right eyes used in analysis.

† Bolded *P* values are significant at $\alpha = 0.05$ level.

some college but no degree, (4) College Associate's or bachelor's degree, and (5) College Master's, Professional, or Doctoral degree." For final analyses, we grouped subjects according to any formal education beyond a high school degree versus less than or equal to a high school degree.

For smoking status, we asked: "Have you ever been a smoker? (1) Yes, currently, (2) Previously: quit < 12 months ago, (3) Previously: quit > 12 months ago, and (4) Never or rarely: smoked less than a total of 50 cigarettes (2½ packs) over my lifetime." We then grouped subjects as "current," "former," or "never" smokers, and then "ever" versus "never" smokers for final models. We considered subjects as former smokers if they had quit smoking > 1 year prior to the examination, and we asked ever smokers to indicate what they had smoked (i.e. "(1) Cigarettes only or nearly always, (2) Cigars / pipe only or nearly always, and (3) Other, please describe." We also asked subjects how much they had

smoked (half pack increments if cigarettes), the age they began smoking, and when they had stopped if applicable.

To determine alcohol use status, we asked: "Do you drink alcohol? (1) Yes, I do currently, (2) Previously: quit < 12 months ago, (3) Previously: quit > 12 months ago, and (4) Never or rarely because I have not drunk alcohol more than 10 times during my life." We considered subjects as former drinkers if they had quit drinking > 1 year prior to our examination. Otherwise, they were considered a current drinker. To improve categorization, we asked subjects how many days per week they drank (less than weekly, 1–2 days, 3–4 days, or 5–7 days), how much they usually drank (1–2 drinks, 3–4, 5–7, or ≥8). We also asked how many years they had drunk alcohol and, if applicable, when they had stopped. Based on information obtained, we categorized subjects as "current," "former," or "never" drinkers," and regression model explorations included various

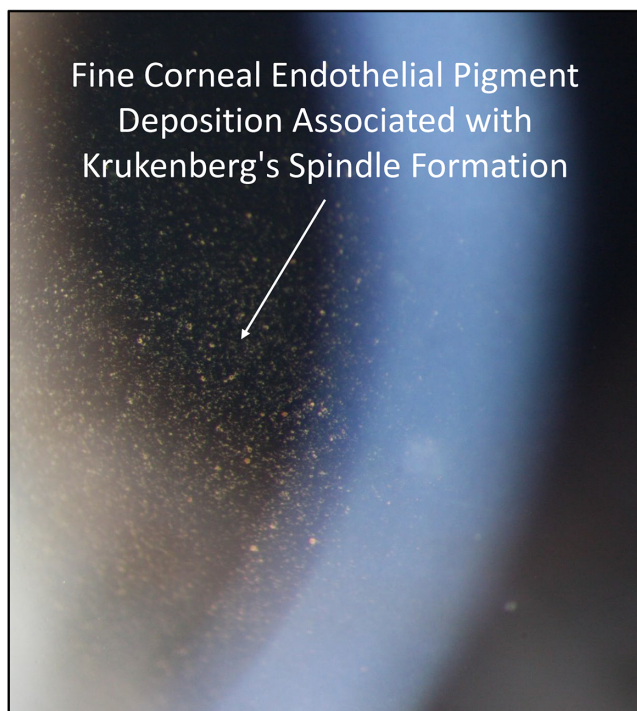


FIGURE 2. Example image of fine corneal endothelial pigment dusting with Krukenberg's spindle formation.

combinations of these categories (e.g. "current" versus "ever/never" drinker and "ever" versus "never" drinker).

We considered subjects to have diabetes if they were taking prescribed medication or stopped taking it against medical advice. Likewise, we considered subjects to have a formal hypertension diagnosis only if they were taking medication at the time of examination or stopped taking it against medical advice. Blood pressure was obtained prior to eye drop instillation for pupillary dilation. Student clinicians obtained these measurements using either automated wrist cuffs or manual arm sphygmomanometers.

