Pseudoexfoliation syndrome in Icelandic families

R Rand Allingham, Margret Loftsdottir, María Soffía Gottfredsdottir, Erikur Thorgeirsson, Fridbert Jonasson, Thordur Sverisson, William G Hodge, Karim F Damji, Einar Stefánsson

Abstract

***Aim*—To examine the distribution and clinical ophthalmic characteristics of pseudoexfoliation syndrome (pseudoexfoliation) and glaucoma in Icelandic families.**

***Methods*—Icelandic families containing three or more members aged 70 or older with at least one member with pseudoexfoliation were indentified. All family members over age 45 were invited to participate. Visual acuity, Goldmann applanation tonometry, gonioscopy, slit lamp examination before and after dilatation, and dilated fundus examination were performed on all available family members. Pertinent data were obtained from medical records, including ophthalmic history and a medical history of cardiovascular disease, cerebrovascular disease, systemic hypertension, and diabetes mellitus. Participants were classified according to affected status for pseudoexfoliation, glaucoma, and age related macular degeneration.**

***Results*—Six families were identified who met the criteria for entry into the study. Of 94 family members who were invited to participate 82 were enrolled (87%). Of these 25 (30%) had pseudoexfoliation syndrome, 51 (62%) were unaffected, and six (7%) were suspects. At least one individual with pseudoexfoliation was identified in the second generation of every family. A parent with pseudoexfoliation was identified in all cases either by examination (4/6) or a review of ophthalmic records (2/6). In all cases the mother was the affected parent. The prevalence of glaucoma was significantly greater in the group with pseudoexfoliation (p <0.0001). Although the presence of age related macular degeneration (ARMD) was highly associated with the presence of pseudoexfoliation, the significance was lost after correction for age (p = 0.69). Although the sample size was small, no association between pseudoexfoliation affected status and cardiovascular disease, cerebrovascular disease, systemic hypertension, or diabetes mellitus was found.**

***Conclusions*—Multiple Icelandic families with pseudoexfoliation in two generations were identified. In all cases where determination was possible, transmission to the second generation was through an affected parent. In each case the affected parent was the mother. Pseudoexfoliation was strongly associated with the presence of glaucoma, but was not associated with either ARMD or systemic disease in this study. These data clearly indicate that pseudoexfoliation is a familial condition and although not conclusive, supports the hypothesis that pseudoexfoliation syndrome is genetically inherited.**

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Duke University Eye Center, Durham, NC, USA
R R Allingham

University of Iceland, Reykjavik, Iceland
M Loftsdottir
M S Gottfredsdottir
E Thorgeirsson
F Jonasson
T Sverisson
E Stefánsson

University of Ottawa Eye Institute, Ottawa, Ontario, Canada
W G Hodge
K F Damji

Correspondence to:
R Rand Allingham, MD, Duke University Eye Center, Box 3802, DUMC, Durham, NC 27710, USA
allin002@mc.duke.edu

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Pseudoexfoliation syndrome (pseudoexfoliation) is a condition found worldwide. It is characterised by the presence of a white flake-like material on the pupillary border, lens surface, and other intraocular structures.[1–5] Pseudoexfoliation is a major risk factor for the development of open angle glaucoma. It is found in 20–60% of patients with glaucoma in many regions of the world, including Scandinavian countries, Russia, and in the Bantu people in South Africa.[5 6] It has also been associated with narrow angle glaucoma.[7 8] Pseudoexfoliation material has a characteristic appearance by transmission electron microscopy and has been identified in a wide variety of intraocular, periocular, and non-ocular tissues. These observations support the concept that pseudoexfoliation is a systemic condition.[9–11]

Surprisingly, for such a common condition, there are relatively few descriptions of the occurrence of pseudoexfoliation within families.[12–16] A recent twin study by Gottfredsdottir *et al* supports the contention that pseudoexfoliation is genetically transmitted.[14] Pseudoexfoliation onset is rarely found before age 50 and is usually noted after age 70.[5 16 17] Owing to the late onset of pseudoexfoliation, parents of individuals with pseudoexfoliation are often deceased and their offspring are too young to be affected, making the determination of genetic transmission problematic.

