Published in final edited form as:

Curr Ophthalmol Rep. 2016 December ; 4(4): 206–212. doi:10.1007/s40135-016-0113-0.

Genetics, Diagnosis, and Monitoring of Pseudoexfoliation Glaucoma

Niraj Nathan, M.D. and

2311 Pierce Ave, Nashville, TN 37232-8808, 615-936-2020, 615-936-1540 (Fax),
niraj.r.nathan@vanderbilt.edu

Rachel W. Kuchtey, M.D., Ph.D.

2311 Pierce Ave, Nashville, TN 37232-8808

Abstract

Recent studies have shed new light on the genetic factors underlying pseudoexfoliation syndrome, growing our understanding of the role of the lysyl oxidase-like 1 (LOXL1) gene and its various polymorphisms as well as identifying new genetic associations. Recent years have brought new insight on how these genetic factors interact with other factors, including environmental, to confer risk to individuals and populations worldwide. All of these findings may hold importance to the screening, diagnosis, and monitoring of pseudoexfoliation and may also help lead to the identification of novel therapeutic targets. This review serves as an update on the recent trends and findings in pseudoexfoliation syndrome.

Keywords

pseudoexfoliation; glaucoma; exfoliation; diagnosis; monitoring

Introduction

Pseudoexfoliation is the most common identifiable cause of glaucoma. Despite much having been discovered about pseudoexfoliation syndrome and pseudoexfoliation glaucoma over the past few decades, many questions have remained unanswered. Recent years have brought new knowledge about the genetic basis for pseudoexfoliation and how these genetic factors interact with other factors to confer risk to individuals and populations worldwide. We expect that greater understanding of these pathogenetic mechanisms will improve our ability to diagnose pseudoexfoliation as well as monitor those at risk for pseudoexfoliation. Our growing understanding of pseudoexfoliation both as a systemic condition and as an ocular condition should guide our monitoring of these patients. This review is intended to serve as

Corresponding Author, Rachel W. Kuchtey M.D., Ph.D., 615-936-7190, 615-936-1540 (Fax), rachel.w.kuchtey@vanderbilt.edu.

Compliance with Ethical Guidelines

Conflict of Interest

Niraj Nathan declares no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

an update, highlighting some of the recent trends and findings in pseudoexfoliation syndrome.

Genetics and Pathogenesis

The association of single nucleotide polymorphisms in the lysyl oxidase-like 1 (LOXL1) gene with pseudoexfoliation syndrome has been well-established, though its precise role in the pathogenesis of pseudoexfoliation remains yet to be fully elucidated. In the past several years, multiple genetic associations with pseudoexfoliation have variably and inconsistently emerged, including clusterin, matrix metalloproteinase 1 (MMP1), glutathione transferase, contactin-associated protein-like 2 (CNTNAP2), and tumor necrosis factor alpha (1).

Some novel studies have added to our evolving understanding of the genetics and pathogenesis of pseudoexfoliation. LOXL1 is an enzyme that plays a role in the crosslinking of collagen and elastin in the extracellular matrix (2). While it seems reasonable that alterations of interactions in the extracellular matrix of various tissues could lead to the production and accumulation of pseudoexfoliation material, the exact role of LOXL1 in the pathogenesis of pseudoexfoliation has still not been specifically demonstrated. Sharma et al. were the first to demonstrate a specific biologic effect of two of the single nucleotide polymorphisms strongly associated with pseudoexfoliation: s1048861 and rs3825942, which lead to the amino acid substitutions Arg141Leu and Gly153Asp, respectively (3). They posited that molecular modeling indicates that these amino acids were on the surface of the LOXL1 protein and thus likely to affect protein-protein interactions. They found in fetal rat lung tissue that LOXL1 variants with these substitutions were processed differently by endogenous proteins, most likely including bone morphogenic protein-1 (BMP1), which activates LOXL1 by enzymatic cleavage. These variants did not show a significant increase in extracellular accumulation, though.

Recently, a multiethnic genome-wide association study by Aung et al. implicated a variant mapping to the gene encoding CACNA1A, a subunit in voltage-gated calcium channels; this is the first such genome-wide association aside from the LOXL1 gene, though its significance is yet to be determined (4). CACNA1A-containing channels are expressed in cerebral cortex, thalamus, hypothalamus, and cerebellum, with various reports in the literature of associations with episodic ataxia, familial hemiplegic migraine, and spinocerebellar ataxia. Aung et al. further demonstrated that CACNA1A is widely expressed in most ocular tissues, except the optic nerve (4). While the role of CACNA1A in pseudoexfoliation is not known, using electron microscopy, high calcium content has been demonstrated in pseudoexfoliation material (5), leading some to postulate that alterations in calcium transport could contribute to aggregation of pseudoexfoliation material.

Elevated plasma and aqueous homocysteine has been observed in pseudoexfoliation patients in a number of studies (6). It is unclear whether homocysteine plays a causative role in pseudoexfoliation, with one proposed mechanism by Pasquale et al. being the disruption of disulfide bonds of cysteine residues in extracellular matrix proteins (6). They further posited that one way this association may be correlative rather than causative could be through

chronic folate deficiency, which could disrupt the methionine-homocysteine cycle, which could theoretically also affect the methylation and expression of LOXL1.

