A global genetic epidemiological review of pseudoexfoliation syndrome

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Abstract

Pseudoexfoliation (PXF) syndrome is an important public health concern requiring individual population level analysis. Disease prevalence differs by geographic location and ethnicity, and has environmental, demographic, genetic, and molecular risk factors have been demonstrated. Epidemiological factors that have been associated with PXF include age, sex, environmental factors, and diet. Genetic and molecular components have also been identified that are associated with PXF. Underserved populations are often understudied within scientific research, including research about eye disease such as PXF, contributing to the persistence of health disparities within these populations. In each population, PXF needs may be different, and by having research that identifies individual population needs about PXF, the resources in that population can be more efficiently utilized. Otherwise, PXF intervention and care management based only on the broadest level of understanding may continue to exacerbate health disparities in populations disproportionally burdened by PXF.

Keywords

Global, genetic, epidemiological, review, pseudoexfoliation

Introduction

Pseudoexfoliation (PXF) syndrome, first described by Lindberg [1-3] in 1917, is a systemic disease. It causes various tissues, including the tissues in the eye, to accumulate gray and white material. The etiology of PXF is still unknown. Over 100 years later, it still represents a significant clinical problem. The disease affects more than 60 to 70 million people globally [3-10]. PXF pathophysiology is characterized by systemic deposition
Ocular deposition occurring in the trabecular meshwork, cornea, lens, and pupillary iris border leads to significant ocular and visual morbidity. This can include cataract formation, and zonular weakness, leading to lenticular dislocation and glaucoma. Other conditions including coronary artery disease, hypertension (HTN), dementia, and sensory hearing loss have also been correlated with PXF pathogenesis due to abnormalities in the breakdown, production, and extracellular deposit of fibrillary material in the visceral organs and blood vessels. While the full spectrum of pathogenesis resulting from fibrillary deposition is unknown, it has been speculated that oxidative stress, elastosis, endothelial dysfunction, and weakened autonomic regulation result from its accumulation. This is evidenced by the finding that PXF syndrome is an independent risk factor for coronary artery disease. Specifically, significant correlations were found between PXF and cardiovascular disease outcomes (ischemic heart disease, cardiomyopathy, and aortic aneurysm) in a case-control study of 6,046 cases of PXF in the Veteran's Health Administration databases. PXF confers significant morbidity and mortality, and there remains no cure. Treatment is directed at the resultant pathobiology and includes systemic medications and ocular laser or incisional intervention. Thus, PXF is an important public health concern requiring individual population level analysis. Disease prevalence differs by geographic location and ethnicity, and environmental, demographic, genetic, and molecular risk factors have been identified.

**Ophthalmic effects of PXF**

PXF ocular manifestations are directly evident through visualization of fibrillar material deposition using slit lamp biomicroscopy. PXF can be seen unilaterally or bilaterally. Unilateral cases may become bilateral over time, as this is a systemic disease that increases in severity with age. Whether unilateral or bilateral, PXF has significant ocular morbidities, all of which can result in significant visual impairment or blindness. This highlights the importance of investigation to better understand the etiology of PXF with a goal of identifying curative, rather than temporizing, treatments.

**Glaucoma**

Glaucoma is a leading cause of blindness globally and results in progressive visual field loss due to optic nerve damage. Globally, PXF is the leading cause of the open-angle glaucoma, accounting for up to 25% of all glaucoma cases. Conversely, 15 to 30 percent of those diagnosed with PXF will subsequently develop PXF glaucoma (PXG). PXG demonstrates increased severity compared with other forms of primary open-angle glaucoma (POAG). In PXG, increased IOP results from the deposition of fibrillary material in the trabecular meshwork, the drain of the eye. This unique characteristic results in PXF specific ocular morbidity. IOP is often more significantly elevated in PXG, resulting in a greater degree of visual field loss. There is also a blunted treatment response in PXG patients compared to POAG patients. Therefore, PXG patients who do not seek care for their glaucoma or are not adherent to medical treatment can more often suffer irreversible blindness. Ocular manifestations of PXG have been linked to both epidemiological and genetic risk factors. The prevalence of PXG and its risk factors have been found to differ by geographic location and a person’s ethnicity. Improved identification of risk factors associated with individual populations to best identify screening implications for PXF around the globe will aid in the prevention of PXG-associated blindness.