The goal of this investigation was to examine the distribution and clinical ophthalmic characteristics of pseudoexfoliation and glaucoma in Icelandic families. Pseudoexfoliation is a common condition in Iceland where it is found in up to 45% of individuals over age 80 and accounts for approximately half of all glaucoma.[18 19] Icelanders are long lived[20] and have historically had large families. The majority of Iceland's population is located in discrete regions, which facilitates ascertainment. For these reasons it was decided to conduct this investigation in Iceland.

Methods

There were two principal objectives to this study. The first was a descriptive component

where demographic and ophthalmic characteristics of patients and families with pseudoexfoliation, suspected pseudoexfoliation, and no pseudoexfoliation were tabulated. The second objective was to perform an analytic study where the definite pseudoexfoliation group was compared with the no pseudoexfoliation group with respect to the following variables: age, glaucoma, visual acuity, highest recorded IOP, angle pigmentation, the cup to disc ratio, and presence of age related macular degeneration (ARMD). For the analytic study, a cross sectional study was carried out as observers measured both outcome and predictor variables simultaneously.

FAMILY SELECTION

Patients with pseudoexfoliation at the Landakots Hospital Eye Clinic, Reykjavik, Iceland, who had at least one relative with a history of pseudoexfoliation or glaucoma were queried regarding their family size and structure. Families with three or more living members over age 70 were identified. All family members of these families over age 45 were invited to participate. Spouses of examined family members were also examined.

FAMILY ASCERTAINMENT

A team of ophthalmologists examined family members. Visual acuity, Goldmann applanation tonometry, gonioscopy, slit lamp examination before and after dilatation, and dilated fundus examination were performed on all available family members. Pertinent data were obtained from medical records, including ophthalmic history and a medical history of cardiovascular disease, cerebrovascular disease, systemic hypertension, and diabetes mellitus.

Pseudoexfoliation and glaucoma status was assigned separately after examination by two masked examiners. If there was disagreement between the first two examiners, a third masked examiner was employed to determine the final status.

The main predictor variable was pseudoexfoliation; this was defined as the presence of a central disc of pseudoexfoliation material, a clear annular zone (partial or complete), or flakes of pseudoexfoliation material on the lens surface, iris, or corneal endothelium in either eye. Individuals were considered a suspect if there was a hazy appearance to the lens capsule or if there was fine white specks and/or pigmentation of the anterior lens capsule.

Pseudoexfoliation was quantified in three levels—light if only a thin layer of pseudoexfoliation was visible on the lens surface, medium if there were identifiable flakes of pseudoexfoliation material, and heavy if there was a sheet of pseudoexfoliation or large flakes of pseudoexfoliation material on the iris pupillary margin. Patients were excluded if there was a history of exposure to intense infrared light—for example, glass blowing.

The main outcome variables measured were visual acuity, highest measured IOP, glaucoma, and ARMD. Visual acuity was converted to logMAR vision for analytical purposes. Highest IOP was the higher of the measured IOP on the day of examination or that recorded in the individual's medical record. The criteria for the diagnosis of glaucoma were the presence of *at least two of* the following. These criteria were obtained at the time of examination or were documented in the individual's medical record:

(1) Documented intraocular pressure (IOP) $\geqslant$ 22 mm Hg in either eye
(2) Glaucomatous optic nerve cupping defined as a cup to disc ratio greater than 0.7 in either eye, notching of the neuroretinal rim, or an asymmetric cup to disc ratio greater than 0.2
(3) Glaucomatous visual field loss consistent with the optic nerve appearance.

Patients were considered glaucoma suspects if either the IOP was $\geqslant$ 22 mm Hg in one or both eyes or in the presence of optic nerve abnormality suspicious for glaucoma.

ARMD was defined as the presence on examination of any of the following:

(1) Soft or dry drusen within the posterior pole
(2) Choroidal neovascular membrane or disciform macular scar
(3) Atrophy of the retinal pigment epithelial membrane.

In addition to the above, angle pigmentation and the optic nerve cup to disc ratio were recorded. Angle pigmentation was graded on a scale of 1–4 where 1 designated trace pigmentation and 4 designated dense pigmentation of the trabecular meshwork spilling onto Schwalbe's line. Both angle pigmentation and the cup to disc ratio were determined by averaging the data obtained by the independent observers.

Blood samples were obtained for DNA extraction on all participating family members for future genetic analysis. Investigational review board approval for this project was obtained through the University of Iceland and Duke University. Informed consent was obtained from all participants before entry into the study.