Clusterin, an extracellular matrix protein that is involved in preventing protein misfolding and has been implicated in the pathogenesis of Alzheimer's disease, has garnered increasing interest in understanding its role in pseudoexfoliation. Multiple studies have investigated the association of specific single-nucleotide polymorphisms in the clusterin gene with pseudoexfoliation syndrome and pseudoexfoliation glaucoma, but the results remain mixed, with association of certain SNPs in some populations but not others (7-9).

Other investigators have targeted inflammation and oxidative stress as elements in pseudoexfoliation syndrome. Vulovic et al. reported increased levels of TNF- α , IL-6, and IL-17 in aqueous humor of early stage pseudoexfoliation syndrome patients, suggesting an inflammatory component early in the disease (10). Dursun et al. found elevated total oxidative stress and decreased antioxidant capacity in serum and aqueous humor in pseudoexfoliation and pseudoexfoliation glaucoma patients compared to controls (11).

The past several years have brought many interesting insights on the impact of environmental risk factors for pseudoexfoliation as well as how the effect of a given genetic polymorphism can vary widely among different populations. Further, some populations have been shown to have a disproportionately high burden of pseudoexfoliation compared to others. While the increased prevalence of pseudoexfoliation in Scandinavian populations is well-known, Olayowe et al. reported a high prevalence in sub-Saharan Africa, far higher than African-American populations in the United States. Interestingly, they pointed out that some studies in Ethiopia, the Congo, Gambia, and South Africa report high prevalence, while studies from adjacent Ghana and Tanzania report almost none (12). The reasons for these differences in prevalence remain unclear.

Similarly, Kang et al. reported in a U.S. cohort that Scandinavian ancestry was not found to be a risk factor for pseudoexfoliation glaucoma or glaucoma suspect (13). The results suggested that the increased prevalence noted in Scandinavia may be related less to genetic factors alone and rather more to environmental factors or, perhaps more likely, the interaction between environmental factors with specific risk alleles. Previously reported environmental and behavioral risk factors for pseudoexfoliation include higher latitude, caffeine/coffee intake, low folate, increased outdoor activity and solar exposure (particularly reflected sunlight off snow/ice/water), and increased number of sunny days and daylight hours (14). Multiple recent studies have reconfirmed the importance of these risk factors. Kang et al. showed an adjusted odds ratio of 2.0 for those who spent more than eleven hours per week outdoors during high school until the age 24 compared to those who spent less than five hours per week outdoors (15). Pasquale et al. reported in a case-control study conducted in the United States and Israel that each degree of weighted lifetime residential latitude from the equator was associated with eleven percent increased odds of pseudoexfoliation, while every hour per week spent outdoors in the summer was associated with four percent increased odds (16).

Putting together the complex interplay of external factors with genetic factors to better understand pseudoexfoliation risk has been revealing. While it has been shown previously that some LOXL1 polymorphisms confer risk of pseudoexfoliation while others are protective, multiple recent studies have indicated that the same polymorphism allele may be a protective allele in some populations but a risk allele in others (Table 1) (4, 17, 18). These findings suggest that each allele interacts with environmental factors and/or other genetic factors within each population to increase risk of or protect against pseudoexfoliation.

Systemic manifestations

Pseudoexfoliation syndrome is a systemic disorder, but to date its clinical relevance has been almost exclusively with the regard to the eye. Pseudoexfoliation deposits have been shown throughout the body in visceral organs, such as the lung, kidney, liver, gall bladder, and even the meninges. While some studies have found association between pseudoexfoliation and cerebrovascular and cardiovascular disease (19, 20), other studies have not (21). More recently, Gökce et al. reported that pseudoexfoliation syndrome is associated with a tendency toward increased carotid intima media thickness as well as increased renal artery resistance (22). A meta-analysis concluded that the overall body of literature does indeed suggest that pseudoexfoliation syndrome is associated with increased risk of vascular disease, including coronary heart disease, cerebrovascular disease, and aortic aneurysm (23).

The literature is more consistent, though, on pseudoexfoliation and mortality. Multiple studies have previously shown no increase in all-cause mortality in patients with pseudoexfoliation (19, 24, 25), with Shum et al. specifically reporting a decrease in overall mortality and no difference in cardiovascular or cerebrovascular mortality (26). Recent studies have corroborated this (27). Interestingly, in a Finnish cohort, Tarkkanen and Kivela found increased life expectancy in pseudoexfoliation glaucoma patients when compared to patients with primary open angle glaucoma (28).