Body mass index (BMI, kg/m^2) was derived using height and weight information collected via the questionnaire. During analyses, BMI was explored as a continuous variable and using combinations of standard BMI categories for adults (i.e. "underweight" [< 18.5], "normal or healthy weight" [18.5 to 24.9], "overweight" [25 to 29.9], and "obese" [≥ 30]).³⁶

To explore cholesterol-lowering medication use, we used two approaches. For one, we determined if there was a medical record notation indicating current use of cholesterol-lowering medications, and for the other approach, we also asked via questionnaire about a history of high cholesterol and medication use (i.e. "Have you ever been diagnosed with high cholesterol and taken medication for it?" Because subjects often did not know the names of medication(s), we did not assess specific cholesterol medications or classes.

We used spherical-equivalent values for refractive error, which were based on the pre-dilation subjective refraction. We excluded eyes with a history of trauma, uveitis, and intraocular surgery.

Statistical analyses were performed using the SAS System, Release 9.3 for Microsoft Windows (SAS Institute, Cary, NC, USA). We used the Student's *t*-test for univariate comparisons involving normal distributions and the Wilcoxon rank-

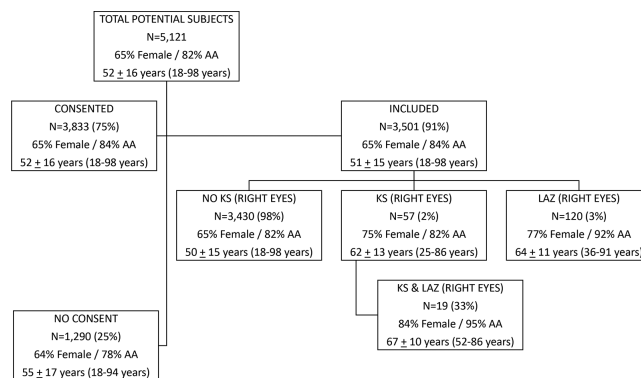


FIGURE 3. Flow diagram illustrating subject recruitment.

sum test for non-normal variables. Chi-squared tests were used for categorical variables. An exploratory analysis was first performed using all available variables (see Tables 1, 2) to search for potential relationships, and we used multiple logistic regression to model explanatory variables against the dependent variable (i.e. presence of a KS). Model building included stepwise, forward, and backward regression techniques, and variables were explored using varied continuous and categorical formats. Assumptions were checked for analyses, and variables were assessed for correlation and interaction. Our research followed the tenets of the Declaration of Helsinki, subjects provided written informed consent prior to participation, and institutional review board approval was received.

RESULTS

The recruitment of subjects is summarized in Figure 3. Among 5121 potential subjects, there were 3833 (75%) who consented to participate. Consenters were slightly younger than non-consenters (mean age = 52 ± 16 years, 18–98 years vs. 55 ± 17 years, 18–94 years; $P < 0.0001$), and the consenters also had a slightly higher proportion of African Americans (84% vs. 78%, $P < 0.0001$). Gender proportions were similar among consenters and non-consenters (65% vs. 64%, $P = 0.55$).

Among the consenters, 332 of 3833 (8.7%) were excluded because: (1) they had comorbidity or a history of intraocular surgery that may have caused anterior chamber pigment dispersal; (2) their maximum LAZ grade was trace; or (3) there was missing information. This left 3501 subjects used in the final analysis who had a mean age of 51 ± 15 years (18–98 years, 65% women, 83.6% African American, 7.2% Hispanic, 5.7% white, 1.9% Asian, and 1.6% other).

The final inclusion group had 59 subjects (1.7%) with a KS in at least one eye. Of these 59 subjects, 46 (77.9%) had bilateral KS, 11 (18.6%) had a KS only in the right eye, and 2 (3.4%) had a KS only in the left eye. Furthermore, there were 57 of 59 subjects (96.6%) who had a right-eye KS and 48 of 59 subjects (81.4%) who had a left-eye KS.

To begin the analysis, we assessed unadjusted associations with the presence of a KS (see Tables 1, 2). Presence of the LAZ trait, presence of hypertension, use of cholesterol medications, age, and systolic blood pressure all had significant associations with KS presence ($P < 0.05$). To check for collinearity, we also evaluated the relationship of LAZ (i.e. the main explanatory variable of interest), with other potential confounding variables (Tables 3, 4).