**Cataract**

Cataract is the leading cause of preventable blindness and vision loss, accounting for 51% of global blindness. Cataract is present when the natural lens becomes opaque and can result in low night vision, decreased vision, blindness, double vision, and decreased contrast sensitivity. Most cataracts involve central, nuclear lenticular changes and are age-associated. Cataract blindness disproportionately affects low-resource areas worldwide due to limited access to preventative eye care services. PXF is associated with an increased risk of nuclear cataract. The molecular pathobiology underlying this clinical finding is unknown, but the preponderance of data suggests this...
is due to oxidative stress [59, 60, 62]. Importantly, PXF not only increases risk for cataract, due to zonular fibrillary deposition and resultant weakness, cataract surgery can be more complex in the presence of PXF and often results in surgical complications. These surgical challenges include poor pupillary dilation, postoperative IOP increase, capsular bag dislocation, and prolonged postoperative inflammation [8]. Therefore, the presence of PXF is an important clinical determinant of the degree of successful treatment of cataract-associated vision loss, and those with PXF should be counseled on the potential complications associated with cataract surgery. Further investigation into the molecular etiology and natural history of PXF is necessary to minimize the primary and secondary sequela of cataract blindness in these patients.

**Other ocular manifestations**

Other less well-characterized ocular manifestations of PXF include lens dislocation and dry eye syndrome. As a result of ocular surface and eyelid fibrillary deposition, tear production and osmolarity are altered, resulting in decreased tear break up time, poor tear quality, and dry ocular surface [63-65]. Individuals with PXF are therefore at a higher risk for developing dry eye disease [63, 66, 67]. Lens dislocation may occur in individuals with PXF after cataract surgery [27, 68, 69]. Additionally, research has shown that individuals with PXF are at a higher risk of developing intraocular lens dislocations than individuals having cataract surgery without PXF [68, 69].

**Epidemiological risk of PXF**

**Age**

PXF is an age-related disease as its risk increases with age [70-72]. Clinical evidence of PXF is uncommon under 40 to 50 years of age. To date, only 12 cases of PXF have been identified in those aged less than 40 years [9, 73]. In contrast, PXF can affect up to 25% of individuals aged 60+ years old [73]. PXF is associated with other diseases of aging, and it remains unclear if this is due to aging as a standard risk variable or shared pathogenesis. For example, among 777 Greek individuals aged 40-99 years, those with PXF were more likely to have age-related macular degeneration [74]. Additional investigation is needed to clarify the role of aging in this association. Indeed, the clinical importance of aging diseases will increase going forward as the number of individuals aged 60+ years old is projected to increase 12 to 22% globally between the years 2015 to 2055 [75, 76]. Moreover, the aging population is becoming more ethnically and racially diverse, including more non-Hispanic whites within the elderly population [77-80]. As PXF risk factors and prevalence differ by ethnicity and geographic location, it will be essential to identify how these differences may impact the prevention and management of secondary outcomes such as ocular manifestations and systemic disease with PXF [24, 25].

**Sex**

As is the case with other medical conditions, including osteoarthritis, stroke, and lupus, women experience PXF at higher rates than men [81-83]. This may because in most places around the globe, women live longer than men, and age is a risk factor for PXF [84-86]. Additionally, women in low-resource countries/regions have poorer detection and prevention of PXF due to less access to general preventative and medical care [87]. Over and above age and health care access discrepancies, it appears women may have different social and biological risk factors for the disease compared to men [88]. Understanding biologic determinants of PXF disease that exacerbate the risk for women is vital across geographies and populations. It is essential to include women from different ethnicities and cultures within clinical research, as advancements from this research can help to benefit the health and healthcare of women around the globe [81, 88-91].