STATISTICAL ANALYSIS

For the descriptive portion of the study, the data were tabulated as mean (SD) for continuous variables and presented as proportions for binary variables. In the analytic portion of the analysis, continuous variables were compared via multiple linear regressions taking into account family clustering (which violates the assumption of independence) using variances produced by Huber regression with age as a covariate. For binary outcomes such as glaucoma, the same methods were employed but Huber multivariate logistic regression was used. A p value less than or equal to 0.05 was considered significant.

Results

Six families were identified who met the criteria for entry into the study (Fig 1). Of 94 family members over age 45 who were invited to participate 82 were examined (87%). Four individuals were unable to attend centralised

examinations because of distance from the examination site or illness. In these individuals the patient's local ophthalmologist conducted the clinical assessment.

Interobserver reproducibility of the diagnosis and quantification of pseudoexfoliation was excellent. There was agreement between the initial two examiners on pseudoexfoliation affected status in 24 of 25 (96%) individuals. Quantification of pseudoexfoliation material was consistent between examiners in 92% (23/25) of individuals. Thirteen individuals were diagnosed with glaucoma. The diagnosis of glaucoma was consistent between examiners in 12 of 13 (92%) cases. Medical records were required to establish the type of glaucoma in two cases.

Pseudoexfoliation was identified in two generations in all families. In each case, a single affected individual was identified in the second