Some recent interest has been given to the association of systemic markers to pseudoexfoliation syndrome. In a small case control series, Vulovic et al. reported elevated serum IL-6 levels in early and late pseudoexfoliation patients, supporting the idea of a systemic pro-inflammatory state (10). Similarly, Ozgunul et al. reported an elevated neutrophil-to-lymphocyte ratio on complete blood counts in pseudoexfoliation syndrome and pseudoexfoliation glaucoma patients when compared to normal controls; they also noted an elevated platelet-to-lymphocyte ratio in pseudoexfoliation glaucoma patients when compared to pseudoexfoliation syndrome patients and controls (29). The authors posited that these ratios may eventually be useful in predicting the progression to glaucoma in pseudoexfoliation patients, but a favorable sensitivity and specificity profile of such screening compared to current ophthalmic examination methods are yet to be demonstrated. It has also been recently reported that pseudoexfoliation patients have lower serum levels of adiponin, a metabolic regulator that modulates glucose-mediated insulin release (30, 31). The implications and reproducibility of this association are unclear.

Ocular manifestations

The association of pseudoexfoliation with glaucoma is well-established; glaucoma can be caused by an open angle mechanism, angle closure mechanism, or a combination of the two. The Early Manifest Glaucoma Trial Group has reported that pseudoexfoliation glaucoma progresses significantly faster than primary open angle glaucoma or normal tension glaucoma, with pseudoexfoliation glaucoma associated with more rapid annual IOP increase (32-34). Pseudoexfoliation has also been associated with greater short-term lability in IOP (35). The open angle mechanism has been attributed largely to obstruction of the trabecular meshwork by pseudoexfoliation material and subsequent decrease in aqueous outflow. The angle closure mechanism has been thought to be largely related to zonular weakness and subsequent anterior displacement of the iris.

It has been shown previously that pseudoexfoliation patients with ocular hypertension progress to glaucoma about twice as much as patients with ocular hypertension without pseudoexfoliation, even while matching for baseline IOP, age, and gender (36). While it may be possible that increased IOP fluctuation may contribute to this finding, this finding suggests that factors other than intraocular pressure may be contributing to the conversion to and progression of glaucoma in pseudoexfoliation patients. Moghimi et al. recently found, using enhanced-depth spectral domain OCT, that the lamina cribrosa is significantly thinner in nonglaucomatous pseudoexfoliation eyes compared to controls (37). Further, they found that inferior and superior lamina cribrosa depth was greater in the pseudoexfoliation group than controls, but they found no significant difference in central lamina cribrosa depth between the two groups. The relevance of these findings to glaucomatous progression in pseudoexfoliation eyes is not yet determined.

Pseudoexfoliation has additional clinical relevance beyond the field of glaucoma, though. The importance of pseudoexfoliation syndrome and its association with poor pupillary dilation and zonular compromise to cataract surgery is well-known. The presence of pseudoexfoliation holds further significance aside from the risk of intraoperative complications, however. Ascaso et al. observed that more than half of all late (greater than three months after surgery) IOL-capsule complex dislocations are attributable to pseudoexfoliation syndrome (38).

Pseudoexfoliation has effects on the cornea as well. Wang et al. noted decreased mean corneal endothelial cell density in a small cohort of eyes of Chinese patients with pseudoexfoliation (39). Other groups have taken this a step further, finding decreased endothelial cell, anterior stromal keratocyte, and posterior stromal keratocyte density as well as decreased length, branching, and density of the sub-basal nerve plexus (40, 41). Pseudoexfoliation syndrome has also been associated with decreased tear production and tear film stability (42, 43).

Multiple groups have taken interest in assessing the effects of pseudoexfoliation syndrome on the vasculature of the eye and ocular blood flow. In 1994, Helbig et al. demonstrated progressive degeneration of the iris vasculature on electron microscopy, progressing from the adventitia to the endothelium; they concurrently demonstrated relative hypoxia in the

aqueous humor of pseudoexfoliation patients when compared to control (44). More recently, decreased subfoveal choroidal thickness has been demonstrated in pseudoexfoliation eyes, with the suggestion that this may be due to decreased choroidal perfusion related to carotid flow as well as impairment of the choroidal microcirculation (45, 46). Kocaturk et al. has reported increased vascular resistance in the ophthalmic artery in pseudoexfoliation glaucoma patients, as identified using color Doppler imaging (47).

Treatment

Just as it has been observed that the natural history and pathogenetic mechanisms of pseudoexfoliation glaucoma differ in important ways from other types of glaucoma, determining whether the treatment of pseudoexfoliation glaucoma patients warrants a different approach has been a robust area of interest. When it comes to selecting a first-line topical agent for the treatment of pseudoexfoliation patients with elevated eye pressures, researchers have primarily compared prostaglandin analogues with fixed combination drops, both with regard to magnitude of IOP reduction as well as reduction of diurnal variation. In 2003, Konstas et al. found similar efficacy of latanoprost and timolol/dorzolamide fixed combination drops in lowering IOP in patients with a mean IOP baseline of 31 mm Hg (48). The same group found that bimatoprost provides better diurnal control of IOP than latanoprost in pseudoexfoliation patients with high baseline IOP (49). They additionally reported that the fixed combination of bimatoprost-timolol outperformed either bimatoprost or latanoprost alone in IOP reduction in these same ocular hypertensive pseudoexfoliation patients (50, 51).