**Environmental factors**

PXF has been linked to certain environmental factors that increase the likelihood of developing or hastens its development. Research focused on the potential association between geographic location and PXF has found that elevation may increase the risk for PXF [74, 92]. In Greece, those living in higher altitudes had
a higher prevalence of PXF than those at lower elevations [74]. Time spent outdoors and solar exposure are also associated with PXF risk [92-95]. In a retrospective observational study conducted with 626,901 participants in the US, PXF was positively associated with altitude, more time spent outdoors, and increased sunlight exposure. A cross-sectional study conducted in Andhra Pradesh examined 10,293 participants of all ages and found that those who had occupations that required them to work outdoors had higher rates of PXF [95]. Another study of 49,033 women and 20,066 men aged 60+ years old found that people who spend more time outdoors in youth (i.e., high school to 24 years old) had a higher risk for PXG or being considered a PXG suspect [94]. A clinic-based case-control study in US and Israeli populations investigated solar exposure and development of PXF [93]. The study, which included 185 cases and 178 controls, found that cases of PXF were more likely to be seen in those who were older, had lighter colored eyes, and had a family history of glaucoma [93]. Therefore, those in public health should consider individuals who live in areas of high altitude or those who have greater sunlight exposure to be more closely followed for early detection of PXF. Increased awareness should also be brought to these populations at a higher risk for PXF as some of these risk factors are modifiable and thus preventable.

**Diet**

Diet has been linked to PXF [73, 96-98]. A cross-sectional study in East India with 346 participants found that those who had PXF were more likely to be non-vegetarians and primarily consume fish [96]. This study also found that individuals that consumed a higher amount of coffee (more than 3 cups per day) had a higher likelihood of developing PXF and PXG [96]. Similarly, higher coffee consumption, was associated with PXF and PXG in a cohort study of 78,977 women and 41,202 men [97]. The association was higher in women who had a family history of glaucoma [97]. Vitamin deficiency has also been associated with PXF and PXG [98]. A prospective cohort study, including men and women, found that higher folate intake was associated with a lower risk for developing PXG or becoming a PXG suspect [98]. Diet is another modifiable risk factor that those in public health may address within populations at a higher risk for developing PXF.

**Genetic risk**

**LOXL1**

*LOXL1*, a gene for a lysyl oxidase, is the principal genetic contributor to PXF with a well-established association [99-102]. Specifically, three single nucleotide polymorphisms (SNPs) of interest have been associated with PXF and PXG [99-102]. Two of these SNPs, rs1048661, and rs3825942, are missense variants located in exon one and yield the G allele associated with PXF [103, 104]. The third SNP, rs2165241, is located in intron 1 [103, 104]. These *LOXL1* SNPs and their association with PXF have been confirmed in varied populations around the world, including Europe [99, 103, 105], North America [104, 106-109], Asia [100, 110-112], Africa [113, 114], and Australia [115]. Though the association between *LOXL1* and PXF has been demonstrated in many populations, the association between the G allele and PXF was not the same in every case. In a matched, hospital-based case-control study in South Africa, an association was found with *LOXL1*. However, the associated G allele with SNP rs3825942 was found to have a decreased risk for PXF [114]. In some instances, *LOXL1* may not be associated with PXF. In a North Indian population, a case-control study conducted with 118 study participants found a lack of association between *LOXL1* and PXF [116]. A candidate gene approach may be implemented to determine if *LOXL1* is associated with these other populations. Notably, *LOXL1* has not been researched explicitly in South American populations but has been confirmed within a Latin American population from Mexico City [109]. There has been one case report from Brazil that has confirmed the association of *LOXL1* and PXF [117]. Further research is needed to confirm that the genetic association is manifested within individual populations that have not yet been studied.