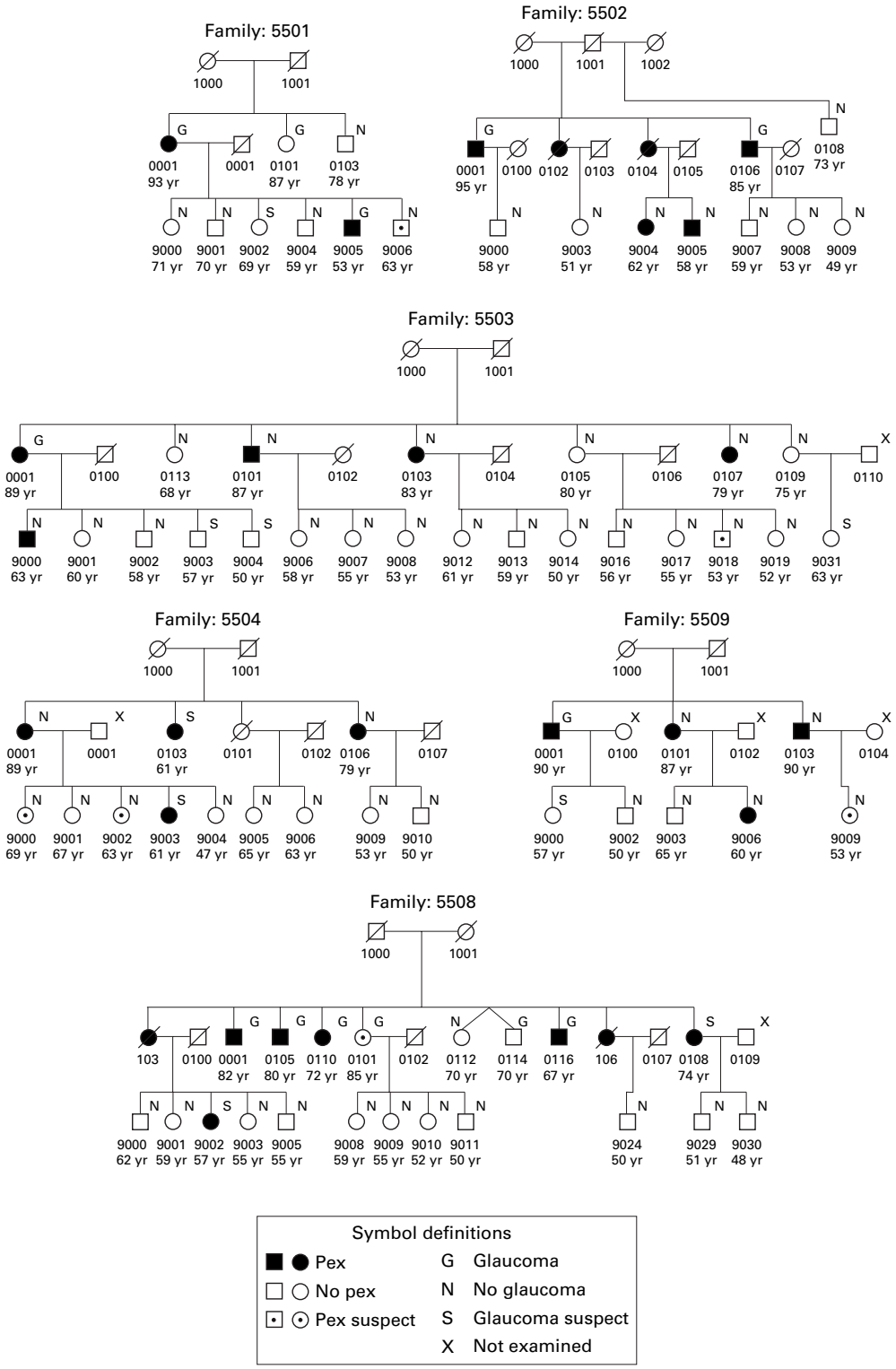

Figure 1 Pedigrees of Icelandic families with pseudoexfoliation syndrome.

Table 1 The number of individuals per family, mean age, sex distribution, pseudoexfoliation status, and number of individuals with glaucoma (PEX = pseudoexfoliation)

Family	*Individuals per family*	*Mean age (SD)*	*Sex (M/F)*	*PEX*	*No PEX*	*PEX suspect*	*Glaucoma*
5501	9	71.4 (12.9)	5/4	2	6	1	3
5502	10	64.3 (15.3)	6/4	4	6	0	2
5503	23	63.4 (12.3)	8/15	5	17	1	1
5504	12	63.9 (11.7)	1/11	4	6	2	0
5508	20	62.4 (11.8)	10/10	6	13	1	6
5509	8	69.1 (15.3)	4/4	4	3	1	1
Total	82	64.9 (12.8)	34/48	25	51	6	13

Table 2 Comparison of individuals with and without pseudoexfoliation

	PEX (n = 25)	*No PEX (n = 51)*	*p Value*	*p Value adjusted for age*
Age (SD)	75.5 (13.0)	59.5 (9.2)	<0.0001	
Glaucoma	11/25 (44%)	2/51 (4%)	<0.0001	<0.0001
VA RE	0.33 (0.46)	0.02 (0.11)	<0.0001	0.46
VA LE	0.43 (0.71)	0.02 (0.16)	<0.0001	0.11
IOP max RE	22.45 (8.44)	16.73 (4.41)	0.004	0.13
IOP max LE	25.00 (9.18)	16.45 (4.18)	<0.0001	0.003
Angle pigment RE	1.76 (0.42)	1.42 (0.64)	0.004	0.0001
Angle pigment LE	1.93 (0.71)	1.38 (0.60)	0.013	0.026
Cup to disc ratio RE	0.49 (0.24)	0.41 (0.20)	0.039	0.167
Cup to disc ratio LE	0.53 (0.26)	0.41 (0.21)	0.055	0.165
ARMD	12/25 (48%)	7/51 (14%)	<0.0001	0.69

PEX = pseudoexfoliation; VA = visual acuity; ARMD = age related macular degeneration.

Table 3 Number and percentage of people with bilateral glaucoma, unilateral glaucoma, glaucoma laser treatment, or glaucoma surgery in groups with pseudoexfoliation, pseudoexfoliation suspects, and those without pseudoexfoliation. (PEX = pseudoexfoliation)

	Glaucoma bilateral	*Glaucoma unilateral*	*Narrow angles*	*Laser surgery*	*Filtering surgery*
With PEX	7/25 (28%)	4/25 (16%)	1/25 (4%)	4/25 (16%)	3/25 (12%)
PEX suspect	1/6 (17%)	0 (0%)	1/6 (17%)	0 (0%)	0 (0%)
No PEX	1/51 (2%)	1/51 (2%)	0 (0%)	1/51 ((2%)	0 (0%)

generation except in family 5502 where there were two. Investigators were able to examine at least one parent of an affected individual with pseudoexfoliation in four of six families (5501, 5503, 5504, and 5509). In each of these cases the mother was affected. In the remaining two affected individuals both parents were dead (5502 and 5508). In these cases available medical records indicated that the mother had pseudoexfoliation. Only two of 12 fathers of an affected individual were living (individual 5504/0100, individual 5509/0102). Neither was able to come for the examination. Individual 5504/0100 was examined by his local ophthalmologist and was determined to be unaffected. The second individual, 5509/0102, was not located or examined. Medical records obtained on the deceased fathers of individuals with pseudoexfoliation did not indicate the presence of pseudoexfoliation.

