Eye (2014) 28, 162–168

www.nature.com/eye

CAMBRIDGE OPHTHALMOLOGICAL SYMPOSIUM

Molecular pathogenesis and management strategies of ectopia lentis

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Abstract

Ectopia lentis (EL) is a condition that can either herald underlying systemic conditions, or be isolated. The recent expansion in the genetics of these conditions has furthered the understanding of the underlying molecular aetiology. It is becoming apparent that novel genes, and in particular the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) family, are important in ocular development. The common link in these genes seems to be EL. The clinical management of EL is challenging. In particular, the options for addressing surgically induced aphakia in the context of an ectopic capsule are varied. Little evidence exists to direct management of these issues. This review summarises the molecular pathogenesis of EL and conditions associated with it, using the genetic aetiology as a framework. Furthermore, it summarises some of the issues involved in its clinical management.
Eye (2014) **28,** 162–168; doi:10.1038/eye.2013.274; published online 10 January 2014

Keywords: ectopia lentis; vitreolensectomy; Marfan syndrome

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Received: 16 October 2013
Accepted in revised form: 14 November 2013
Published online: 10 January 2014

The Austrian ophthalmologist Karl Stellwag[1] is credited with coining the term ectopia lentis (EL) in 1856. It describes abnormal movement of the crystalline lens from within its natural position (Figure 1). Although trauma is a common cause, a genetic predisposition was first proposed by Williams,[2] in 1875, by describing a family with EL in two generations. The genetic aetiology of EL is an ever growing topic.

Anatomy

The critical structures for maintaining the crystalline lens in its natural position are the zonular filaments (ZF). These form a circular structure between the equatorial lens and the ciliary body through a triangular structure with the apex of the triangle on the equatorial margin of the lens covering an area of up to 55 nm[23] that is rich in fibrillin fibres.[4] They were first described as being part of the family of microfibrils in 1971[5] and the most important macromolecular component of ZF are fibrillins.

The three distinct fibrillins are fibrillin-1, -2, and -3, which are encoded by the genes *FBN1* (OMIM 134797), *FBN2* (OMIM 612570), and *FBN3* (OMIM 608529), respectively. *FBN1* is a 237-kb gene consisting of 65 exons located at 15q21.1.[6] It encodes fibrillin-1, the most abundant macromolecule in ZF. This protein consists of 47 epidermal growth factor domains, 43 of which are calcium binding (cbEGF) and two cysteine rich domains (transforming growth factor-binding protein-like domain).[7] The latter of these are unique to this family of proteins, and their specific function is unclear, although they may have a role in integrin binding.[8] cbEGF domains, in particular, form intradomain disulphide bonds and also contain a calcium-binding consensus sequence. When calcium binds to these bonds, the molecule strengthens and is more resistant to degradation. It is these structures that are crucial to the extracellular matrix (ECM) function of these proteins. It is proposed that fibrillin-1 provides force-bearing structural support, whereas fibrillin-2 acts mostly in the early process of fibre assembly.[9]

The structure of the fibrillin microfibril is of a 'beads on a string' of 10–15 nm diameter with beads 50 nm apart.[10] The bead-like structures

are mostly encoded for by exon 24 of FBN1.[11] Mutations in this exon lead to severe Marfan syndrome (MFS). Other constituents of ZF include elastin, proteoglycans, and GAGs. The most important associated glycoprotein is MAGP-1, which probably has a role in cross linking the microfibrils.[10]

FBN1 and Marfan syndrome

Heterozygous mutations in *FBN1* lead to haploinsufficiency of fibrillin-1. This results in disrupted microfibrillar architecture in the ECM.[12] Mutations in this gene result in classical MFS, neonatal MFS, autosomal dominant ascending aortic aneurysms, familial arachnodactyly, Shprintzen–Goldberg syndrome and severe progressive kyphoscoliosis, the 'MASS' phenotype (myopia, mitral valve prolapse, borderline aortic root enlargement, skin and skeletal findings), mitral valve prolapse syndrome, and autosomal dominant EL. There may be significant overlap between these conditions.

As fibrillin is a significant element of the ciliary zonules, it is unsurprising that EL manifest in up to 60% of MFS cases.[13] MFS is an autosomal dominant disorder encompassing characteristic features of the cardiovascular, skeletal, and ocular systems.[14] The ocular features include EL, flat corneal curvature, glaucoma, and axial myopia.[15] The former of these (EL), with the genetic and cardiovascular features form the major components of the diagnostic Ghent criteria.[14]

The Ghent criteria for MFS were updated in 2010,[14] emphasising the importance of the aortic root diameter in this syndrome. Diagnostic dilatation of the aortic root in the presence of either a diagnostic *FBN1* mutation, or EL or seven points of skeletal features results in the diagnosis of MFS. The update in 2010 to the Ghent criteria had important implications for ophthalmologists and geneticists. Specifically, this was in relation to patients with EL and a *FBN1* mutation with no aortic root dilatation. If the particular mutation had been previously described in classical MFS, these patients' diagnosis is now MFS. A summary of this is shown in Figure 2.

