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Is ectopia lentis in some cases a mild phenotypic expression of Marfan syndrome? Need for a long-term follow-up

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Purpose: Ectopia lentis (EL) and Marfan syndrome (MFS) are considered two distinct clinical entities. We performed genetic and clinical studies to investigate whether EL is actually distinct from MFS or if it is a mild phenotypic expression of it.

Methods: Seven patients with EL were followed for 5-10 years. Mutation screening analysis of the 65 exons of *FBN1* was performed by polymerase chain reaction (PCR) amplification of genomic DNA, denaturing high pressure liquid chromatography analysis, and direct sequencing of heteroduplexes.

Results: Yearly examinations during the 10 years of follow-up allowed the detection of a late onset of dural ectasia in six out of seven patients (age range: 32-64 years versus 8-55 years in MFS previously reported). We also detected the onset of mild thoracic aortic dilatation in a sporadic case (age 45). Six out of seven index cases of EL turned out to be mild forms of Marfan syndrome with possible late cardiovascular involvement as detected in one case. Four novel missense mutations and one known splicing mutation were detected in five out of seven (71%) patients. Their localization confirmed the presence of a first hot spot within exons 1-15 and suggested the presence of a second one between exons 31-39.

Conclusions: The presence of a second major criterion in six EL patients shifted the clinical diagnosis from EL to MFS. These data demonstrate that some cases, which are initially diagnosed as EL, turn out to be mild Marfan patients. A clinical cardiovascular follow-up is therefore highly recommended for all EL patients since they may develop thoracic aortic aneurysm (TAA) or dissection later in life. Also magnetic resonance imaging (MRI) for dural ectasia (DE) should be performed in a complete follow up for a MFS diagnosis.

Familial ectopia lentis (EL; OMIM 129600) is an inherited connective tissue disorder with a prevalence of 1/100,000 mostly transmitted as a dominant trait. Autosomal recessive cases have also rarely been reported [1,2].

In the literature, few cases are reported as isolated EL [3-6] while the others present mild skeletal features with or without mitral valve prolapse (MVP) or with or without mild nonprogressive aortic root dilatation (NPARD), as reviewed by Ades et al. [7].

Marfan syndrome (MFS; OMIM 154700) is a dominantly inherited connective tissue disorder with a prevalence of 1/5,000-10,000. A major criterion in two organs/systems and the involvement of a third organ/system are required for the clinical diagnosis. Since ectopia lentis is a major criterion for the diagnosis of MFS, a differential diagnosis between the two diseases is necessary. [8,9]

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While EL mainly requires a clinical ocular follow-up, Marfan morbidity and mortality is mainly related to cardiovascular manifestations as thoracic aortic dissections/aneurysms and arrhythmias, which cause sudden death in the young. [10] In 1992, the fibrillin 1 gene (*FBN1*) on chr.15q21.1 was shown to be linked not only to Marfan syndrome but also to ectopia lentis [11], and in 1994, the first mutation was found in a British four-generation family with dominant EL and mild skeletal features: the G7339A nucleotide substitution in exon 59 of *FBN1* causing an E2447K change. [12] Most of the EL mutations are localized in the 5' end of the gene between exons 1 and 15. [13]

The aims of the present study were to investigate if EL is a clinical trait distinct from Marfan syndrome as reported by Ghent's diagnostic criteria [8] or if it represents a mild phenotypic expression (form) of Marfan syndrome characterized by a milder severity and/or later onset and to perform a genotype-phenotype analysis in EL patients.

METHODS

Patients: Among the 300 patients referred to the Regional Center for Marfan Syndrome and Related Disorders, Univer-

sity of Florence-Azienda Ospedaliera Universitaria Careggi-Italy, four families and three sporadic cases with ectopia lentis and mild skeletal and/or cardiovascular manifestations did not meet the MFS clinical criteria [8].

Patients underwent clinical (cardiological, orthopedic, optical, genetic) and radiological examinations (MRI) to search for the presence of dural ectasia (DE) and for its degree of severity (grade 1-3) according to Fattori et al. [14]. Patients underwent a yearly check-up including an eye examination. Echocardiogram was performed once every two to three years. Aortic diameter was evaluated at the sinuses of Valsalva. Aortic dilatation was detected by plotting observed aortic root di-

