Supplementary information

Supplementary Note

Membership of consortia and study groups.

The Blue Mountains Eye Study GWAS team

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Details for XFS case-control collections

The criteria for diagnosis of exfoliation syndrome was harmonized and made uniform across all 17 participating countries. The enrollment criteria for patients with exfoliation syndrome are the following:

a) Patients should be ≥50 years of age at time of recruitment, in keeping with general clinical views that exfoliation syndrome is an age-related disease.

b) Patients with clear evidence of exfoliative exfoliation material at the pupil margin, anterior lens surface, or other anterior segment structures as visualized by slit lamp examination will be diagnosed as having exfoliation syndrome and included in the study.

Patients under the age of 50 will be excluded, as well as patients with neovascular glaucoma or uveitis.

GWAS discovery collection

Exfoliation patients were drawn from 7 clinical sites throughout Japan (Hayashi Eye Hospital in Fukuoka, Mizoguchi Eye Hospital in Nagasaki, Department of Ophthalmology, Oita University Faculty of Medicine, as well as four sites in Miyazaki: Ideta Eye Hospital, Shinjo Eye Clinic, Miyata Eye Hospital, and Ozaki Eye Hospital). Each participating hospital (with the exception of Miyata Eye Hospital) also enrolled matching healthy, elderly controls (aged ≥ 60 years) without Exfoliation syndrome, macular degeneration, primary closed angle glaucoma, and primary open angle glaucoma. A further 276 such controls from Kyoto and neighboring Nagahama city was also added to this collection. The relevant Institutional Review Board of each Hospital reviewed and provided ethical approval for this study.

Stage 1 Validation collections

This stage comprised exfoliation syndrome cases and controls from Japan, Singapore, Saudi Arabia, Greece, Turkey, Mexico, South Africa, United States of America, and Russia.

For Japan, the cases and geographically matching controls were enrolled from 18 clinical sites throughout Japan:

1. Kyoto University

2. Kyoto Prefectural University,

3. Sensho-kai Eye Institute in Kyoto,

4. Inoue Eye Hospital in Tokyo,

5. Asahikawa Medical University from Hokkaido,

6. Ohashi Eye Center from Hokkaido,

7. Department of Ophthalmology, Faculty of Medical Science, University of Fukui,

8. Hiroshima University,

9. Yotsuya Shirato Eye Clinic in Tokyo,

10. Nagahama City,

11. Department of Ophthalmology Kanazawa University Graduate School of Medical Science,

12. Hayashi Eye Hospital in Fukuoka,

13. Mizoguchi Eye Hospital in Nagasaki,

14. Department of Ophthalmology, Oita University Faculty of Medicine,

15. Ideta Eye Hospital in Miyazaki,

16. Shinjo Eye Clinic in Miyazaki,

17. Miyata Eye Hospital in Miyazaki,

18. Ozaki Eye Hospital in Miyazaki.

The relevant Institutional Review Board of each Hospital reviewed and provided ethical approval for this study.

For Singapore, the patients with exfoliation syndrome were of self-reported Chinese descent and enrolled at the Singapore National Eye Center. The controls were drawn from the Singapore Chinese Eye Study, which has been described elsewhere[1,2], and were shown to not have exfoliation syndrome on slit lamp examination. Ethical approval was granted by the SingHealh Centralised Institutional Review Board (IRB).

For Saudi Arabia, all patients with Exfoliation syndrome and unaffected controls were of Saudi Arabian descent as self reporting and medical record shows. Patients were recruited from the ophthalmology clinic at the King Abdulaziz University Hospital, King Saud University, Riyadh, Saudi Arabia, as well as King Khaled Eye Specialist Hospital, Riyadh. All participants underwent a standardized detailed ophthalmic examination, which included measurement of intraocular pressure (IOP) by applanation, slit lamp biomicroscopy, gonioscopy, and dilated pupil examination of the lens and fundus. Saudi Arabian subjects with normal anterior segment and optic nerve examination, an IOP of less than 18 mmHg and without clinical signs of exfoliation were recruited as control subjects. The study was approved by College of Medicine IRB committee, King Saud University, and the IRB of the King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia. All participants signed an informed consent.

For Greece, patients with exfoliation syndrome were identified from the Thessaloniki Eye Study, which is a comprehensive prevalence-based study of eye diseases in Thessaloniki, Greece[3]. Ethical approval for the Thessaloniki Eye Study was granted by the Aristotle University Medical School Ethics Committee.