The use of pilocarpine in pseudoexfoliation glaucoma is intriguing from a mechanistic standpoint. In 2009, Angelilli et al. reported that the combination of latanoprost and pilocarpine improved IOP reduction compared to timolol or the fixed combination dorzolamide/timolol; more interestingly, they reported increased outflow facility and decreased pigmentation of the trabecular meshwork in the latanoprost plus pilocarpine group (52). Angelilli and Ritch suggested that improved outflow and decreased pupillary movement may lead to less deposition in the trabecular meshwork, especially when compared to using aqueous suppressants, making pilocarpine theoretically a particularly useful agent in pseudoexfoliation glaucoma (53). Still, since then, no large-scale studies of the efficacy of pilocarpine in pseudoexfoliation glaucoma have been performed, likely attributable to the less favorable side effect profile of pilocarpine.

Laser trabeculoplasty has been known to be particularly effective in pseudoexfoliation patients for over 30 years, albeit with diminishing effects on IOP over time (54). In a randomized controlled trial, Kent et al. found no significant difference between argon laser trabeculoplasty (ALT) and selective laser trabeculoplasty (SLT) at the six month posttreatment time point (55).

Cataract surgery alone has been shown to produce IOP reduction in many eyes and has been shown to be even more effective in pseudoexfoliation patients (56). It has been shown by two groups that despite an increased risk of postoperative day 1 IOP spikes, pseudoexfoliation eyes continue to have IOP lowering benefit from cataract surgery even at a

seven year postoperative time point (57, 58). These studies reported lower than expected rates of glaucoma development and glaucoma progression in this seven year time frame, suggesting that cataract surgery may be protective in these patients. As an additional benefit, cataract surgery has been shown to blunt diurnal IOP fluctuations in pseudoexfoliation patients (59).

The rapidly evolving armamentarium of angle-based minimally invasive glaucoma surgery (MIGS) seems particularly well suited for pseudoexfoliation glaucoma. Given that clogging of the trabecular meshwork and decreased trabecular outflow is the predominant mechanism for IOP elevation in many eyes with pseudoexfoliation, procedures specifically targeting trabecular meshwork outflow, especially those that clear the trabecular meshwork and Schlemm's canal, seem particularly intriguing. Klamann et al. reported a 35% average decrease in intraocular pressure (IOP) and reduction from 2.3 mean medications preoperatively to 1 medication postoperatively in pseudoexfoliation patients treated with the iStent inject (60). Hassan and Awadalla noted promising results of combined viscocanalostomy and cataract surgery, with a 90% complete success rate (defined as IOP less than 21 mm Hg without medication) and a 51% reduction in mean IOP at last follow-up (mean follow-up 18.6 months) from mean preoperative IOP (61).

The Trabectome (ab interno trabeculectomy) is the best studied MIGS procedure in pseudoexfoliation patients. Ting et al. reported a 79% success rate (defined as IOP less than 21 mm Hg, greater than 20 percent reduction in IOP, and no secondary surgery) at one year with Trabectome alone and 87% success with Trabectome with cataract surgery (62). Klamann et al. reported a 40% reduction in mean IOP at one year with Trabectome plus cataract surgery in pseudoexfoliation eyes but no change in the mean number of medications (63). Jordan et al. reported a 30% reduction in IOP and 44% reduction in glaucoma medications with Trabectome with or without cataract surgery in pseudoexfoliation glaucoma eyes after a mean follow-up of 204 days, similar to the reduction observed in POAG eyes (64). Widder et al. found a 38% reduction in IOP and reduction in mean number of medications from 2.4 preoperatively to 2.1 postoperatively in eyes with pseudoexfoliation glaucoma after Trabectome and cataract surgery plus trabecular aspiration (65).

Trabeculectomy and aqueous tube shunts are still the go-to procedures for pseudoexfoliation glaucoma patients with advanced disease or poorly controlled IOP despite maximum tolerated medical and noninvasive treatment. The Ex-PRESS miniature glaucoma shunt has emerged as viable option for these patients as well. In a retrospective review, Moisseiev et al. found no differences in IOP reduction, number of postoperative medications, hypotony, or rates of failure between standard trabeculectomy and the Ex-PRESS mini shunt (66). In a twenty year follow-up study, Landers et al. reported that even after trabeculectomy eyes with pseudoexfoliation were still more likely to progress to blindness than those with other types of glaucoma, though (67). Aqueous tube shunts remain a viable surgical option in pseudoexfoliation glaucoma, though no studies have specifically assessed their outcomes in pseudoexfoliation glaucoma. Trubnik et al. reported a trend toward increased tube erosion in pseudoexfoliation glaucoma eyes (odds ratio 2.7), but the finding was not statistically significant.

Conclusions

Our understanding of the pathogenesis of pseudoexfoliation continues to evolve, with the hope that future research will provide further clarity to the underlying mechanisms as well as identify novel therapeutic targets. These growing insights will help us improve our diagnosis of pseudoexfoliation as well as identification and monitoring of high-risk patients. Fortunately, the array of treatment options for pseudoexfoliation glaucoma is also rapidly expanding, largely due to the rise of minimally-invasive glaucoma surgery, holding promise for the future to better manage and monitor this difficult condition.