TABLE 3. Unadjusted Relationships to LAZ – Categorical Variables

Variable	LAZ Present <i>N</i> = 120*	LAZ Absent <i>N</i> = 3367	<i>P</i> Value†
Gender, Female	78%	65%	0.002
Race			
African American	92%	82%	0.006‡
Asian	0%	2%	
Hispanic	5%	7%	
White	2%	6%	
Other	2%	2%	
Education greater than high school	59%	62%	0.54
Diabetes	33%	22%	0.005
Hypertension	73%	47%	<0.0001
Body mass index			
Underweight, < 18.5	3%	4%	0.07‡
Normal weight, 18.5 to 24.9	16%	23%	
Overweight, 25.0 to 29.9	31%	29%	
Obese, ≥ 30	50%	45%	
Cancer history - any site	8%	4%	0.09
Cholesterol med – current (per record)	28%	16%	<0.001
Cholesterol med – ever (per survey)	44%	28%	<0.001
Alcohol use			
Current	47%	49%	0.56
Ever	60%	60%	0.96
Smoking			
Current	27%	30%	0.45
Ever	53%	47%	0.26
Smoking in home when child	50%	44%	0.22

LAZ, long anterior zonule trait; N, number of subjects.

* Right eyes used in analysis.

† Bolded *P* values are significant at $\alpha = 0.05$ level.

‡ Statistical comparison is African American versus non-African American; overweight/obese versus underweight/normal weight.

TABLE 4. Unadjusted Relationships to LAZ - Continuous Variables

Variable	LAZ Present (<i>N</i> = 120)*	LAZ Absent (<i>N</i> = 3367)	<i>P</i> Value†
Age, y	63.9 ± 10.7	50.1 ± 15.4	<0.0001
Refractive error, SE, diopters	0.59 ± 2.11	−0.96 ± 2.93	<0.0001
Body mass index, kg/m ²	31.1 ± 7.3	30.6 ± 7.8	0.47
Systolic blood pressure, mm Hg	135.6 ± 20.5	128.7 ± 18.0	<0.001
Diastolic blood pressure, mm Hg	79.3 ± 11.1	79.2 ± 11.2	0.94
Pack years smoking	14.5 ± 21.4	10.0 ± 27.2	0.01

Kg/m², kilograms per meter-squared; LAZ, long anterior zonules; mm Hg, millimeters of mercury; SE, spherical equivalent.

* Right eyes used in analysis.

† Bolded *P* values are significant at $\alpha = 0.05$ level.

This indicated that LAZ had significant unadjusted associations with female gender, African American race, diabetes, hypertension, use of cholesterol medications, age, refractive error, systolic blood pressure, and pack years of smoking ($P < 0.05$).

After the univariate analyses, we then checked which variables maintained significant relationship to KS presence while controlling for other variables (Table 5). This demonstrated that presence of LAZ, refractive error, and age retained the greatest relationship to the presence of a KS. In addition, while controlling for age and refractive error, we found that the people who had a KS were 12× more likely to also exhibit the LAZ trait than people who did not have a KS (odds ratio [OR] = 12.2, 95% confidence interval [CI] = 6.5 to 22.8, $P < 0.0001$). Similar results were found for left eyes (OR = 10.2, 95% CI = 5.5 to 19.1, $P < 0.0001$).

Among the right and left eyes with LAZ, we assessed the relationship between estimated LAZ grade and the propor-

tion of eyes having a KS present. For these subanalyses, we found 90 LAZ (16 also with KS) right eyes and 86 LAZ (14 also with KS) left eyes with a recorded LAZ grade. Based on this, the proportion of LAZ right eyes having a KS increased as LAZ grade increased (i.e. 2 of 47 eyes [4.3%] with grade 1 LAZ had a KS, 4 of 23 eyes [17.4%] with grade 2 LAZ had a KS, and 10 of 20 eyes (50.0%) with either grade 3 or grade 4 LAZ had a KS ($P < 0.0001$). The left eyes with LAZ demonstrated similar KS proportions for the increasing LAZ grades (i.e. 1 of 44 [2.3%], 3 of 18 [16.7%], and 10 of 24 [41.7%], respectively; $P < 0.0001$).