For Turkey, patients with exfoliation syndrome together with controls were enrolled at the Department of Ophthalmology, Eskisehir Osmangazi University, Meselik, Eskisehir, Turkey. Ethical approval for the study was granted by Eskişehir Osmangazi university Rectorship and project number was PR-10-03-19-52.

For Mexico, patients with exfoliation syndrome and controls were enrolled from the Conde de Valenciana Institute of Ophthalmology in Mexico City. All patients were of self-reported Mexican Mestizo descent, defined as a person who was born in Mexico, has a Spanish-derived last name, and has a family of Mexican ancestors going back to the third generation [22]. All exfoliation syndrome patients and controls underwent detailed ophthalmological examinations, including slit-lamp biomicroscopic assessment, applanation tonometry, gonioscopy, dilated inspection of the lens, and funduscopy, as previously described[4]. Written informed consent was obtained from all participants, the study protocol was approved by the Hospital ethics committee, and the study was performed according to the tenets of the Declaration of Helsinki.

For South Africa, all patients with Exfoliation syndrome and unaffected controls were of self reported South African Black descent and recruited from the St. John Eye Hospital, Soweto, Johannesburg, South Africa and the East London Hospital Complex (Eastern Cape, South Africa), as previously described. The home language of participants and that of their parents and grandparents was used to establish their ethnic affiliation. All participants underwent a standardized detailed ophthalmic examination, which included measurement of intraocular pressure (IOP) by applanation, slit lamp biomicroscopy, gonioscopy, and dilated pupil examination of the lens and fundus. Southern African subjects with normal anterior segment and optic nerve examination, an IOP of less than 18 mmHg and without clinical signs of exfoliation were recruited as control subjects. The research protocol was approved by the University of the Witwatersrand Human Research Ethics Committee (Johannesburg, South Africa; protocol number M080817). The Stellenbosch University Faculty of Medicine & Health Sciences Health Research Ethics Committee also gave approval for this study (N08/08/208). Southern African black participants with clinically diagnosed XFG or POAG and unaffected southern African control subjects were recruited from the St. John Eye Hospital in Soweto, Johannesburg, South Africa. Written informed consent was obtained from all participants. The home language of participants and that of their parents and grandparents was used to establish their ethnic affiliation.

For United States of America, patients with exfoliation syndrome were enrolled from Duke University, University of Iowa, New York University, and Glaucoma Consultation Service at the Massachusetts Eye and Ear Infirmary. Exfoliation changes were identified as the presence of a central disk of XFS material, a clear annular zone (partial or complete), or flakes of XFS material on the lens surface, iris, or corneal endothelium in either eye. Patients were excluded if there was a history of exposure to intense infrared light, for example, glassblowing is associated with ‘true’ exfoliation of the lens capsule rather than exfoliation syndrome. All cases and controls were of self-reported European descent. Controls were individuals of similar age as the patients without any evidence of pseudoexfoliation deposits on intraocular tissues. This study was approved by the Institutional Review Boards of the Massachusetts Eye and Ear Infirmary (Boston, U.S.A.). The study was also approved by the IRB of the New York Eye and Ear Infirmary of Mount Sinai, New York, NY, as well as the Duke University IRB. All participants from Iowa provided informed consent and the study were approved by the University of Iowa’s IRB Board.

For Russia, patients with exfoliation syndrome and controls were enrolled from Department of Ophthalmology at Pavlov First Saint Petersburg State Medical University, St. Petersburg Russia. All patients and unaffected controls were of self-reported European descent. Controls were individuals of similar age as the patients without any evidence of exfoliation deposits on intraocular tissues. All

participants underwent detailed ophthalmic examination including Goldmann tonometry, SAP, HRT, slit lamp biomicroscopy, gonioscopy, and dilated pupil examination of the lens and fundus. Ethical approval was granted by the Ethical Committee of the St. Petersburg Academic University RAS 03/14.

Stage 2 Replication collections

This stage comprised exfoliation syndrome cases and controls from Australia, India, Germany, Italy, China, Iran, Poland, and Argentina.

