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The epidemiology of ectopia lentis and outcomes after surgery in a Danish population

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The authors have no conflicts of interest to declare.

Abstract

Purpose

To describe the causes of ectopia lentis (EL) and the outcomes after surgery in a Danish population.

Setting

The Eye Clinic Rigshospitalet and Kennedy Center in Copenhagen.

Design

Retrospective cohort study.

Methods

Medical records of patients with non-traumatic EL born after 1980 and seen at the Eye Clinic Rigshospitalet and Kennedy Center from 1983-2019 were reviewed. Clinical information regarding family history, comorbidities, genetic work-up, ophthalmological examinations and surgical history were retrieved.

Results

We identified 72 patients (38 males), of whom 68 had bilateral EL (94.4%). Marfan syndrome (MFS) was found in 34 (47.2%) and bi-allelic variants in ADAMTSL4 in 4 (5.6%). Surgery was performed in 38 (52.8%) patients, 66 eyes, with a median age at the time of first eye surgery of 8.4 years (range 0.8-39.0) and a follow-up of 2.3 years (range 0-25.7). Intraocular lenses were implanted in 9 (23.7%) (11 eyes).

Best corrected distance visual acuity improved from 0.7 to 0.2 LogMAR (median) in right eyes and from 0.7 to 0.3 LogMAR in left eyes postoperatively. 21 patients (56.8%), 42 eyes, did not experience any surgery-related complications. 3 patients (3 eyes) experienced a peri-operative tear in the posterior capsule. Temporary postoperative ocular hypertension was reported in 3 patients

(7.9 %) (3 eyes) and 2 patients (5.4%) (2 eyes) developed persistent ocular hypertension. There were no cases of postoperative retinal detachment.

Conclusion

The main reason for EL was MFS. Surgery improved visual acuity and postoperative ocular hypertension was the most common complication whereas retinal detachment was not observed.

Key words: Ectopia Lentis, Dislocatio Lentis, Luxatio Lentis, Subluxatio Lentis, Marfan Syndrome, Homocystinuria, ADAMTSL4

Introduction

Ectopia lentis (EL) is a displacement of the lens in the eye due to zonular dysfunction and can be partial or complete. In partial EL, the lens is displaced but remains in the pupillary field. In complete EL, all the zonular fibers are detached from the lens and the lens is out of the pupillary field[1]. The displacement of the lens can be divided into traumatic and non-traumatic cases. Non-traumatic EL can be seen in systemic diseases such as Marfan syndrome[1, 2, 3, 4] or in isolated, idiopathic cases or related to variants in *ADAMTSL4*.

ADAMTSL4 (OMIM#610113) encodes ADAMTS-Like 4 protein that is expressed in several organs where its role is still unclear[5]. In the eye, the role of ADAMTS-Like 4 protein is believed to be a fibrillin-1–binding protein that facilitates microfibril genesis[6]. Ectopia lentis is thought to be caused by inadequate attachment of microfibrils to the lens due to impaired transformation of fibrillin-1 into microfibrils[7].

Several systemic diseases are associated with EL, e.g. Marfan Syndrome (MFS), homocystinuria, Weill-Marchesani syndrome (WMS), sulfite oxidase deficiency and Ehlers Danlos syndrome (EDS). Marfan syndrome is inherited in an autosomal dominant manner, caused by pathological variants in the *FBN1* gene (OMIM#154700) with a minimum prevalence of 6.5/100.000 in the Danish population[8]. The pathophysiology of EL in MFS is believed to be due to altered fibrillin microfibrils of the zonular fibers and abnormalities of the lens capsule[9, 10]. Homocystinuria (caused by variants in *Cystathionine beta-synthase* gene: OMIM#236200) causes high levels of homocysteine that cannot be transformed to cysteine due to an enzymatic defect. This is thought to

lead to zonular fiber disruption because of the high content of cysteine in the normal zonular fibers[11, 12].

Weill-Marchesani syndrome is a genetically heterogeneous disorder that can be inherited in both autosomal dominant (*FBN1*: OMIM# 613195) and autosomal recessive manner (*ADMATS10*: OMIM# 277600 *ADAMTS17*: OMIM# 613195). ADAMTS-proteins in interaction with fibrillin-1 have been suggested to be a part of both structural and regulatory roles of microfibrils. The lens in patients with WMS often has a spherical shape and seems to have no microfibrils around its equator.[1, 13]

The pathophysiology of EL in sulfite oxidase deficiency and EDS is unknown, but variants in *COL5A1* (OMIM#130000) are associated with EDS. The *COL5A1* genes are involved in the encoding process for collagen fibrillogenesis[1].