Among the 57 subjects with a right eye KS, there were 4 principal groups, which consisted of 19 (33.3%) with LAZ, 16 (28.1%) with “classic” or primary pigment dispersion syndrome, 1 (1.8%) with exfoliation syndrome, and 21 (36.8%) whose KS was considered idiopathic (Table 6). Among subjects who did not have LAZ in this subgroup, we considered primary PDS present when we detected

TABLE 5. Multivariate Analysis of KS* as a Function of Presence of LAZ, Adjusting for Other Variables

Variable	Coefficient β	Standard Error	Wald χ^2	P Value [†]	Odds Ratio	95% CI
Intercept	-7.05	0.67	112.1			
LAZ trait present	2.50	0.32	60.8	<0.0001	12.2	6.50 to 22.84
Myopic refractive error, SE, per diopter	0.11	0.04	7.4	0.007	1.11	1.03 to 1.20
Age, per decade	0.45	0.10	17.5	<0.0001	1.27	1.27 to 1.94

CI, confidence interval; KS, Krukenberg's spindle; LAZ, long anterior zonule trait; SE, spherical equivalent.

* Right eyes used in analysis.

[†] Variables included only if significant at $P < 0.05$ level.

TABLE 6. Distribution of Krukenberg's Spindles Among Subjects

Group ($N = 57^*$)	Age [†] (Range)	Proportion African American	Proportion Women	Refractive Error [‡] (Range)
LAZ trait, $N = 19$, 33%	67.1 \pm 9.9 (52 to 86)	94.7%	84.2%	+0.59 \pm 2.46 (+7.50 to +3.50)
Primary PDS, $N = 16$, 28%	50.6 \pm 11.8 (26 to 66)	50.0%	56.3%	-2.84 \pm 3.61 (-10.86 to +1.13)
Idiopathic, $N = 21$, 37%	63.9 \pm 12.7 (36 to 85)	95.2%	81.0%	-1.02 \pm 4.03 (-14.75 to +3.75)
XFS, $N = 1$, 2%	81	100%	100%	+2.50

LAZ, long anterior zonule trait; PDS, pigment dispersion syndrome; XFS, exfoliation syndrome.

* Right eyes used in analysis.

[†] Mean \pm SD, years.

[‡] Mean \pm SD, spherical equivalent in diopters.

and documented midperipheral iris transillumination defects and/or equatorial lens pigment (Scheie line).^{37,38} The rationale for the pathognomonic sign of equatorial lens pigment has been discussed previously, which is especially important for the characterization of dark-brown eyes, which very often mask iris transillumination.³⁹⁻⁴¹ Because the original protocol for the collection of this dataset did not require examination for iris transillumination and assessment of the equatorial lens region, presence or absence of these signs could not always be established. Thus, it is possible that some of the "idiopathic" KS group could have had primary (i.e. classic) PDS. We emphasize, however, that none of the primary PDS subjects had any LAZ, and none of the LAZ subjects had signs, other than LAZ-related pigment dispersal, that suggested they had primary PDS.

Compared with the KS subjects who had LAZ, the KS subjects with primary PDS had lower proportions of African Americans (50.0% vs. 94.7%, $P = 0.005$), they were younger (mean age = 50.6 \pm 11.8 years vs. 67.1 \pm 9.9 years, $P < 0.0001$), and they were more myopic (mean spherical-equivalent refractive error = -2.84 \pm 3.61 diopter [D] vs. +0.59 \pm 2.46 D, $P < 0.0001$). The KS subjects with primary PDS also tended to have lower proportions of women, but the difference did not reach statistical significance (56.3% vs. 84.2%, $P = 0.13$). The idiopathic KS group was more similar in composition to the LAZ group relative to age, race, and gender, but they were more myopic on average (mean = -1.02 \pm 4.03 D) than the LAZ group. The difference in myopia between the KS group with LAZ and the idiopathic KS group did not reach statistical significance, even when including an outlier among the idiopathic group who had a refractive error of -14.75 D ($P = 0.11$).