The number of individuals in each family, mean age, sex distribution, pseudoexfoliation status, and number of individuals with glaucoma is shown in Table 1. Families ranged in size from nine to 23 individuals. The mean age of the individuals within each family was 62.4 to 71.4 years. Of the 82 individuals examined, the overall mean age was 64.7 years (range 47–95). There were 34 male and 48 female participants (59% female). Family structures varied from 44 to 92% female.

Data comparing groups with and without pseudoexfoliation are given in Table 2. These data were analysed with and without correction for age. The mean age of individuals with and without pseudoexfoliation was 75.5 (SD 13) and 59.5 (9.2), respectively ($p \leq 0.0001$). The prevalence of glaucoma with correction for age was significantly greater in the group with pseudoexfoliation ($p < 0.0001$). Visual acuity was not significantly different after correction for age. Maximum IOP was significantly greater in both eyes, but only for the left eye after correction for age. Angle pigmentation was greater in eyes with pseudoexfoliation. The cup to disc ratio was not significantly different between the two groups after age correction. Although the presence of ARMD was highly associated with the presence of pseudoexfoliation, the significance was lost after age correction ($p = 0.69$).

In the pseudoexfoliation, pseudoexfoliation suspect, and no pseudoexfoliation groups the percentage of females was 56%, 67%, and 59%. Pseudoexfoliation was bilateral in 15 of 25 (60%). In 46 eyes of 25 individuals with pseudoexfoliation, the amount of pseudoexfoliation was considered heavy in five eyes (10%), moderate in 22 eyes (44%), light in nine eyes (18%), and was not found in 10 eyes (20%). Quantitation of pseudoexfoliation was not possible in four (8%) eyes owing to media opacity or loss of the eye. By gonioscopy the angle was open in all cases except in a single individual (family 5502, individual 9005) where prophylactic laser peripheral iridectomies were performed for narrow angles. Glaucoma was bilateral in nine and unilateral in five cases of the 14 individuals with glaucoma. Of the nine individuals with bilateral glaucoma seven had pseudoexfoliation, one was a pseudoexfoliation suspect, and one was normal. Pseudoexfoliation was bilateral in four of seven individuals with bilateral glaucoma and unilateral in the remaining three. Five individuals had unilateral glaucoma; in these cases bilateral pseudoexfoliation was present in two cases and only one eye could be evaluated owing to presence of aphakic bullous keratopathy in the third case. No pseudoexfoliation was seen in the remaining two cases. There was no association between the amount of pseudoexfoliation and glaucoma for either eye after correction for age (right eye $p = 0.799$, left eye $p = 0.130$), nor was there an association of the amount of pseudoexfoliation with age of the individual.

In family members with pseudoexfoliation bilateral and unilateral glaucoma was present in 28% and 16%, respectively (Table 3). Narrow angles were present in one individual with pseudoexfoliation and one pseudoexfoliation suspect. Glaucoma laser trabeculoplasty and filtration surgery was performed on 16% and 12% of pseudoexfoliation patients, respectively.

There was no significant difference in the distribution of cardiovascular disease, cerebrovascular disease, systemic hypertension, and diabetes mellitus between those with and without pseudoexfoliation ($p = 0.42$).

Discussion

To our knowledge, this is the largest published study of families in Iceland with pseudoexfoliation. Eighty two individuals in six Icelandic

families were examined. In all of these families pseudoexfoliation was present in two generations. In each family, at least one affected family member had an affected parent. There were no cases where an affected individual had unaffected living parents.