Acknowledgments

Rachel Kuchtey received a grant support from the National Eye Institute (EY020894) for work unrelated to this manuscript.

References

Papers of particular interest, published recently, have been highlighted as:

•Of importance

••Of major importance

1. Elhawry E, Kamthan G, Dong C, Danias J. Pseudoexfoliation syndrome, a systemic disorder with ocular manifestations. *Hum Genomics*. 2012; 6(22)
2. Kagan H, Li W. Lysyl oxidase: properties, specificity, and biological roles inside and outside of the cell. *J Cell Biochem*. 2003; 88(4):660–72. [PubMed: 12577300]
- 3 •. Sharma S, Martin S, Sykes M, Dave A, Hewitt A, Burdon K, et al. Biological effect of LOXL1 coding variants associated with pseudoexfoliation syndrome. *Exp Eye Res*. 2016 This study is the first to show a biological effect of two LOXL1 polymorphisms, affecting LOXL1 processing by other proteins, likely including bone morphogenic protein-1 (BMP1), which enzymatically activates LOXL1.
- 4 •. Aung T, Ozaki M, Mizoguchi T, Allingham R, Li Z, Haripriya A, et al. A common variant mapping to CACNA1A is associated with susceptibility to exfoliation syndrome. *Nat Genet*. 2015; 47(4):387–92. [PubMed: 25706626] This study identified CACNA1A, a subunit for voltage-gate calcium channels, as the first other genome-wide association with pseudoexfoliation syndrome since LOXL1.
5. Schlötzer-Schrehardt U, Körtje K, Erb C. Energy-filtering transmission electron microscopy (EFTEM) in the elemental analysis of pseudoexfoliative material. *Curr Eye Res*. 2001; 22(2):154–62. [PubMed: 11402393]
6. Pasquale L, Borrás T, Fingert J, Wiggs J, Ritch R. Exfoliation syndrome: assembling the puzzle pieces. *Acta Ophthalmol*. 2015
7. Padhy B, Nanda G, Chowdhury M, Padhi D, Rao A, Alone D. Role of an extracellular chaperone, Clusterin in the pathogenesis of Pseudoexfoliation Syndrome and Pseudoexfoliation Glaucoma. *Exp Eye Res*. 2014; 127:69–76. [PubMed: 25057782]
8. Dubey S, Hejtmancik J, Krishnadas S, Sharmila R, Haripriya A, Sundaresan P. Evaluation of genetic polymorphisms in clusterin and tumor necrosis factor-alpha genes in South Indian individuals with pseudoexfoliation syndrome. *Curr Eye Res*. 2015; 40(12):1218–24. [PubMed: 25849827]
9. Fan B, Pasquale L, Kang J, Levkovitch-Verbin H, Haines J, Wiggs J. Association of clusterin (CLU) variants and exfoliation syndrome: An analysis in two Caucasian studies and a meta-analysis. *Exp Eye Res*. 2015; 139:115–22. [PubMed: 26272660]
10. Vulovic TS, Pavlovic S, Zdravkovic N. Proinflammatory Cytokines Induce XFG Development. *Ocul Immunol Inflamm*. 2015:1–7.