Homozygous variants in the *latent transforming growth factor-beta binding protein gene, LTBP2,* are associated with Microspherophakia and/or megalocornea, with EL and with or without secondary glaucoma (OMIM# 251750). LTBP2 expression have been seen in several ocular structures, including the lens capsule.[14]

Ectopia lentis may also be associated with pseudoexfoliation syndrome, caused by exfoliation material that weakens the zonulae, however this is rarely seen before the age of 50 [15].

The symptoms and signs associated with EL are decreased vision, monocular diplopia, refractive errors such as myopia and astigmatism, and iridodonesis. The lens may dislocate anteriorly causing chronic angle closure and/or pupillary block or it may dislocate into the anterior chamber and lead to reverse pupillary block. It can also dislocate into the vitreous body. Children with dislocated lenses are at great risk of deprivation amblyopia if the refractive error is not detected and treated in time[2].

The purpose of this study was to evaluate the causes of EL in a Danish population younger than 40 years and to describe surgical outcomes and complications.

Methods and materials

The study was approved by the Danish Data Protection Agency for the Capital Region of Denmark (RH-2016-336, I-Suite number: 05070) and the Danish Patient Safety Authority (Protocol number 3-3013-1935/1/NAAN). According to the Scientific Ethics Committees for the Capital Region of Denmark the study did not require medical ethics board approval (Protocol number 16038234).

The medical records of patients with EL seen at the Eye Clinic Rigshospitalet, Rigshospitalet-Glostrup and Kennedy Center from November 1983 until December 2019 were reviewed. The patients were identified through diagnosis code of *Ectopia Lentis, Dislocatio Lentis, Luxatio Lentis and Subluxatio lentis* in The Danish National Patient Registry and through electronical medical files. We included all patients with non-traumatic EL born after January 1st 1980 with an ophthalmological medical record, older patients were not included due to insufficient medical records.

Information about age, gender, family history and genetic work-up, prior and current systemic diseases, visual acuity, refractive errors, intraocular pressure, slit lamp bio microscopy and anterior segment imaging, surgical procedures, and A-scan/optical biometry measurements were obtained from the medical records. Biometric data included corneal topography, ocular biometry and autorefraction measurements.

The diagnosis of ectopia lentis was made with the slit lamp examination. Visual impairment was defined according to The International Classification of Diseases 11 (2018) for distance vision where *no visual impairment* is defined as visual acuity of ≤ 0.3 LogMAR, *mild visual impairment* as >0.3 LogMAR, *moderate visual impairment* as >0.5 LogMAR, *severe visual impairment* as >1.0 LogMAR and *blindness* as ≥ 1.3 LogMAR.

Genetic analyses

Genetic findings were obtained from the Danish Family Archive for Hereditary Eye Diseases or from the medical records.

Genetic analysis was done in a diagnostic setting. In many cases, patients had more than one genetic analysis performed. Sanger sequencing of *ADAMTSL4*, *ADAMTS10* and *FBN1* was done in 5, one and 4 patients, respectively. In six patients with Marfan syndrome, the variant was already known in the family, and Sanger sequencing was done for the family FBN1 variant only. Sanger sequencing

and Multiplex ligation-dependent probe amplification (MLPA) of *PAX6* was performed in one patient. Array comparative genomic hybridization (Array CGH) was performed in 4 patients. Targeted NGS panels was performed in 25 patients: One patient was examined with a panel consisting of 13 ectopia lentis genes. In 24 patients a panel of Marfan/aortopathy genes was examined (varying gene content over time – the most recent and extensive panel including *FBN1, TGFBR1, TGFBR2, TGFB2, SMAD3, ACTA2, MYH11, COL3A1* and *SLC2A10*), including an analysis for deletions/duplications (either MLPA of *FBN1* and *TGFBR2* or a quantitative analysis of NGS data). Variants were evaluated according to *The American College of Medical Genetics and Genomics guidelines*[16].

Marfan syndrome was defined according to *the Revised Ghent Nosology for the Marfan Syndrome*[17]. Patients with EL with a family history of MFS received the diagnosis of MFS. In the absence of family history, patients with EL were diagnosed with MFS if aortic dilatation with a Z-score (the number of standard deviations a given data point varies from the mean) ≥ 2 was present or a *FBN1* variant had been identified in an individual with aortic aneurysm.

Surgical techniques

Different surgical techniques for EL were used depending on the degree of dislocation and the surgeon. For partial EL, the standard procedure at our institution varied over the years but generally an anterior approach was used with extracapsular removal of the lens while stabilizing the capsule with capsular tension hooks if necessary. If the zonular dehiscence was not extensive, a capsular tension ring or a Cionni ring was placed in the capsule, suturing the Cionni ring to sclera – in both cases facilitating implantation of an intraocular lens (IOL) in the capsule. In lack of sufficient capsular support, the capsule was removed, anterior vitrectomy was performed, and the patient was either left aphakic or an iris claw IOL was placed. For the completely dislocated lenses a pars plana vitrectomy and lensectomy was performed, here the patients either were left aphakic or an iris claw/scleral-fixated IOL was implanted.