For Australia, this project was approved by the Western Sydney Area Health Service and the Southern Adelaide Clinical Human Research Ethics Committees. Patients were ascertained through several ocular genetic studies being conducted in Australia; the Blue Mountains Eye Study (BMES), The Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG), and The Glaucoma Inheritance Study in Tasmania (GIST). The BMES is a population based cohort study of individuals aged over 49 years living in the Blue Mountains region, west of Sydney, Australia, designed to investigate common ocular diseases[5]. DNA was available from 59 PXF cases from this study. ANZRAG aims to recruit patients from Australia and New Zealand with advanced glaucoma, and also recruits patients with risk factors for severe secondary glaucoma such as PXF, regardless of glaucoma status[6]. The registry provided 232 cases for inclusion in this study. In all cases PXF was defined as the presence of characteristic deposits visible on the lens capsule under slit lamp examination or a diagnosis of PXF recorded in the medical record prior to cataract extraction. It was not required to have pseudoexfoliation glaucoma. All cases were of European descent. The control cohort consisted of 2621 unaffected participants of the Blue Mountains Eye Study. All controls were free of PXF by slit-lamp examination. DNA was extracted from peripheral whole blood for all participants. Genotyping of the cases was performed Illumina HumanCNV370 array or the Illumina Human 610 Quad Array at the Diamantina Institute, Brisbane, Australia. The controls were genotyped on Illumina Human 610 Quad Array as part of the Wellcome Trust Case Control Consortium 2 project. All individuals had >98% genotyping call rate. Following data cleaning, association analysis was conducted in plink.

For India, a total of 1064 case patients under the Aravind Exfoliation IOL Study with PXF as diagnosed by ophthalmologists from four centres of Aravind eye hospital in Tamilnadu, India were enrolled. A further 50 patients from Narayana Nethralaya Eye Hospital, Bangalore were also enrolled. All cases with exfoliation were from Southern Indian descent. A total of 627 normal control subjects of Southern Indian descent without PXF, without uveitis, and without any evidence of secondary glaucoma, and no other ocular disease were also recruited from the Aravind eye hospitals. A further 2,931 Southern Indians who have undergone eye examinations and had no evidence of exfoliation syndrome or glaucoma were also enrolled as controls. These individuals had genome-wide genotyping data and were confirmed by self report and genetic analysis to be of Southern Indian descent, and have been extensively described[7,8]. Ethical approval was granted by the Narayana Nethralaya Hospital Ethics Committee. The Institutional Review Board of Aravind Eye care System also reviewed and approved the Project.

For **Germany** and **Italy**, the XFS cases study was approved by the ethical review boards of the Medical Faculty of the Universities of Erlangen-Nuremberg, Tuebingen, Wuerzburg (Germany), of the hospital in Monfalcone-Gorizia (Italy) and that of the University Hospital in Siena (Italy). All were conducted in

accordance with the tenets of the declaration of Helsinki. All subjects gave informed consent before entering the study. The patients group consisted of 1693 subjects of German origin (1084 PEX and 609 PEXG) and 510 subjects of Italian origin (all collected from a small region in the North of Italy). The healthy German and Italian subjects serving as were recruited from the same geographic regions as the patients. Recruitment and clinical evaluation were performed as previously described[9-12]. Additional German controls were enrolled from the University of Tubingen. All subjects are healthy blood donors without having diseases. By law, blood donors are checked routinely including laboratory and clinical examinations. The study was approved by the ethical committee of the University Tübingen, Germany and all participant gave written informed consent to use DNA for further investigations. Data of study subjects are anonymized. The study cohort was in part previously reported[13,14]. Genomic DNAs were extracted from peripheral blood leukocytes of patients and control individuals with automated techniques (AutoGenFlex 3000, MA, USA) using Flexigene chemistry (QIAGEN, Hilden, Germany). SNP rs4926244 was genotyped using pre-developed TaqMan™ assay from Applied Biosystem (ABI, Foster City, CA). Reactions were prepared according to manufacturer's instructions and performed in the QuantStudio™ 12K Flex system using standard thermal cycling conditions.

For China (Beijing), all patients with Exfoliation syndrome and unaffected controls were of Han Chinese descent as self-reporting and medical record shows. They came from Beijing or nearby areas, representing a northern Chinese group. All patients and control subjects were recruited from the Eye Center of Beijing Tongren Hospital (Beijing, China). The diagnostic criterion for exfoliation syndrome is the existence of exfoliation material on the anterior lens capsule with dilation of the pupils or on the pupil margin in either eye. Patients with intraocular pressure (IOP) of less than 21 mmHg and no clinical evidence of glaucomatous optic neuropathy were classified as XFS. Exfoliation glaucoma (XFG) was diagnosed if the patient had the above characteristics of exfoliation syndrome and the following features: (1) IOP ≥22 mmHg in either eye; (2) glaucomatous changes on the optic disc, defined as cup to disc ratio >0.7 in either eye or an asymmetric cup to disc ratio of >0.2 or notching of the disc rim; and (3) characteristic glaucomatous visual field loss. Cases with other causes for secondary glaucoma, such as uveitis, pigment dispersion syndrome, and iridocorneal endothelial syndrome, were excluded. Controls were individuals randomly selected from a population-based healthy entity in which 6830 people were recruited in a previous, comprehensive, ophthalmic, epidemiologic study in a county in north China near Beijing[15]. The controls were enrolled by the following criteria: (1) having no signs of XFS or XFG, (2) no glaucomatous changes on optic disc, (3) normal visual field and intraocular pressure, (4) no family history of glaucoma, and (5) no other eye diseases except mild refractive errors. As exfoliation syndrome is a late-onset disorder and rarely develops before the age of 50 years, only individuals aged 50 years or above were included into this study as controls. They received comprehensive ophthalmic examinations, including visual acuity testing and refraction, Goldmann applanation tonometry, gonioscopy, slit lamp biomicroscopy in mydriasis, fundus examination, and automated static perimetry (Humphrey Visual Field Analyzer; Carl Zeiss Ophthalmic Systems, Inc. Humphrey Division, Dublin, CA). Peripheral venous blood was obtained from each subject.