11. Dursun F, Ozec AV, Aydin H, Topalkara A, Dursun A, Toker M, et al. Total oxidative stress, paraoxonase and arylesterase levels at patients with pseudoexfoliation syndrome and pseudoexfoliative glaucoma. *Int J Ophthalmol*. 2015; 8(5):985–90. [PubMed: 26558214]
12. Olawoye O, Pasquale L, Ritch R. Exfoliation syndrome in sub-Saharan Africa. *Int Ophthalmol*. 2014; 34(5):1165–73. [PubMed: 24844849]
13. Kang J, Loomis S, Wiggs J, Stein J, Pasquale L. Demographic and geographic features of exfoliation glaucoma in 2 United States-based prospective cohorts. *Ophthalmology*. 2012; 119(1): 27–35. [PubMed: 21982415]
14. Miglior S, Bertuzzi F. Exfoliative glaucoma: new evidence in the pathogenesis and treatment. *Prog Brain Res*. 2015; 221:233–41. [PubMed: 26518081]
15. Kang J, Wiggs J, Pasquale L. Relation between time spent outdoors and exfoliation glaucoma or exfoliation glaucoma suspect. *Am J Ophthalmol*. 2014; 158(3):605–14. [PubMed: 24857689]
16. Pasquale L, Jiwani A, Zehavi-Dorin T, Majd A, Rhee D, Chen T, et al. Solar exposure and residential geographic history in relation to exfoliation syndrome in the United States and Israel. *JAMA Ophthalmol*. 2014; 132(12):1439–45. [PubMed: 25188364]
17. Fan B, Pasquale L, Rhee D, Li T, Haines J, Wiggs J. LOXL1 promoter haplotypes are associated with exfoliation syndrome in a U.S. Caucasian population. *Invest Ophthalmol Vis Sci*. 2011; 52(5):2372–8. [PubMed: 21212179]
18. Founti P, Haidich A, Chatzikyriakidou A, Salonikiou A, Anastasopoulos E, Pappas T, et al. Ethnicity-Based Differences in the Association of LOXL1 Polymorphisms with Pseudoexfoliation/Pseudoexfoliative Glaucoma: A Meta-Analysis. *Ann Hum Genet*. 2015; 79(6): 431–50. [PubMed: 26404116] This study demonstrated that some LOXL1 polymorphism alleles have different effects in different populations, with a given allele increasing risk in certain populations but providing protection in others.
19. Ritland J, Egge K, Lydersen S, Juul R, Semb S. Exfoliative glaucoma and primary open-angle glaucoma: associations with death causes and comorbidity. *Acta Ophthalmol*. 2004; 82:401–4.
20. Mitchell P, Wang J, Smith W. Association of pseudoexfoliation syndrome with increased vascular risk. *Am J Ophthalmol*. 1997; 124(5):685–7. [PubMed: 9372724]
21. Allingham R, Loftsdottir M, Gottfredsdottir M, Thorgeirsson E, Jonasson F, Sverrisson T, et al. Pseudoexfoliation syndrome in Icelandic families. *Br J Ophthalmol*. 2001; 85(6):702–7. [PubMed: 11371492]
22. Gökce S, Deren T, Köz O, Yilmaz P, Ba kan C, Duman R, et al. Evaluation of Carotid Intima Media Thickness and Renal Artery Resistive Index in Patients With Pseudoexfoliation Syndrome: A Prospective Case-Control Study. *J Glaucoma*. 2015
23. Wang W, He M, Zhou M, Zhang X. Ocular pseudoexfoliation syndrome and vascular disease: a systematic review and meta-analysis. *PLoS One*. 2014; 9(3):e92767. [PubMed: 24667689]
24. Ringvold A, Blika S, Sandvik L. Pseudo-exfoliation and mortality. *Acta Ophthalmol Scand*. 1997; 75:255–6. [PubMed: 9253968]
25. Grodum K, Heiji A, Bengtsson B. Glaucoma and mortality. *Graefes Arch Clin Exp Ophthalmol*. 2004; 42:397–401. [PubMed: 15029499]
26. Shrum K, Hattenhauer M, Hodge D. Cardiovascular and cerebrovascular mortality associated with ocular pseudoexfoliation. *Am J Ophthalmol*. 2000; 129(1):83–6. [PubMed: 10653417]
27. Svensson R, Ekstrom C. Pseudoexfoliation and mortality: a population-based 30-year follow-up study. *Acta Ophthalmol*. Mar. 2015; 93(2):162–4.
28. Tarkkanen A, Kivela T. Mortality in primary open-angle glaucoma and exfoliative glaucoma. *Eur J Ophthalmol*. 2014; 24(5):718–21. [PubMed: 24557754]
29. Ozgonul C, Sertoglu E, Mumcuoglu T, Ozge G, Gokce G. Prediction of Pseudoexfoliation Syndrome and Pseudoexfoliation Glaucoma by Using Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio. *Ocul Immunol Inflamm*. 2015:1–6.
30. O urel T, O urel R, Topuz M, Örnek N, Örnek K. Plasma adropin level in patients with pseudoexfoliation. *Int Ophthalmol*. O urel T1, O urel R2, Topuz M3, Örnek N2, Örnek K2.
31. Aydin S. Three new players in energy regulation: preptin, adropin and irisin. *Peptides*. 2014; 56:94–110. [PubMed: 24721335]