Temporary postoperative ocular hypertension was defined as intraocular pressure (IOP) over 25 mmHg with need for pressure lowering medical therapy for < 3 months and no sign of glaucomatous damage to the optic nerve. Permanent postoperative ocular hypertension was defined as intraocular pressure over 25 mmHg with need for pressure lowering medical therapy for > 3

months and no sign of glaucomatous damage to the optic nerve. In both definitions, the IOP should be normal preoperatively

Postoperative glaucoma was diagnosed if there was high IOP postoperatively and glaucomatous optic nerve damage and/or glaucomatous visual field defects which was not noted preoperatively, following the guidelines from World Glaucoma Association consensus[18].

Statistical methods

Mean and standard deviations were used as descriptive statistics for normally distributed data, median and range was used for non-normally distributed data.

Results

Baseline characteristics

We included 72 patients (38 males/34 females) with non-traumatic EL. The majority of patients had bilateral EL (n=68, 94.4%). Median age at the first visit to the Eye department was 6.0 years (range 0.1-38.7) and 13.3 years (1.7-39.2) for the last visit. The median follow-up time was 4.8 years (range 0.0-26.1). A family history of isolated EL was reported in 17 (23.6%) patients while 20 (27.8%) had a family history of MFS, see Table 1.

Best corrected distance visual acuity, BCVA, for the non-operated patients was 0.3 LogMAR (median, range 0-1.5) in the right eye and 0.4 LogMAR (range 0-1.3) in the left eye. The distribution in the visual function in impairment groups are shown in Table 2.

Ocular co-pathology was found in 32 (44.4%) patients with ectopia pupillae being the most common followed by bilateral persistent pupillary membrane and cataract, see Table 1.

Genetics

Genetic testing was performed in 43 (59.7%) patients. *Pathogenic/likely pathogenic* variants were found in 31 (72.1%) of those and *variants of uncertain significance* (VUS) were found in 2 (4.7%). Novel variants were found in 4 (9.3%) patients. A genetic diagnosis had been made in a first degree relative in 4 (5.6%) patients, who had not themselves been tested. Genetic findings are listed in Table 3. For 8 (11.1%) patients information on whether genetic tests had been performed was not

reported in the medical files. Nine patients (40.9 %) without known comorbidities had not been genetically tested.

Thirty-four patients (47.2%) fulfilled the criteria for MFS according to *the revised Ghent Nosology for Marfan syndrome*[14]. The diagnosis was confirmed by molecular genetic analyses with a variant in *FBN1* in 24 patients (70.5%). A variant in *FBN1* was present in a first degree relative in three patients (8.8%). One patient with a VUS in *FBN1* did not fulfill the criteria for MFS according to *the revised Ghent Criteria for Marfan syndrome* because the variant has not been identified in an individual with aortic dilatation.

Variants in *ADAMSTL4*, Homocystinuria and WMS were other causes to EL in our population. Ectopia lentis due to pseudoexfoliation syndrome was not found in our young population. One patient had a variant in *PAX6*, this patient also had aniridia. A novel variant in *LTBP2* was found in a patient with megalocornea and EL.

Biometric data

Axial length, AL, pre-operative measurements were available in 25 (34.7 %) patients, 10 of those had MFS. Mean AL was 23.01 mm (range 22.53-27.41) in right eyes and 22.83 mm (range 20.28-26.47) in left eyes for all patients. The mean axial length was 1.97 mm longer in the right eyes and 1.45 mm in left eyes for patients with MFS compared to those without.

Preoperatively myopic spectacles of -1 D spherical or larger was prescribed to 23 patients (41 eyes) with a median value of -6.03 D (range -18.00 to -1.00) in right eyes and -7.90 D (-15.50 to -1.00) in left eyes. Axial length measurements were available in 5 patients, 9 eyes with mean values of 23.56 mm (range 22.36-24.59) in right eyes and 24.51 mm (range 23.31-26.47) in left eyes. The biometric measurements are summarized in Table 4.

Preoperative anterior chamber depth measurements were available in 24 patients with mean values of 2.86 mm (range 1.39-4.16) for right eyes and 2.97 mm (range 1.69-5.00) for left eyes.