The research protocol was approved by the ethics committee for human research of Beijing Tongren Hospital, Capital Medical University in Beijing, China. Informed consent was obtained from all participants

after explaining the objective and nature of the study. The study was conducted in accordance with the Declaration of Helsinki.

For Xinjiang China, all XFS patients and unaffected controls were recruited from the first people's hospital of Kashgar, Xinjiang, China. All subjects are Uighurs. All the participants signed the informed consent. All participants underwent a standardized detailed ophthalmic examination, which included slit lamp biomicroscopy, gonioscopy, dilated pupil examination of the lens and fundus and measurement of intraocular pressure (IOP). All patients have a typical XFS substances exist in the lens capsules. For controls: no abnormal material gathered on the side of anterior segment or the pupil, intraocular pressure is less than 22mmHg. We excluded samples with a history of strong infrared contact, malignant tumor, autoimmune disease, hypertension, hepatitis, diabetes, cardiovascular disease, neurological disease, and with a history of surgery. Ethical approval for this study was granted by the ethical committee of the First Affiliated Hospital of Xinjiang Medical University,Urumchi.

For Iran, all cases with exfoliation syndrome and controls were of Iranian descent based on their medical records. Patients were recruited from the ophthalmology clinic at Labbafinejad Medical Center affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran. All participants underwent a detailed ophthalmic examination including intraocular pressure (IOP) measurement using Goldmann applanation tonometry, slit lamp biomicroscopy, gonioscopy, and examination of the lens and fundus after pupillary dilation. Subjects with normal anterior segment and optic nerve with IOP less than 21 mmHg with no sign of exfoliation were recruited as control subjects. Prior to enrollment, all patients were informed about the goals and procedures involved in the study and written informed consent was obtained from all participants. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee at the Ophthalmic Research Center

For Poland, all patients with exfoliation syndrome and unaffected controls were of Polish descent as self reporting and medical record shows. As Polish society is hugely homogenous not a single patient was of foreign descent. Patients were recruited from Department of Diagnostics and Microsurgery of Glaucoma, Medical University, Lublin, Poland. In fact, all of the blood samples were collected from Glaucoma Outpatient Department that constitutes the part of the part of the Department. This is why, majority of patients are exfoliation glaucoma patients or at least exfoliation syndrome with ocular hypertension. All participants underwent detailed ophthalmic examination, which included measurement of intraocular pressure (IOP) by Goldman applanation tonometry, slit lamp examination, BCVA, dilated pupil examination of the lens and fundus. In fact majority of patients from the exfoliation syndrome group had visual field testing. Polish subjects with normal anterior segment and optic nerve examination, an IOP of equal or less than 21 mmHg and without signs of exfoliation were recruited as control subjects. Ethical approval for the study was granted by Ethical Commitee of Medical University, Lublin, Poland. KE - 0254/159/2013.

For Argentina, patients were recruited from 2 institutions in Buenos Aires (Organizacion Medica de Investigacion and Fundacion para el Estudio del Glaucoma), and 1 in Tucuman (Centro Oftalmologico Lischinsky). All patients and controls provided informed consent. All subjects underwent a detailed ophthalmological examination. This included best-corrected visual acuity, dilated slit-lamp examination, applanation tonometry, gonioscopy and dilated fundus examination. All cases had exfoliation material in the anterior surface of the lens. Controls had no exfoliation material in the eye, and no evidence of glaucoma or ocular hypertension. Ethical approval for the study was granted by ¨Comite de Etica en Investigacion Clinica¨ (CEIC), Buenos Aires, Argentina.

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