32. Leske M, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E. Factors for Glaucoma Progression and the Effect of Treatment. *Arch Ophthalmol*. 2003; 121(1):48–56. [PubMed: 12523884]
33. Heijl A, Bengtsson B, Hyman L, Leske M. Natural history of open-angle glaucoma. *Ophthalmology*. 2009; 116(12):2271–6. [PubMed: 19854514]
34. Hyman L, Heijl A, Leske M, Bengtsson B, Yang Z. Natural history of intraocular pressure in the early manifest glaucoma trial: A 6-year follow-up. *Arch Ophthalmol*. 2010; 128(5):601–7. [PubMed: 20457982]
35. Huchzermeyer C, Horn F, Lämmer R, Mardin C, Jünemann A. Short-term fluctuation of intraocular pressure is higher in patients with pseudoexfoliation syndrome despite similar mean intraocular pressure: a retrospective case-control study. *Graefes Arch Clin Exp Ophthalmol*. 2015; 253(1):107–14. [PubMed: 25308782]
36. Grødum K, Heijl A, Bengtsson B. Risk of glaucoma in ocular hypertension with and without pseudoexfoliation. *Ophthalmology*. 2005; 112(3):386–90. [PubMed: 15745763]
37. Moghimi S, Mazloumi M, Johari M, Abdi P, Fakhraie G, Mohammadi M, et al. Evaluation of Lamina Cribrosa and Choroid in Nonglaucomatous Patients With Pseudoexfoliation Syndrome Using Spectral-Domain Optical Coherence Tomography. *Invest Ophthalmol Vis Sci*. 2016; 57(3):1293–300. [PubMed: 26998715]
38. Ascaso F, Huerva V, Grzybowski A. Epidemiology, Etiology, and Prevention of Late IOL-Capsular Bag Complex Dislocation: Review of the Literature. *J Ophthalmol*. 2015
39. Wang M, Sun W, Ying L, Dong X. Corneal endothelial cell density and morphology in Chinese patients with pseudoexfoliation syndrome. *Int J Ophthalmol*. 2012; 5(2):186–9. [PubMed: 22762047]
40. Oltulu R, Satirtav G, Kayitmazbatir E, Bitirgen G, Ozkagnici A, Karaibrahimoglu A. Characteristics of the cornea in patients with pseudoexfoliation syndrome. *Arq Bras Oftalmol*. 2015; 78(6):348–51. [PubMed: 26677035]
41. Yüksel N, Emre E, Pirhan D. Evaluation of Corneal Microstructure in Pseudoexfoliation Syndrome and Glaucoma: In Vivo Scanning Laser Confocal Microscopic Study. *Curr Eye Res*. 2016; 41(1):34–40. [PubMed: 25612165]
42. Škegro I, Sui S, Kordi R, Jandrokovi S, Petri ek I, Kuzman T, et al. Ocular surface disease in pseudoexfoliation syndrome. *Coll Antropol*. 2015; 39(1):43–5. [PubMed: 26040066]
43. Akdemir M, Kirgiz A, Ayar O, Kaldirim H, Mert M, Cabuk K, et al. The Effect of Pseudoexfoliation and Pseudoexfoliation Induced Dry Eye on Central Corneal Thickness. *Curr Eye Res*. 2016; 41(3):305–10. [PubMed: 25974410]
44. Helbig H, Schlötzer-Schrehardt U, Noske W, Kellner U, Foerster M, Naumann G. Anterior-chamber hypoxia and iris vasculopathy in pseudoexfoliation syndrome. *Ger J Ophthalmol*. 1994; 3(3):148–53. [PubMed: 8038683]
45. Eroglu F, Asena L, Simsek C, Kal A, Yilmaz G. Evaluation of choroidal thickness using enhanced depth imaging by spectral-domain optical coherence tomography in patients with pseudoexfoliation syndrome. *Eye (Lond)*. 2015; 29(6):791–6. [PubMed: 25853396]
46. Turan-Vural E, Yenerel N, Okutucu M, Yildiz E, Dikmen N. Measurement of Subfoveal Choroidal Thickness in Pseudoexfoliation Syndrome Using Enhanced Depth Imaging Optical Coherence Tomography. *Ophthalmologica*. 2015; 233(3-4):204–8. [PubMed: 25676024]
47. Kocaturk T, Isikligil I, Uz B, Dayanir V, Dayanir Y. Ophthalmic artery blood flow parameters in pseudoexfoliation glaucoma. *Eur J Ophthalmol*. 2016; 26(2):124–7. [PubMed: 26391169]
48. Konstas A, Kozobolis V, Tersis I, Leech J, Stewart W. The efficacy and safety of the timolol/dorzolamide fixed combination vs latanoprost in exfoliation glaucoma. *Eye (Lond)*. 2003; 17(1):41–6. [PubMed: 12579169]
49. Konstas A, Holló G, Irkec M, Tsironi S, Durukan I, Goldenfeld M, et al. Diurnal IOP control with bimatoprost versus latanoprost in exfoliative glaucoma: a crossover, observer-masked, three-centre study. *Br J Ophthalmol*. 2007; 91:757–60. [PubMed: 17124241]
50. Konstas A, Holló G, Mikropoulos D, Tsironi S, Haidich A, Embeslidis T, et al. Twenty-four-hour intraocular pressure control with bimatoprost and the bimatoprost/timolol fixed combination