Surgery

Thirty-eight patients (52.8%), 66 eyes, underwent surgery for EL, 28 (73.7 %) had bilateral surgery and 10 (26.3%) had unilateral surgery. The surgeries were mainly performed in general anesthesia (94.3 %, n=33), none of the patients had simultaneous bilateral surgery. The main indication for

surgery was poor visual acuity that could not be adequately alleviated optically (n=25, 65.8%). In one patient, the lenses were removed because of retinal detachment on one eye related to posterior dislocation of the lens into the vitreous body and phacolytic ocular hypertension on the other eye. Pressure remained high postoperatively in the eye with phacolysis. One patient had the lens removed because of high intraocular pressure preoperatively due to iridocorneal synechiae caused by anterior lens dislocation on one eye. This patient underwent trabeculectomy with Mitomycin C one year after lens removal. One patient was operated outside Denmark and surgical notes were not available and the patient was excluded from the analyses below. The indication for surgery was unreported in 11 (28.9%) of the patients. The main reason for not receiving surgery was that the patients could achieve a satisfactory visual acuity with contact lenses and/or glasses.

The median age at time of first eye surgery was 8.4 years (range 0.8-39.0 years) and 8.1 years (0.8-39.2) for the second eye. The median age of patients with unilateral surgery was 12.3 years, therefore the median age for the second eye is less than the first eye. An overview of the age distribution at the time of surgery in the first eye is listed in Table 5. The median time between surgery of the first and the second eye was 0.21 years (range 0.0-5.83). The median follow-up time from the surgery of the last eye until the last visit at the eye clinic was 2.3 years (range 0.0-25.7).

Of the patients where genetic analyses had been performed, nine patients with dominant variants and four patients with recessive variants received surgery. The median age for surgery for patients with a dominant variant was 10.1 years (range 3.4-32.8 years) and the median age for patients with recessive variants was 2.6 years (range 1.1-15.8 years).

Anterior approach for surgery was performed in 22/22 (right/left eyes) and pars plana vitrectomy was performed in 3/2 (right/left eyes) for ectopia lentis. Intraocular lenses were implanted in the same surgical setting as lens removal in 11 eyes (2 bilateral, 7 unilateral). One of these patients (both eyes) received a scleral fixated IOL. One patient (one eye) had an iris claw lens implanted in a second surgery. A capsular tension ring was used in 7 eyes (6 patients), in 3 eyes (3 patients) the capsule teared and the capsular tension ring was abandoned and the eyes were left aphakic. Prepupillary iris-claw lens was primarily implanted in 3 eyes (3 patients), one of them developed postoperative macular edema. Of the patients receiving surgery for EL, 30 were left aphakic.

Visual acuity improved from a median of 0.7 LogMAR to 0.2 LogMAR postoperatively for both the right and the left eye; see Table 5 and Figure 1.

No peri- and/or post-operative complications were registered in 21 (56.7%) of the patients undergoing surgery. A temporary increase in the intraocular pressure was found in 3 (8.1%)

patients; two responded well to medical therapy including one who had an iris-coloboma and one was managed by a surgical iridectomy in addition to a YAG-laser iridotomy that had been performed prior to initial surgery. Permanent postoperative ocular hypertension was found in 2 (5.4%) patients. None of the patients fulfilled the criteria for postoperative glaucoma.

One patient experienced a posterior dislocation of the IOL and received a second procedure with scleral fixation of the IOL, notes of the primary surgery was unavailable for this patient. On the first day after this surgery, the optic of the IOL was in the anterior chamber and a third procedure where the optic of the IOL was repositioned, was performed.

One patient lost the vision in one eye due to decompensated cornea secondary to an IOL in the anterior chamber (the specific type of anterior chamber lens was unknown as medical records for the surgical procedure were unavailable).

There were no cases of postoperative retinal detachment during the follow-up time. An overview of the surgery-related complications is shown in Table 5.

Discussion

We evaluated the causes of non-traumatic EL and outcomes after surgery in a Danish cohort. We found that MFS was the most common cause of EL which is consistent with the data from a Danish National survey study in 1998[19], where 68.2% (n=187) of the patients classified as systemic/non-systemic, had MFS. This was followed by bi-allelic variants in *ADAMTSL4*. A Dutch study from 2017 used targeted Next Generation Sequencing (of *ADAMTS10, ADAMTS17, ADAMTSL2, ADAMTSL4* and *FBN1*) and MLPA analysis of *FBN1*, and found a genetic cause in 16/24 patients with EL with variants in *ADAMTSL4* in 75% of the patients and in *FBN1* in 25%. Genetic analyses were not performed in 40.9% (n=9) of the patients without a known comorbidity. This suggests that the true prevalence of *ADAMTSL4* variants in our EL population might be higher than we found[12] and including *ADAMTSL4* analysis as standard work-up for patients with ectopia lentis seems to be valuable. Knowing the genetic background of ectopia lentis is important in planning future follow-up, e.g. is lifesaving repeated cardiac evaluation - or reassuring parents that systemic symptoms are not likely if *ADAMTSL4* related ectopia lentis is found. Furthermore, parents can be informed of recurrence risk in siblings and reproductive options.