Over 800 pathogenic mutations in *FBN1* have been described.[16] It is suggested that a significantly higher proportion of missense mutations involving cysteine residues (responsible for the structurally critical disulphide bonds) and mutations at the 5′ end are causative in EL,[16,17] in particular within the first 15 exons. These exons encode the N-terminus of fibrillin-1. This portion of the protein is thought to be integral to homodimer formation of the fibrillin-1 molecules, which eventually leads to polymers of fibrillin-1 and thus microfibrils.[18]

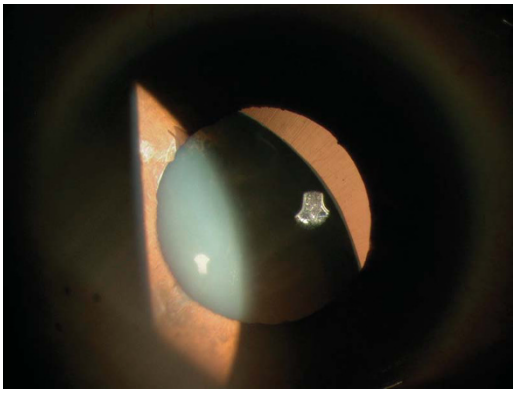

Figure 1 Ectopia lentis—note attenuated zonules offering very limited capsular support.

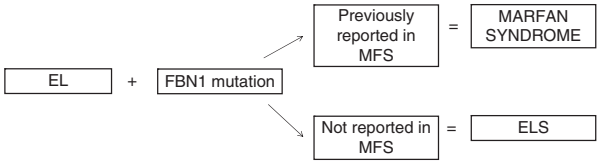

Figure 2 Summary of the importance of the Ghent criteria 2010 in those without diagnostic cardiovascular features of MFS. ELS, ectopia lentis syndrome; *FBN1*, fibrillin-1 gene.

The mutations in *FBN1* result in abnormal distribution and structure of microfibrillary bundles in the capsule of MFS patients, particularly at the site of zonule attachment,[4,19] conjunctiva,[20] and zonules themselves.[21]

Alternative genetic causes of EL

It became apparent in the intervening years since MFS was first described that numerous other genetic conditions are associated with EL. Although no clear epidemiological data is available, it has been suggested that congenital EL may have a prevalence of six per 100 000.[22] It is probable that the second most common cause of EL is a condition termed isolated ectopia lentis (IEL).[22,23] As the term suggests, this condition does not manifest features of other conditions, ocular or systemic; in particular MFS. It is thought to be inherited in an autosomal dominant (OMIM 129600) or autosomal recessive (OMIM 225100) manner.

Autosomal dominant EL

There are many reports of pedigrees in which the classical features of MFS are not reported, but EL segregates in an autosomal dominant fashion.[17,24,25] Heterozygous mutations in *FBN1* cause this condition, and it has thus occasionally been termed autosomal dominant isolated ectopia lentis (OMIM 129600).

However, these patients are likely to represent part of a phenotypic spectrum of MFS,[26] and the exclusion of MFS in these patients must be undertaken carefully and in view of the most recent Ghent criteria for MFS,[14] as described above. In particular, detailed understanding of the history of any *FBN1* mutation found must be gained before MFS can be excluded.

Examples of the importance of this recent alteration include a report by Edwards and colleagues,[27] who presented a family with autosomal dominant EL with some mild skeletal features but no cardiological features of MFS, hence diagnosing IEL. However, the mutation they found in *FBN1* (R240C) was subsequently described in a family with classical MFS.[28] Because of the report of this mutation in MFS, the diagnosis would alter in the family to MFS. Further examples of such misdiagnoses continue,[29,30] suggesting that the updated Ghent criteria should be highlighted to those involved in an EL research. Furthermore, it has been demonstrated that patients with EL secondary to *FBN1* mutations may progress to develop cardiovascular features of MFS.[31,32] It is thus recommended that these patients have long-term cardiology follow-up.[14] The authors of the 2010 Ghent criteria[14] therefore suggested that those with EL and a previously unreported *FBN1* mutation should be termed ectopia lentis syndrome, to illustrate the potential for cardiovascular complications. This may be somewhat misleading, as these patients may never develop extraocular features of fibrillin-1 dysfunction. We would therefore simply recommend the term 'isolated' not be used in the context of *FBN1* mutations. We suggest simply 'dominant ectopia lentis' in this situation.