- administered in the morning, or evening in exfoliative glaucoma. *Br J Ophthalmol*. 2010; 94:209–13. [PubMed: 19825835]
51. Konstas A, Holló G, Mikropoulos D, Haidich A, Dimopoulos A, Empeslidis T, et al. 24-hour efficacy of the bimatoprost-timolol fixed combination versus latanoprost as first choice therapy in subjects with high-pressure exfoliation syndrome and glaucoma. *Br J Ophthalmol*. 2013; 97(7): 857–61. [PubMed: 23686322]
 52. Angelilli A, Ritch R, Krupin T, Konstas A, Liebmann J, Ilitchew E, et al. The International Collaborative Exfoliation Syndrome Treatment (ICEST) Study: Results. *Invest Ophthalmol Vis Sci*. 2009; 50:2474.
 53. Angelilli A, Ritch R. Directed Therapy: An Approach to the Improved Treatment of Exfoliation syndrome. *Middle East Afr J Ophthalmol*. 2009; 16(1):35–40. [PubMed: 20142958]
 54. Ritch R, Podos S. Laser trabeculoplasty in the exfoliation syndrome. *Bull N Y Acad Med*. 1983; 59(4):339–44. [PubMed: 6575844]
 55. Kent S, Hutnik C, Birt C, Damji K, Harasymowycz P, Si F, et al. A randomized clinical trial of selective laser trabeculoplasty versus argon laser trabeculoplasty in patients with pseudoexfoliation. *J Glaucoma*. 2015; 24(5):344–7. [PubMed: 23835670]
 56. Zetterström C, Behndig A, Kugelberg M, Montan P, Lundström M. Changes in intraocular pressure after cataract surgery: analysis of the Swedish National Cataract Register Data. *J Cataract Refract Surg*. 2015; 41(8):1725–9. [PubMed: 26432131]
 57. Shingleton B, Laul A, Nagao K, Wolff B, O'Donoghue M, Eagan E, et al. Effect of phacoemulsification on intraocular pressure in eyes with pseudoexfoliation: single-surgeon series. *J Cataract Refract Surg*. 2008; 34(11):1834–41. [PubMed: 19006727]
 58. Kristianslund O, Østern A, Råen M, Sandvik G, Drolsum L. Does cataract surgery reduce the long-term risk of glaucoma in eyes with pseudoexfoliation syndrome? *Acta Ophthalmol*. Jan 9.2016 2016.
 59. Rao A. Diurnal curve after phacoemulsification in patients with pseudoexfoliation syndrome and cataract. *Semin Ophthalmol*. 2012; 27(1-2):1–5. [PubMed: 22352815]
 60. Klamann M, Gonnermann J, Pahlitzsch M, Maier A, Jousen A, Torun N, et al. iStent inject in phakic open angle glaucoma. *Graefes Arch Clin Exp Ophthalmol*. 2015; 253(6):941–7. [PubMed: 25912085]
 61. Hassan K, Awadalla M. Results of combined phacoemulsification and viscocanalostomy in patients with cataract and pseudoexfoliative glaucoma. *Eur J Ophthalmol*. 2008; 18(2):212–9. [PubMed: 18320513]
 62. Ting J, Damji K, Stiles M. Ab interno trabeculectomy: outcomes in exfoliation versus primary open-angle glaucoma. *J Cataract Refract Surg*. 2012; 38(2):315–23. [PubMed: 22322166]
 63. Klamann M, Gonnermann J, Maier A, Ruokonen P, Torun N, Jousen A, et al. Combined clear cornea phacoemulsification in the treatment of pseudoexfoliative glaucoma associated with cataract: significance of trabecular aspiration and ab interno trabeculectomy. *Graefes Arch Clin Exp Ophthalmol*. 2013; 251(9):2195–9. [PubMed: 23812010]
 64. Jordan J, Wecker T, Oterendorp Cv, Anton A, Reinhard T, Boehringer D, et al. Trabectome surgery for primary and secondary open angle glaucomas. *Graefes Arch Clin Exp Ophthalmol*. 2013; 251(12):2753–60. [PubMed: 24158374]
 65. Widder R, Dinslage S, Rosentreter A, Jordan J, Kühnrich P, Cursiefen C, et al. A new surgical triple procedure in pseudoexfoliation glaucoma using cataract surgery, Trabectome, and trabecular aspiration. *Graefes Arch Clin Exp Ophthalmol*. 2014; 252(12):1971–5. [PubMed: 25212496]
 66. Moisseiev E, Zunz E, Tzur R, Kurtz S, Shemesh G. Standard Trabeculectomy and Ex-PRESS Miniature Glaucoma Shunt: A Comparative Study and Literature Review. *J Glaucoma*. 2015; 24(6):410–6. [PubMed: 24633088]
 67. Landers J, Martin K, Sarkies N, Bourne R, Watson P. A twenty-year follow-up study of trabeculectomy: risk factors and outcomes. *Ophthalmology*. 2012; 119(4):694–702. [PubMed: 22196977]

Table 1

Differential effects of LOXL1 polymorphisms in various ethnic groups. (4, 18)

Allele	Populations in which allele confers increased risk	Populations in which allele is protective
rs4886776 – A allele	Japanese ancestry (OR = 9.87)	Non-Japanese (OR = 0.49)
rs3825942 – G allele	Caucasian (OR = 7.99) Japanese (OR = 18.7) Korean (OR = 8.79) Chinese (OR = 14.15) South Asian (OR = 7.03) Middle Eastern (OR = 6.98) Hispanic (OR = 19.9)	Black South African (OR = 0.10)
rs1048661 – G allele	Caucasian (OR = 2.17) Middle Eastern (OR = 2.35) South Asian (OR = 2.01) Black South African (OR = 23.12)	Japanese (OR = 0.03) Korean (OR = 0.10)
rs2165241 – C allele	Japanese (OR = 7.49) Korean (OR = 6.63) Chinese (OR = 5.44)	Caucasian (OR = 0.31) South Asian (OR = 0.35) Hispanic (OR = 0.42)