The frequencies of the systemic comorbidities as Homocystinuria and WMS found in our study were also consistent with data presented by Fuchs et al from 1998 [19], were 0.8% (n=3) had Homocystinuria and 0.7% (n=2) had WMS.

The main indication for surgery for the patients in this study was poor vision and surgery was performed before the age of 18 in 70.2% of the operated patients. The optimal age for performing surgery can be difficult to predict and there is to date no consensus on the optimal age or time of performing surgery for the non-traumatic EL. Several factors must be considered in the management of EL e.g. visual symptoms, visual acuity, risk of amblyopia, surgery-related complications and the resources of the family. As long as visual acuity remains acceptable, observation is usually preferred. However, if there are visual symptoms and visual acuity deteriorates with optimum optical correction, surgery should be considered, especially in small children where there is a potential risk of deprivation amblyopia. The tedious follow-up after lens surgery in childhood may put a substantial load on the family, this should also be considered in the decision of whether performing surgery or not in children with EL[20]. The decision of surgery must thus be tailored individually in close collaboration with the patient and the patient's family.

As expected, visual acuity improved after surgery in our population, where 19/22 patients (right eye) and 18/21 patients (left eye) had a postoperative visual acuity of ≤ 0.3 LogMAR. Postoperative retinal detachment was not observed in our population during the follow-up period. This is consistent with two earlier studies [9, 21] whereas one study reported one case of retinal detachment which occurred in direct relation to an ocular trauma 4 years after lens surgery[2]. In a more recent study from 2021, with a mean follow up period of 39± 27, all the patients received scleral fixated IOL. Postoperative retinal detachment occurred in 6 eyes, 7.8%, 2 of these were related to ocular trauma [22]. The higher rate of retinal detachment could be related to the method of scleral fixated IOLs. Only one patient received scleral fixated IOL in our study. None of the patients in this study fulfilled the criteria for postoperative glaucoma. The apparently low incidence of glaucoma as a complication to surgery is consistent with two earlier studies. Konradsen et al found (2007) no cases of postoperative glaucoma with a median follow up time of 27 months (range 1-59 months)[23]. Anteby et al (2003) reported no cases of postoperative glaucoma in 38 eyes with a mean follow-up time of 3.2 years (range 18 months - 6 years) and in 18 eyes with a follow up time of minimum 11 years (mean 14.5 ± 2.7 SD)[2]. One should keep in mind that patients with EL are also at risk of developing glaucoma due to lens instability[24].

This study is limited by the retrospective study design and therefore the partial limited follow-up period for the postoperative complications. Also, some relevant genes might not have been included in the genetic work-up, as the genetic tests have developed quickly in the last decades. There are case-studies of patients with recessive variants in *LEPREL1*, some of which had ectopia lentis as the presenting feature[25]. The patients in this study have not been examined for variants in *LEPREL1*.

Not all Danish patients with MFS/EL are seen at Rigshospitalet-Glostrup or Kennedy Center, therefore, unfortunately a deduction of the frequency of MFS/EL in the Danish population cannot be made. Even with the relatively short follow-up time, our data suggest, that the risk of postoperative retinal detachment or other major postoperative complications after lensectomy in patients with EL is low why surgery should be considered when the visual development and/or visual acuity is compromised.

In conclusion, we found a high yield in genetic testing, with MFS as the main reason for EL in our young population, followed by biallelic variants in *ADAMTSL4*. Surgery improved visual acuity with only a small risk of postoperative glaucoma and retinal detachment.

Value Statement

What Was Known

- There are several known causes for Ectopia Lentis.

What This Paper Adds

- The causes of Ectopia Lentis can be established by a high yield of genetic testing.
- Surgery for Ectopia Lentis, when indicated, seems to be safe with a low risk for complication and improves visual acuity.

Figure 1. The pre and postoperative visual acuity measurements.

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Table 1. Baseline characteristics of patients with non-traumatic ectopia lentis

General information	
Gender (Male/ Female), n	38/34
Laterality (unilateral/bilateral), n of patients	4/68
Follow up time, months (median (range))	58 (0-313)
Age at the first visit at the hospital, months (median (range))	71.5 (1-464)
Age at the last visit at the hospital, months (median (range))	159 (20-470)
Comorbidities related to ectopia lentis, n of patient	
Marfan Syndrome	34
ADAMTSL4 variant	5
Homocystinuria	2
PAX6 variant	1
LTBP2 variant	1
Weill Marchesani syndrome	1
Ocular comorbidities, n of patients (n of eyes)	
Cataract	3 (5)
Cataract, ectopia pupillae and megalocornea	1 (2)
Congenital aniridia, nystagmus and secondary glaucoma	1 (2)
Ectopia pupillae,	5 (10)
Iris and lens coloboma (bilateral)	1 (2)
Iris heterochromia	1
Megalocornea	3 (6)
Microftalmia, posterior embryptoxon, dysmorphic retina, glaucoma, ectopia pupillae and cataract(unilateral)	1 (2)
Microsherophakia, anterior chamber malformation with peripheral anterior synechiae and glaucoma	1 (2)
Periferal and posterior synechia	3 (6)
Persistent prepupillary membrane	6 (12)
Retinal detachment (one eye), Phacolytic glaucoma (other eye)	1
Shallow anterior chamber	1 (2)
Esotropia	3 (5)
Exotropia	4 (5)
Unreported	3