The role of inheritance in pseudoexfoliation syndrome is not clear. A twin study conducted in Finland had insufficient power to demonstrate heritability.[21] A well conducted study of twins in Iceland over age 60 by Gottfriedsdottir *et al* found concordance for pseudoexfoliation in five of eight identical twin pairs.[14] These investigators concluded that pseudoexfoliation has a strong genetic component. Several studies demonstrate familial aggregation of pseudoexfoliation. In a Norwegian population, Aasved found an increased prevalence of pseudoexfoliation in relatives of family members affected with pseudoexfoliation compared to the general population.[12] Other studies describe multiple family members affected with pseudoexfoliation.[16 22]

In the current study, where the affected parent could be determined, it was the mother who was affected in each case giving the appearance of matrilineal inheritance. This finding, however, should be interpreted with caution since the presence or absence of pseudoexfoliation in the father was not possible to determine owing to lack of availability or death. In a similar study of pseudoexfoliation in Canadian families Damji and co-workers also found the appearance of maternal transmission and have proposed that pseudoexfoliation may be transmitted by mitochondrial inheritance, X linked inheritance, or autosomal inheritance with genomic imprinting.[3 15] However, similar to the current study, the fathers of affected individuals with pseudoexfoliation were not available for examination. Larger scale studies of families with pseudoexfoliation are clearly needed to investigate this intriguing hypothesis.

Genetic studies of pseudoexfoliation are difficult to perform because of the late onset of this condition. Pseudoexfoliation is usually not diagnosed before the sixth decade of life. In most cases individuals with pseudoexfoliation have no living parents. Additionally, since the condition frequently exists undiagnosed, medical records, if available, may not be helpful in determining the affected status of deceased individuals. Therefore it is often impossible to make an extended pedigree of families with this condition. This study was constructed to identify families that had elderly members affected with pseudoexfoliation. Families were selected from a glaucoma clinic on the basis of having at least one additional family member diagnosed with pseudoexfoliation. Therefore bias in selecting families with glaucoma associated with pseudoexfoliation was unavoidable. Additionally, this selection process may have affected the number and distribution of those with pseudoexfoliation in these families. However, the percentage of those with pseudoexfoliation in this study (30%) was very similar to the prevalence of pseudoexfoliation described by Als in the Icelandic population (28%), although the prevalence of glaucoma in those with pseudoexfoliation (44%) is greater (31%).[19]

In individuals with pseudoexfoliation, 44% were also diagnosed with glaucoma whereas only 4% of those without pseudoexfoliation had glaucoma. We found no association between the amount of pseudoexfoliation seen at examination and glaucoma. Glaucoma was open angle in all cases except one where laser iridectomies were performed for narrow angles. Als also observed this relatively low percentage with narrow angles in a study of Icelandic patients with pseudoexfoliation.[19] This is in sharp contrast with other studies of individuals with pseudoexfoliation in Canada and the United States, where narrow angles or angle closure was found in 31–39% of those with pseudoexfoliation.[7 8] The reason for this difference in angle configuration between these populations with pseudoexfoliation is unknown. In the study by Damji and co-workers the ethnic background of those with pseudoexfoliation was largely Irish and Scottish. Although not specifically stated, the Boston population studied by Epstein and co-workers was likely to contain many individuals of Irish ancestry and relatively few from Iceland. Therefore, the observed differences may be secondary to differences in ethnic background. Alternatively, this could also represent genetic subtypes of pseudoexfoliation or environmental influences.

The association of macular degeneration in patients with pseudoexfoliation is controversial. An association between ARMD and pseudoexfoliation has been described by Kozobolis and co-workers, who described a relation with age and altitude.[23] Hirvela and co-workers, however, failed to detect an association of ARMD with pseudoexfoliation after correction for age.[24] Indeed we found ARMD in a high percentage of those with pseudoexfoliation (48%) compared with those who did not have pseudoexfoliation (14%). However, this association was not significant after correction for age ($p = 0.69$). Whether a larger number of age matched controls would support this association or whether this is a true difference in the manifestation of pseudoexfoliation in these two populations is not clear.

Although there is convincing evidence that pseudoexfoliation syndrome is a systemic condition,[9–11] there have been few reports of associated systemic disease. Mitchell and co-workers reported an association with cardiovascular morbidity.[25] We found no association between pseudoexfoliation syndrome and cardiovascular disease, cerebrovascular disease, systemic hypertension, or diabetes mellitus in these families.

In summary, we have identified multiple two generation families with pseudoexfoliation in Iceland. In all cases where determination was possible, transmission to the second generation was through an affected parent. In each case the affected parent was the mother. Pseudoexfoliation was strongly associated with the presence of glaucoma but was not associated with either ARMD or systemic disease in this study.

These data clearly indicate that pseudoexfoliation is a familial condition and although not conclusive, supports the hypothesis that pseudoexfoliation syndrome is genetically inherited.

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