DISCUSSION

This study illustrates that detection of a KS should raise suspicion for presence of the LAZ trait as a potential etiology, particularly among people with age > 50 years. In the population studied, LAZ was present in about one-third of the eyes exhibiting a KS. Thus, had LAZ not been

searched for among the KS eyes, the reason for the KS would have been unexplained a substantial percentage of the time. In addition, this possibly could have caused false suspicion for other etiologies, such as "classic" (i.e. primary PDS). Therefore, knowledge of this strong KS-LAZ association can be important for accurate phenotype recognition in routine clinical examination and in research. Due to the overlapping pigment dispersal features that the LAZ and primary PDS phenotypes share (e.g. KS formation and trabecular pigmentation),²⁹ our study supports the notion that any future investigations of primary PDS must also consider the LAZ phenotype when developing clinical case definitions. This may be especially important when including populations with dark-colored irides, such as African Americans who tend not to exhibit midperipheral iris transillumination defects,³⁹⁻⁴¹ a key hallmark sign of primary PDS.

Although a KS may alert the examiner to underlying LAZ, KS are often absent in LAZ eyes. We do not know why many LAZ eyes produce a KS while others do not, but these data suggest that eyes with greater numbers of LAZ are more likely to exhibit a KS. Other factors, such as degree of central extension of LAZ fibers and amount of iris-lens apposition, may also play a role. In prior investigations, we have quantified LAZ in terms of number of detectable fibers by clock hour, zonule-free zone size, and LAZ pattern type.^{26,35} Determining these parameters, which required detailed photographic documentation, could not be done in the current study. Future work may show whether these factors have any relationship to KS.

This study's LAZ prevalence was about 3.4% among right eyes, which is higher than the 1 to 2% prevalence we found in an earlier dataset.¹⁰ The reason for this difference is unclear, but a contributing factor could be improved detection rate. Despite this variation, both studies corroborate how frequently we encounter LAZ. To date, no population-based studies of LAZ have been conducted, but this should be a goal to improve estimates.

Strengths of this investigation include its unique and relatively large dataset of LAZ subjects, a phenotype that

remains understudied. The study also provided the ability to consider many variables during the analysis, such as the presence of diabetes, hypertension, alcohol use, smoking, BMI, etc., which was important for exploration to help rule out a variety of potential confounding factors. As indicated during the unadjusted analysis in Tables 1 and 2, variables, such as hypertension and use of cholesterol medication, showed association with KS presence, but these factors did not exhibit an independent relationship to KS presence when regression analyses controlled for age. This adds a degree of confidence toward conclusions made.

It was not the purpose of this analysis to determine independent factors related to LAZ presence, but we did assess unadjusted relationships (see Tables 3, 4) to identify potential confounding variables for the KS-LAZ relationship. Nearly always, we have found idiopathic LAZ in people > 50 years old, so its age association results in other age-dependent variables (e.g. hypertension), also having an unadjusted relationship to LAZ.^{10,20,31} It is a future goal to find new factors that have an independent causal role in the expression of LAZ.

It is important to comment briefly on refractive error and its relationship to KS presence. Based on the population studied, we found that the odds of a KS being present were 1.1× higher (see Table 5) for each additional diopter of myopia. We surmise that the relationship between refractive error and KS is weakened by an opposing directional relationship between KS eyes with LAZ (hyperopic direction) and the primary PDS-related KS eyes and the idiopathic KS eyes (myopic direction). Because the overall KS subject group has these subgroups with different refractive error directions, the KS-refractive error relationship among all the KS eyes would be expected to reflect the strongest of the two directions (i.e. myopic in our dataset). As shown in Table 6, there are greater numbers of subjects/eyes in the primary PDS and idiopathic groups combined than there are in the LAZ group. Thus, with analysis of the overall KS group, our final regression model indicates that, on average, there is a stronger KS association with myopia than hyperopia.