Table 2. Visual impairment categorization according to WHO criteria

Visual impairment (BCVA in the follow-up period)*, n	
No visual impairment	49
Mild visual impairment	9
Moderate visual impairment	9
Severe visual impairment	1
Blindness	0
Unreported	4

* Visual impairment was categorized according to WHO criteria ('Blindness and vision impairment' n.d.) and according to the best corrected distance visual acuity (BCVA) on the better seeing eye during the follow-up period.

Table 3. Genetic analyses

ID	*Gene*	Variant	Zygosity	Pathogenicity
Marfan Syndrome				
54	*FBN1*	deletion exon 38	Heterozygous	Pathogenic
13	*FBN1*	deletion exon 11-13, (arr[hg19]15q21.1(48805564_48811583)	Heterozygous	Pathogenic
27	*FBN1*	deletion exon 38	Heterozygous	Pathogenic
18	*FBN1*	c. 2375G>A, p.(Cys792Tyr)	Heterozygous	Likely pathogenic
37	*FBN1*	c.1633C>T,p.(Arg545Cys)	Heterozygous	Pathogenic
14	*FBN1*	c.1813T>C, p.(Cys611Arg)	Heterozygous	Pathogenic
53	*FBN1*	c.1850G>A, p.(Cys617Tyr)	Heterozygous	VUS*
25	*FBN1*	c.1879C>T, p.(Arg627Cys)	Heterozygous	Pathogenic
67	*FBN1*	c.2047T>C, p.(Cys683Arg)[x]	Heterozygous	Pathogenic
2	*FBN1*	c.2168-2A>G (splice mutation)	Heterozygous	Pathogenic
9	*FBN1*	c.2168-2A>G (splice mutation)	Heterozygous	Pathogenic
29	*FBN1*	c.2168-2A>G (splice mutation)	Heterozygous	Pathogenic
31	*FBN1*	c.2168-2A>G (splice mutation)[#]	Heterozygous	Pathogenic
50	*FBN1*	*c.2168-2A>G* (splice mutation)[#]	Heterozygous	Pathogenic
52	*FBN1*	*c.2168-2A>G* (splice mutation)[#]	Heterozygous	Pathogenic
11	*FBN1*	c.239G>A, p.(Cys80Tyr)	Heterozygous	Likely pathogenic
8	*FBN1*	c.2420-1G>A (splice mutation)	Heterozygous	Pathogenic
48	*FBN1*	c.2710_2713del, p.(Lys904Glufs*7)[x]	Heterozygous	Pathogenic
1	*FBN1*	c.3037G>A, p.(Gly1013Arg)	Heterozygous	Pathogenic
12	*FBN1*	c.304T>C, p.(Cys102Gly)	Heterozygous	Pathogenic
42	*FBN1*	c.3373C>T, p.(Arg1125*)	Heterozygous	Pathogenic
55	*FBN1*	c.344C>G, p.(Ser115Cys)	Heterozygous	Likely pathogenic
4	*FBN1*	c.415del, p.(Asn1382Ilefs*31)	Heterozygous	Pathogenic
40	*FBN1*	c.4460A>T, p.(Asp1487Val)	Heterozygous	Likely pathogenic
41	*FBN1*	c.4460A>T, p.(Asp1487Val)	Heterozygous	Likely pathogenic
30	*FBN1*	c.5993G>A, p.(Cys1998Tyr)	Heterozygous	Likely pathogenic
35	*FBN1*	c.6698C>G, p.(Pro2233Arg)	Heterozygous	Pathogenic
32	*FBN1*	c.7003C>T, p.(Arg2335Trp)	Homozygous	Pathogenic
58[¤]	*FBN1*	c.3509G>A, p.(Arg1170His)	Heterozygous	VUS*
Isolated ectopia lentis				
61	*ADAMTSL4*	c.1046dupG: p.(Ser349Argfs*11) c.2639del: p.(Gln880Argfs*68)	Compund heterozygous	Pathogenic/pathogenic
38	*ADAMTSL4*	c.1046dupG: p.(Ser349Argfs*11) c.2639del: p.(Gln880Argfs*68)[#]	Compund heterozygous	Pathogenic/pathogenic
73	*ADAMTSL4*	c.2296T>C, p.(Cys766Arg) c.2296T>C, p.(Cys766Arg)	Homozygous	Pathogenic
10	*ADAMTSL4*	c.767_786del, p.(Gln256Profs*38) c.767_786del, p.(Gln256Profs*38)	Homozygous	Pathogenic
22	*ADAMTSL4*	c.767_786del, p.(Gln256Profs*38) c.767_786del, p.(Gln256Profs*38)	Homozygous	Pathogenic
Weill Marchesani syndrome				