**CACNA1A**

*CACNA1A*, a gene encoding a voltage-gated calcium channel subunit, has been established as a genetic contributor to PXF [118-120]. The *CACNA1A* SNP rs492644 had genome-wide significance for association
with increased risk for developing PXF [118-122]. Similar to LOXL1, the G allele was associated with a higher risk for PXF. A genome-wide association study was conducted with 1,188 controls and 1,484 cases within a Japanese population [119]. The genome-wide association study (GWAS) study, which included 13,838 cases and 110,275 controls, validated this finding in 17 other countries, including Argentina, Poland, Greece, Turkey, China, Iran, India, and South Africa [119, 120]. Further research could be conducted in other countries not already included among the 17 used in the GWAS study to confirm CACNA1A SNP rs492644 with PXF in all populations. Similar to the LOX1 associated findings, there may be studies that find that CACNA1A decreases the risk of PXF, or has no association with PXF in specific populations. Further research in understudied populations may determine if the GWAS findings hold.

**Additional identified genes**

GWAS have identified five additional genes, including SEMA6A, AGPAT1, FLT1-POMP, TMEM136-ARHGEF12, and RBMS3 [120]. Some genes have been identified in specific populations, but further research is needed within a multiethnic study to determine if these genes remain associated with other populations around the globe. For example, TBC1D21 is associated with PXF within a Japanese and Uyghur Asian population [123, 124]. The study conducted within the Japanese population used a genome-wide association study, while the Uyghur population study utilized a candidate gene approach [122, 123]. A candidate gene approach could be conducted to determine if these genes remained associated with other ethnic populations or if these associations were unique to these populations.

A recent study has identified a protective variant by conducting a GWAS on 5,570 cases and 6,279 controls [125]. The rare protective variant p.Tyr407Phe in LOXL1 was only identified in the Japanese population, though populations from the United States, Greece, Italy, India, Pakistan, South Africa, Mexico, and Russia. To underscore the rareness of the variant, of the 3,909 Japanese cases with PXF syndrome, only 2 samples were found to have the rs201011613-T (LOXL1 p.Tyr407Phe) compared to 68 in the 5,388 controls [125].

**Potential molecular mechanisms**

Transforming growth factor beta 1 (TGF-β1) has been associated with a higher risk of PXF due to its role in the fibrotic process [118, 124, 126]. TGF-β1 was found to be present in more significant amounts within the aqueous humor, anterior segment, and PXF deposits of eyes with PXF [118, 124]. As mentioned prior, LOXL1 is significantly associated with PXF, and TGF-β1 has been found to increase expression of LOXL1 [118]. Homocysteine levels are also associated with PXF and PXG [127-129]. A cross-sectional study conducted in the US with 124 participants, including Whites, Hispanics, Asians, and Blacks, found that in patients with PXF and PXG, had significantly elevated blood plasma levels of homocysteine, which has been previously associated with cardiovascular disease [127]. Clusterin has also been associated with the risk of PXF [130]. Clusterin is a ubiquitous protein found throughout the body and a component of PXF exfoliation material and Clusterin protein levels are found to be higher in those with PXG [118, 131, 132]. TGF-β1, homocysteine, and Clusterin could be potential biomarkers for PXF and/or PXG.

**PXF around the globe**

**Asia**

As the largest continent globally, the most populous, and with many different cultures and communities in every region, the prevalence of PXF varies across Asia [133, 134]. In Northern China, in one hospital-based study of 8,205 cataract patients aged 60+ years old, PXF was found to be quite low and found in only 0.55% of study participants [135]. In Pakistan, the prevalence of PXF has been reported to be 6.45% of the population [136]. This was confirmed by a prospective study of 1,890 participants aged 45 to 87 years old that found that 40% of those with PXF had high IOP [136]. In Singapore, the prevalence of PXF was reported to be 2.8% [134] and confirmed by a retrospective study of 1,459 male and 1,858 female participants, aged 40+ years old. The Singapore study also observed that those with PXF were more likely to be of Indian
ethnicity than Chinese [134]. This variation by region reinforces the need to conduct further research across populations to understand the prevalence of the PXF and associated risks.