Autosomal recessive IEL

This has been established for over 70 years.[33,34] al-Salem,[35] in 1990, was the first to describe detailed ocular phenotypes of two consanguineous families from Iraq and Jordan with recessive IEL. Ahram and colleagues[36] 19 years later described a homozygous nonsense mutation in *ADAMTSL4* on 1q21.2 in the Jordanian family. Further mutations in this gene have been described causing autosomal recessive IEL[37–40] and ectopia lentis et pupillae (EL&P).[40–42] The genotype/phenotype similarity of IEL and EL&P most likely represents a spectrum of anterior segment dysgenesis.

The role of this protein and gene are unclear, and it has been suggested to interact with fibrillin-1 in microfibril biosynthesis.[43] However, recessive mutations in *ADAMTSL4* result in a more severe ocular phenotype with earlier onset of EL and greater axial length, than dominant mutations in *FBN1*.[40] In addition, the gene and protein are found throughout the human eye.[44] It is therefore probable that this gene may have a role in ocular development, independent of an interaction with fibrillin-1.

Other autosomal recessive mutations resulting in EL

Weill-Marchesani syndrome (WMS: OMIM 277600) is a very rare condition characterised by short stature, brachydactyly, and joint stiffness.[45] The characteristic ocular features include myopia and EL (commonly manifesting as microspherophakia). Although causative heterozygous mutations in *FBN1* has been described,[46] it is more commonly inherited in an autosomal recessive manner, caused by mutations in *ADAMTS10*[47,48] on 19p13.2. EL is described in the majority of both dominant and recessive cases.[49]

In 2009, Morales and colleagues[47] described homozygous mutations in *ADAMTS17* on 15q24 in a consanguineous family causing EL and short stature. This family did not fulfil the diagnosis of WMS. The authors therefore coined this condition as 'Weill-Marchesani-like syndrome' (OMIM 613195) (WML). Distinguishing this from WMS is challenging. The only further report to date of a mutation in this gene causing this condition was later published by the same group in 2012.[50] Finally, mutations in *LTBP2* on 14q24.3 have been described to cause EL, both in the context of WMS[51] and isolated with other ocular features.[52] Unlike other members of its protein family, LTBP2 does not bind to latent transforming growth factor, and instead its C-terminus has high affinity for the N-terminus of fibrillin-1. An ocular phenotype including EL caused by mutations in this gene may therefore not be surprising.

Homocystinuria (OMIM 236200) is a rare metabolic disorder of sulphur metabolism, owing to recessive mutations in cystathionine beta-synthase (*CBS*) on 21q22. Systemic manifestations include mental retardation, hypopigmentation of skin and hair, thromboembolic events, and marfanoid habitus. Ocular manifestations of untreated homocystinuria include myopia and EL.[53,54]

Although congenital vitreoretinopathies commonly cause lenticular changes[55] Knobloch syndrome (OMIM 267750, 608454) (KNO) is the only one in which EL is commonly a feature. This is an autosomal recessive condition first described in 1971,[56] with the cardinal features consisting of high myopia, vitreoretinopathy, and occipital defects. Mutations in *COL18A1* on 21q22.3 are causative of this condition.[57] The encoded protein COL18A1 predominates in basement membranes, including the inner limiting membrane of the neural retina.[58,59] Mutations in this gene therefore understandably contribute towards the preponderance for rhegmatogenous retinal detachment in KNO.
A similar disruption of the basement membrane of the lens capsule, particularly at the insertion of the zonules,

may contribute to EL being the most common further ophthalmic feature of this condition. Very recently, a proband was described with features similar to KNO including EL, smooth irides, high myopia, and cone-rod dystrophy.[60] This patient was found to have a homozygous mutation in *VSX2*, a gene on 14q24.3. Although this protein has a role in retinal development,[61] its potential role in EL is a yet unexplained.

It must be remembered that mutations in *PAX6*, causing aniridia, can also manifest with EL.[62] In addition, it may be expected that pseudoexfoliation and high myopia, both of which are known to manifest weakening of the ZF, may result in EL. However, spontaneous EL has rarely been reported in these conditions. A summary of the genetic aetiology of EL is presented in Table 1.

The continual discovery of genes causing EL has led to the recent interest in the apparent role of the ADAMTS family in ocular disease and development. This is a group of 19 proteases which have roles in ECM degradation, connective tissue structure, cell migration, and angiogenesis.[63] Included in this family are the seven ADAMTS-like proteins that lack the catalytic domain of the ADAMTS family and are thus thought to have a regulatory role of the ADAMTS enzymes.[64] To date four members of this superfamily of genes have been described to cause ocular phenotypes (Table 2), with EL as a common feature. The specific role of the ADAMTS family in ocular development remains to be clarified.