6	*ADAMTSL10*	c.2288_2289insC: p.(Gln765Profs*31) [x] c.2288_2289insC: p.(Gln765Profs*31)	Homozygous	Likely pathogenic
Aniridia				
39	*PAX6*	c.687G>T, p.(Glu109*)	Heterozygous	Pathogenic
Diagnosis not specified				
66	*LTBP2*	c.3617_3621delinsTCT, p.(Gly1206Valfs*39) [x] c.3617_3621delinsTCT, p.(Gly1206Valfs*39)	Homozygous	Pathogenic

[#] Variant found in 1st degree relative

*Variant of uncertain significance

[s]Did not fulfil the Revised Ghent Criteria for Marfan syndrome

[x]Novel mutation

Table 4. Biometry in phakic eyes

ID	AL	Age #	ACD	Keratometry		Refraction, spherical equivalent	
	R/L, mm	Years	R/L, mm	K_1, K_2, R, D	K_1, K_2, L, D	S, R/L, D	C, R/L, D
Marfan syndrome							
67	24.4/23.36	3	-	40.87, 44.87	40.87, 43.0	-	-
37	22.36/22.08	6	2.31/2.48	40.7, 43.5	40.7, 42.3	-1/-0.5	-
54	23.16/23.14	8	1.85/2.02	-	-	-	-
35	22.89/22.65	9	2.83/2.73	-	-	0/0	-7x0/-7x0
14	22.93/22.76	12	3.83/3.52	-	-	-7.62/-7.5	-0,12x171/-0,12x38
13	23.99/24.29	14	3.82/3.01	39.3, 40.5	39.8, 40.2	-18/-15.5	-
68	23.40/23.31	16	1.72/2.08	-	-	-14/-12.75	-/-1.5x90
27	24.59/26.47	16	2.42/3.08	-	-	-6/-6	-
31	27.41/-	18	4.13/5.00	40.4, 41.8	40.6, 41.6	8.5/8.5	-
25	-/24.88	38	-/2.80	38.67, 40.5	39.63, 41.17	-7.75/-7.75	-1.5x7/-2x139
4	-		2.88/3.60	-	-	1/1.5	-6x20/-6x160
12	-		-	39.23, 40.72	39.4, 40.68	-	-
18	-		2.52/2.55	-	-	-0,8/-0,8	-
32	-		2.45/2.84	-	-	+10/+9.5°	-1.25x100/-1x70
42	-		2.76/2.82	-	-	-3.5/-1	-11x10/-5x2
45	-		1.39 /1.69	43.62, 45.5	44.75, 44.75	-12.75/-15.75	-0.75x70/-1.25x109
49	-		-	38.4, 40.4	38.8, 40.3 (Blinked)	-	-
50	-		3.14/3.25	-	-	-15/-15	-
59	-		-/3.21	44.8, 47.4	44.3, 47.4	-	-
70	-		-	42.7, 43.5	42.6, 44.4	-11.5/-11	-
ADAMTSL4-variant							
73	21.22/21.04	1	-	39.8, 42.0	39.6, 41.8	-	-
22	-	-	-	41.7, 42.1	42.0, 42.2	-10/-10	-
38	-		3.45/3.44	39.6, 41.7	47.0, 53.8 (Blinked)	-10.25/-11.25	-2x170/-2x5
Homocysteinuria							
72	22.54/22.24	6	2.33/2.59	41.87, 45.5	41.61, 45.25	-	-
LTBP2-variant							
66	-		-	-	-	-	-
PAX6-variant							
39	-		1.75/1.96	37.62, 38.75	37.62, 39.75	+16/+16	-
Isolated Ectopia lentis							
63	21.58/20.44	0	3.03/2.71	-		-	-
16	20.53/20.28	1	-	39.4, 40.5	40.7, 41.6	-	-
47	20.80/21.14	2	-	-	-	-	-
46	22.53/-	2	-	43.25, 44.50	42.5, 44.37	-10/-10	-
28	21.8/20.98	3	-	-	-	-10/-10	-
15	22.8/22.15	3	-	-	-	-	-
20	-/26.4	12	-	43.0, 44.9	-	-	-