**Africa**

Several studies conducted in Africa have shown that the prevalence of PXF varies by geographic location [137-141]. A cross-sectional study of 2,142 Congolese patients, (57.5% men) showed the prevalence of PXF was 1.7% [137]. This was lower than the prevalence of PXF reported in a cross-sectional study of 1,840 participants in two separate districts in South Africa, Temba (6.0%) and Hlabisa (7.7%), in a cross-sectional study of [138]. The prevalence of PXF in the Congolese was more similar to the 2.7% prevalence of PXF found in Nigeria in a hospital-based study, including 448 participants aged 30-90 years old [139]. In Northern Nigeria, the prevalence of PXF was found to be 1.5% [140]. There are fifty-four states in Africa with varying cultures, tribes, and social constructs [142], research within each population will be needed to truly understand PXF and the unique risk factors driving disease prevalence. Therefore, estimates at the continent level will have lesser utility in understanding the variation of PXF risk and etiology.

**Australia**

There have been several studies conducted in Australia to identify the prevalence of PXF [143, 144]. The Visual Impairment Project study cohort consisted of three distinct populations, including 3,271 urban participants aged 40 to 98 years old, 1,473 nursing home participants aged 46 to 101 years old, and 1,473 rural participants aged 40 to 95 years old [143]. The sex breakdown was 46%, 21%, and 48% men, respectively [143]. Prevalence of PXF was 0.98% in the overall population but 6.0% in those aged 80-89 [144]. This study found that PXF material increased with age and that those with glaucoma were more likely to also have PXF [143]. The Framingham Eye Study evaluated 1,906 Australians aged 52 to 85 years old, of which 56.8% were women [145]. In this population, the prevalence of PXF was 1.8%, and women were more likely to have the PXE adjusting for age [145]. Additionally, the Blue Mountains Eye study conducted in Australia found that PXF was prevalent in 2.3% of 3,654 participants aged 40+ years old [146]. The study also found that PXF was associated with a history of angina or hypertension and with a combined history of angina, stroke, and acute myocardial infarction [146]. In the Blue Mountains Eye Study and the Framingham study, more women had PXF, while in the Visual Impairment Project, more men had PXF. In all three studies, sex was not statistically associated with PXF. In the indigenous population of Central Australia, the prevalence of PXF was found to be 4.7% in a study of 1,884 participants aged 20+ years old (36% males) [147]. None of the participants in this population had glaucoma or ocular hypertension, but the study did find an association between PXF and climatic droplet keratopathy [147]. Prevalence in this population was higher than in the populations in the Visual Impairment Project, the Blue Mountain Eyes Study, and the Framingham Eye Study. It may be that the indigenous population in central Australia has a greater exposure to sunlight coupled with less access to prevention and treatment.

**Europe**

PXF prevalence has been well studied throughout regions in Europe [109, 148-150]. The highest PXF in Europe reported was among Icelanders, Finns, Russians, and Lapps residing in Novosibirsk, Russia of 21% [149]. The lowest prevalence of PXF has been reported in the Greenland indigenous population at 0%, in a population-based study of those were 60+ years old which included multiple ethnicities [32, 146]. Prevalence of PXF in other countries, including England, Germany, and Norway, ranged from about 4-6% [32, 150]. In a cross-sectional study of 2,140 Greek patients with cataract (50.8% men), the prevalence of PXF was found to be 27.9% [71]. It was also found within this study that the risk for PXF increased with age, and those with PXF experienced a higher rate of developing glaucoma [71].

**North America**

The prevalence of PXF can differ throughout North America’s geography as the population is ethnically and racially diverse. In the Navajo American Indian population of Arizona, the prevalence of PXF was 38% [151, 152], as seen in a hospital-based study which included 50 Navajo participants aged 60+
years old [151, 152]. A prospective study conducted in the Southeastern Region of the US found the prevalence to be 1.6% in 1,216 female and 905 male participants aged 60+ years old [153]. A Southern Louisiana study of open-angle glaucoma patients aged 50+ years old found the prevalence of PXF was 2.7% in Whites and 0.4% in black participants [154].