Specific ophthalmic features of the different conditions associated with EL have not been defined. Although superior movement of the crystalline lens has been suggested in MFS[13] and anterior dislocation in homocystinuria,[53] these have not been convincingly replicated. A recently devised clinical grading system[65]

Table 1 Genes confirmed to cause ectopia lentis

Gene	*Inheritance*	*Condition*	*Reference*
FBN1	Autosomal dominant	Marfan syndrome	Dietz *et al* (1991)[73]
		Dominant ectopia lentis	Edwards *et al* (1994)[27]
		Dominant Weill Marchesani Syndrome	Faivre *et al* (2003)[46]
ADAMTSL4	Autosomal recessive	Isolated ectopia lentis	Ahram *et al* (2009)[36]
		Ectopia lentis et pupillae	Christensen *et al* (2010)[41]
		Ectopia lentis and craniosynostosis	Chandra *et al* (2012)[40]
CBS	Autosomal recessive	Homocystinuria	Kraus (1994)[74]
ADAMTS10	Autosomal recessive	Weill Marchesani Syndrome	Daganeau *et al* (2004)[48]
ADAMTS17	Autosomal recessive	Weill Marchesani Like	Morales *et al* (2009)[47]
COL18A1	Autosomal recessive	Knobloch	Sertie *et al* (2000)[57]
PAX6	Autosomal recessive	Aniridia	Jin *et al* (2012)[62]
LTBP2	Autosomal recessive	Weill Marchesani Syndrome	Haji-Seyed-Javadi *et al* (2012)[51]
		Megalocornea, spherophakia	Desir *et al* (2010)[75]
VSX2	Autosomal recessive	High myopia, EL, cone-rod dystrophy	Khan *et al* (2013)[60]

Table 2 Ocular manifestations of recessive mutations in the *ADAMTS* genes

Gene	*Ocular phenotype*	*Reference*
ADAMTSL4	Isolated ectopia lentis (OMIM 225100)	Ahram *et al* (2009)[36]
		Greene *et al* (2010)[37]
		Aragon Martin *et al* (2010)[38]
		Neuhann *et al* (2010)[39]
		Chandra *et al* (2012)[40]
	Ectopia lentis et papillae (OMIM 225200)	Christensen *et al* (2010)[41]
		Chandra *et al* (2012)[40]
		Sharifi *et al* (2013)[42]
	Ectopia lentis and craniosynostosis (OMIM 603595)	Chandra *et al* (2012)[40]
ADAMTS10	Weill-Marchesani (OMIM 277600)	Dagoneau *et al* (2004)[48]
		Kutz *et al* (2008)[76]
		Morales *et al* (2009)[47]
ADAMTS17	Weill-Marcahasni-like (microsherophakia and short stature) (OMIM 613915)	Morales *et al* (2009)[47]
		Khan *et al* (2012)[50]
ADAMTS18	Microcornea, myopic chorioretinal atrophy and telecanthus (MMCAT)	Aldahmesh *et al* (2013)[77]
	Early-onset retinal dystrophy	Peluso *et al* (2013)[78]

may help characterise these features to clarify such suggestions in the future.

Clinical management

Many cases of lens subluxation can be managed without surgical intervention. Appropriate spectacle or contact lens correction will for most individuals provide adequate stable visual acuity.[66] Patients should be counselled that after childhood, lens displacement is very unlikely to progress. Surgery may be indicated where there is progressive lens subluxation, cataract formation, lens instability or less commonly pupil block glaucoma, or retinal detachment. Lens instability can easily be overlooked as patients are frequently unaware that this is the cause of their visual problems.

Subluxed lenses with limited zonular support may in some cases be managed with phacoemulsification surgery, however long-term stability following phacoemulsification has not been consistently reported. Pars plana lensectomy together with vitrectomy has therefore often been utilised to provide stable long-term results. We have previously reported successful outcome from pars plana surgery for subluxed lenses in MFS, initially leaving patients aphakic (many were previous contact lens wearers).[67]

Various options exist for lens replacement following pars lensectomy. Sutured posterior chamber lenses can provide excellent visual results.[68,69] We have documented that late suture breakage (using 10/0 proline) is an important problem using this technique[70] and have therefore moved away from suturing lenses as a technique of choice. Modern designs of anterior chamber lens implant generally have low levels of complications[71] and are suitable for this patient population. Similarly newer designs of iris-supported IOLs[72] and intra-scleral fixation of IOL haptics have been reported with good results recently, although long-term follow-up for these techniques in aphakic eyes has not yet been reported. Currently, there is no consensus on which type of IOL is most suitable for these patients,[71] therefore decisions must be made on individual cases.

Summary

Inherited EL is a condition that may herald numerous syndromes or be isolated. Differentiating these conditions is critical, and this review has summarised some of the important genetic aetiologies involved. Understanding these would help involved ophthalmologists and eye scientists in the crucial role they would have in this process.

Conflict of interest

The authors declare no conflict of interest.

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