It is conceivable that a person could have both primary PDS and LAZ-associated PDS, but the two entities are distinct, sharing only certain signs that result from different pigment liberation mechanisms. Although LAZ distinguishes the two phenotypes, other features also help (e.g. patients with LAZ are usually older and hyperopic with convex irides, whereas patients with primary PDS are mostly younger and myopic with flat or concave irides). In addition, LAZ eyes have peripupillary iris transillumination defects (ITDs), whereas primary PDS eyes have midperipheral ITDs.^{11,29,42} Therefore, we further note that none of the subjects with primary PDS had LAZ, and none of the LAZ subjects had signs suggestive of primary PDS besides the LAZ-induced pigment dispersal signs. LAZ-associated PDS and primary PDS appear to be similar only due to their iris pigment liberation, which occurs for different reasons.^{14,16,29}

Although it was straightforward in our study to designate KS related to LAZ, it was more difficult to attribute KS to other causes, especially among our predominantly African American population. We have previously studied primary PDS signs in African Americans and found that standard slit lamp examination has limited value to detect ITDs in dark-brown irides. Specialized infrared iris examination techniques can help show ITDs in some eyes,⁴⁰ although this was not part of the protocol for this dataset. In lieu of ITD presence, we have previously observed that periph-

eral/equatorial lens pigment can help establish that primary PDS is present when there are other consistent characteristics.³⁹ Had we performed infrared iris testing and also checked for equatorial lens pigment on all subjects in this study, we may have been able to reclassify some of the “idiopathic” KS subjects as primary PDS. Nevertheless, the study’s main message would remain unchanged (i.e. that LAZ may often help explain KS presence).

Although the LAZ trait is suggestive of a pathologic state due to its potential relationship to higher IOP, idiopathic KS that is not associated with LAZ or primary PDS may not be indicative of a pathologic process. When idiopathic KS is present, identifiable reasons for it should be ruled out, but when none exist, the sign may have little, if any, significance.⁸

The assessment of interobserver agreement, with or without use of photographs, was not used with the current dataset, but could have added observational precision. Detection of subtle LAZ can be challenging, especially in some densely cataractous eyes. Therefore, we may have missed some LAZ cases. It is also difficult to know if LAZ is truly present when there are only a few, faint “LAZ-like” lines. For this reason, we excluded subjects with less than five detectable lines, a criterion we have used previously to ensure presence of definitive LAZ cases.^{20,31,43}

We could not draw conclusions about iridocorneal angle pigment among our subjects here because performing gonioscopy was not part of the dataset’s original protocol. Although there are no reports of precise quantification of trabecular pigmentation among LAZ eyes, our group has previously examined LAZ subjects with gonioscopy, with most eyes having “mild-to-moderate” pigment. However, dense trabecular pigmentation can occur.¹⁰

A limitation of this investigation is that it involves a single site with a predominantly African American composition. Although we have not found substantial differences in race predilection relative to LAZ prevalence in this site’s population,¹⁰ we have previously found a lower prevalence of classic PDS among African Americans as compared with whites.³⁹ Thus, it is likely that LAZ-associated KS formation would constitute a smaller proportion of all patients with KS had our population been one with a higher likelihood of classic PDS. Nonetheless, this does not nullify the main message from our study (i.e. that the LAZ trait should be strongly considered as a potential etiology for KS formation), especially when the affected patients are older.

Although a relationship to IOP has been demonstrated, we believe this should be studied further with larger, more diverse groups of subjects, and there should be an effort to determine whether LAZ is an independent risk factor for glaucoma. At present, our LAZ subject groups have been insufficiently powered to assess this relationship. Given the potential prevalence of LAZ we believe this is an important goal. Determining this, coupled with efforts to understand the genetics of LAZ, may add further to knowledge about glaucoma.

CONCLUSIONS

The Krukenberg’s spindle presence is strongly associated with the LAZ trait and is an indicator of LAZ-associated pigment dispersion. In people who exhibit KS formation, the LAZ trait should be searched for, especially in those who have other characteristics that are highly associated with LAZ, including age over 50 years and hyperopia. Improved

awareness of the association between KS and LAZ could lead to more precise diagnosis, which is important to clinical care and research because LAZ is associated with higher IOP and is being studied as a potential independent risk factor for glaucoma.

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