64	21.02/20.96	16	3.47/3.67	-	-	-	-
71	24.12/23.62	18	-	-	-	-4.5/-6.25	-2.5x92/-1.25x16
26	-/24.93	30	4.16/3.89	40.4, 42.5	40.9, 43.5	-5.5/-5.5	-
74	22.37/22.3	38	4.80/4.08	-	-	-9.5/-12	-3.75x131/-3x113
60	-	-	-	-	-	-	-
21	-		2.93/-	-	-	-2/-2,5	-1,25x41/-
57	-		2.87/2.97	-	-	-2.25/-1.75	-6x10/-3x10

K_1, K_2=Keratometry values

L=Left

R=Right

S=spherical

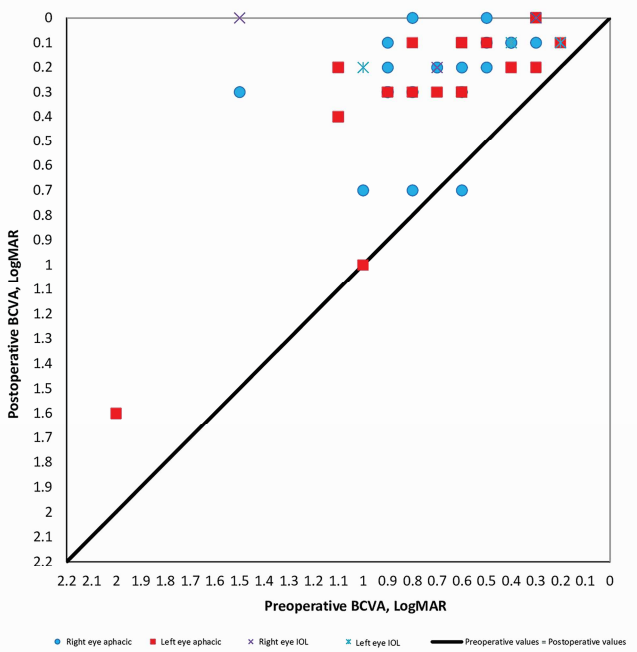
#=At the time of AL measurement

¤ Functionally aphacic

Table 5. Characteristics of patients undergoing lens surgery for ectopia lentis

Surgery (unilateral/bilateral), n of patients	10/28
Median age at surgery for the first eye, years (median (range))	8.4 (0.8-39.0)
Median age at surgery for the second eye, years (median (range))	8.1 (0.8-39.2)
Follow up time from first eye surgery, years (median (range))	3.0 (0-25.8)
Follow up time from last eye surgery, years (median (range))	2.3 (0-25.7)
Age at the time of surgery of the first eye for ectopia lentis, n of patients	
<1 year	1
1-7 years	15
8-18 yeas	10
>18 years	8
Unreported	4
Postoperative intraocular lens-status, n of patients (n of eyes)	
Aphakia	30 (54)
IOL implantation abandoned during surgery because of a tear/rupture in the capsule	3 (3)
IOL , Primary implantation, n of patients, (n of eyes)	9 (11)
In the bag IOL	3(3)
Iris claw-lens	3(3)
Anterior chamber lens (type unknown)	1(1)
Sclerally fixated lens	1(2)
IOL lens (type unknown)	1(2)
Secondary implantation with iris claw	1 (1)
Visual acuity measurement in operated patients	
BCVA for all patients, (right eye/left eye), LogMAR, median (range)	
Preoperative	0.6 (0.1-1.5)/0.7(0.2-1.5)
Post-operative	0.2 (0-1.0)/ 0.2 (0-1.5)
BCVA in aphakic patients, (right eye/left eye), LogMAR, median (range)	
Pre-operative	0.8 (0.3-1.5)/0.6 (0.2-1.5)
Postoperative	0.2 (0-0.7)/0.2 (0-1.5)
BCVA for patients corrected with contact lens	0.1 (0-0.7)/0.2 (0-1.5)
BCVA in patients corrected with spectacles	0.3 (0-0.7)/0.3 (0-1)
BCVA in patients with IOL, (right eye/left eye) LogMAR, median (range)	
Pre-operative	0.7 (0.3-1.5)/0.2 (0.2-1.0)
Post-operative	0 (0-0.2)/0.1 (0.1-0.2)
Complications related to surgery	
Perioperative complications, n of eyes	
Tear in the capsule	3
Anaphylaxis presumably due to “Thiomebumal”- Thiopental	1
Early postoperative complications.(<3 Months)	
Remains of lens material (assumed to be a small piece of capsule)	1
Vitreous prolapse in the anterior chamber	3
<3 months ocular hypertension	3

Vitreous body string in the anterior chamber requiring second surgery	1
Macular edema	1
Late postoperative complications (>3 Months)	
>3 months ocular hypertension	3
Dislocation of the intraocular lens	1
Corneal decompensation	1



BCVA = Best corrected visual acuity
IOL = Intraocular lens