**South America**

PXF prevalence differs across South America [155-157]. In a study that included 159 participants aged 50+ years old in Peru, the prevalence of PXF was 4.4% [156] and increased with age. Prevalence of PXF in Paraguay has been reported to be 17.1% in 268 female and 200 male patients aged 50+ years old with a diagnosis of senile cataract [157]. A lower prevalence was reported in a study of the population in Argentina. Among 337 participants (69.4% male), 14.5% had PXF, and again the prevalence increased with age [155]. Within Guatemala, there have been three studies documenting the prevalence of PXF. In the Guatemala Clinic National of oftalmología, the prevalence of PXF was to be 5% in 4,748 patients, (63.3% women) [158]. A retrospective study of patients with cataract, found that 15% of 259 patients at Hospital de la Familia in Guatemala had PXF [159]. Lastly, a cross-sectional study of a Mayan cohort at Salama Lion's Eye Club Hospital found that 24.6% had PXF [160].

**Underserved populations and PXF**

Underserved populations are often understudied within scientific research, including research about eye disease such as PXF, leading to the persistence of health disparities within these populations [161-163]. By exclusion from research that advances the understanding of risk and treatment of many diseases, including blinding eye disease, understudied populations will benefit less from such advances and be disproportionately burdened by disease because individual population health and preventive care needs will be unknown [161-163]. It is important for research to include underserved populations within the research. It can also suggest unique or tailored paradigms for disease risk and prevention, especially if these populations are within rural areas or are isolated [164]. Isolated populations can help aid the understanding of PXF by providing greater genetic homogeneity as compared to other populations [164-166]. These populations also may be more homogenous in terms of cultural, environmental exposure, and societal norms, including diet, exercise, elevation from sea level, exposure to the sun, and climate change effects [164]. Isolated populations may increase the power to identify unique genetic and/or environmental associations with disease outcomes to be used in future studies with other populations [164, 167, 168]. Moreover, it is ethical to include these underserved populations within research to address health disparities and to achieve global health equity. If research does not understand health disparities within the context of a wide range of diseases, newly emerging diseases, such as COVID-19, will disproportionately burden these populations on a greater scale [169-171].

**Conclusion**

There is a need for research to identify any clinical, environmental, demographic, and genetic risk factors that may differ by populations that may predispose individuals to develop PXF or secondary disease. Identifying genes that may be associated with PXF can also help identify individuals with a predisposition to developing pathology. Further research is needed in geographically isolated populations in which PXF has yet to be studied or understudied. This research may inform those that create policy and other individuals who are planning and providing relevant health care and preventative care services [157]. In each population, PXF needs may be different, and by having research that identifies individual population needs about PXF, the resources in that population can be more efficiently utilized. Otherwise, PXF intervention and care management based only on the broadest level of understanding may continue to create further health disparities in populations disproportionately burdened by PXF. Instead, specific populations’ individual needs should be studied to create a tailored approach for preventative care and medical treatment [164]. If individualized approaches cannot be tailored to meet individual populations’ needs, then health equity
cannot be achieved, and health disparities will remain as these populations will not equally benefit from advancements in medicine [164].

**Abbreviations**

GWAS: genome-wide association study  
IOP: intraocular pressure  
PXF: pseudoexfoliation  
PXG: pseudoexfoliation glaucoma  
SNPs: single nucleotide polymorphism  
TGF-β1: transforming growth factor beta 1

**Declarations**

**Author contributions**

Concept and design: PMH, BH, LAO, EA, MF, MAM and MMD; acquisition, analysis, or interpretation of data: PMH, AS, BH, LAO, EA, MF, MAM, SS, AR, JL, and MMD; drafting of the manuscript: PMH, AS, BH, LAO, EA, MAM, MF, SS, AR, JL, and MMD; critical revision: PMH, BH, LAO, MF, MAM, SS, AR, JL, and MMD; supervision: PMH, LAO, MF, MAM, and MMD.

**Conflicts of interest**

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**Ethical approval**

Not applicable.

**Consent to participate**

Not applicable.

**Consent to publication**

Not applicable.

**Availability of data and materials**

Not applicable.

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