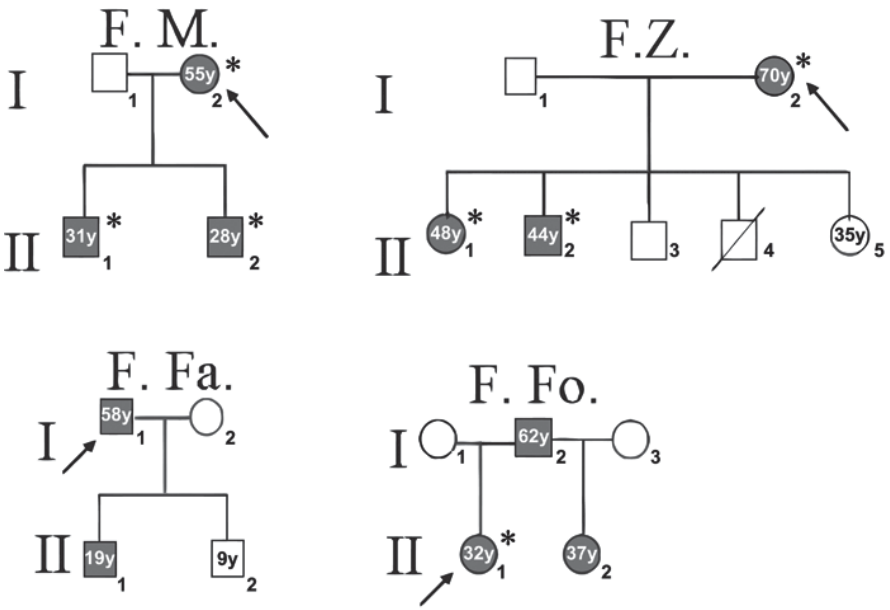

Figure 1. Pedigrees of four families with ectopia lentis. The arrows indicate the proband of each family. Circles indicate female and squares indicate male. Crossed squares mean deceased. Filled symbols mean that the individuals are affected by ectopia lentis. Number inside the symbols is the age of the patient. The asterisk indicates that the individual is carrying the mutation.

Table 1. Clinical and molecular features of patients with ectopia lentis

FEATURES	F.M.			F.Z.			F. Fo.			F.Fa.		CMT	BV	GP
	I-2	II-1	II-2	I-2	II-1	II-2	II-1	I-2	II-2	I-1	II-1			
Age (yrs)	54	31	28	70	48	44	32	62	37	58	19	54	29	47
Familiarity	+	+	+	+										
Follow-up / age range (yrs)	45/54	25/31	22/28	64/70	42/48	38/44	28/32	NP	NP	52/58	13/19	46/54	24/29	42/47
Span:height>1.05	-	-	-	-	-	-	-			+	-	+	-	-
Upper/lower segment	+	-	-	-	-	-	-			+	+	-	+	-
Dolicocephaly	+	-	+	-	-	-	-			-	-	-	-	-
High arched palate/Tooth crowding	+	+	+	-	+	-	-			-	-	+	+	+
Pectus carinatum/excavatum	+	+	+	+	-	-	+			+	-	-	-	-
Scoliosis	+	-	+	-	+	+	+			-	-	+	-	-
Kyphosis	-	+	-	-	-	-	-			+	+	-	-	-
Reduced elbows`extension	+	-	+	-	-	-	-			-	-	-	-	+
Arachnodactyly	-	-	+	-	-	+	-			-	-	-	-	-
Wrist/thumb sign	-	-	-	-	-	+	-			-	-	-	-	+
Pes planus	-	-	-	-	-	-	+			-	-	+	-	-
Joint hypermobility	-	-	-	-	-	-	-			-	+		-	-
Striae	-	+	+	-	+	+	+			-	-	+	+	+
Inguinal hernia	-	+	-	-	-	-	-			-	-	-	-	-
Aortic dilatation	-	-	-	-	-	-	-			-	-	-	-	+
Aortic diameter* cm (2004)	NPe	NPe	NPe	NPe	NPe	3.50	3.30			3.30	NPe	NPe	NPe	3.50
Aortic diameter* cm (2006)	3.70	3.30	3.9	3.70	3.30	3.60	3.58			3.60	3.00	3.20	3.50	3.70
BSA; m^2 (2004)	NPe	NPe	NPe	NPe	NPe	2.03	1.81			2.06	NPe	NPe	NPe	1.44
BSA; m^2 (2006)	2:22	2.31	2.53	1.87	1.85	2.03	1.77			2.01	1.81	1.82	1.73	1.48
AO/BSA; cm/m^2 (2004)	NPe	NPe	NPe	NPe	NPe	1.50	1.80			1.60	NPe	NPe	NPe	2.4
AO/BSA; cm/m^2 (2006)	1.66	1.4	1.56	1.90	1.87	1.70	2.02			1.70	1.65	1.70	2.02	2.5
Mitral valve prolapse/regurgitation	-	-	+	-	-	+	+			-	-	+	+	+
Tricuspid valve regurgitation	-	+	-	-	-	-	+			-	-	-	-	-
Myopia	-	+	-	+	+	+	+	-	-	+	+	+	-	-
Retinal detachment	-	-	-	-	-	-	+	+	-	+	-	-	-	-
Dural ectasia	+	-	-	+	+	+	+	-	-	+	-	+	-	+
Age onset Dural ectasia	50yrs			64yrs	48yrs	44yrs	40yrs			58yrs		52yrs		45yrs
FBN1 mutation Exon	IVS35			Ex 14			Ex 36			ND		ND	Ex 33	Ex39
cDNA	c.4459_4460insTTTTAG			c.1766A>G			c.4577G>C						c.4145A>T	c.4336T>C
Protein	p. Thr1486_Asp1487insValLeu			p.Asn589Ser			p.Cys1526Ser						p.Asn1382Ile	p.Cys1646Arg

The table displays all the EL/Marfan syndrome signs present in our patients, except for ectopia lentis. In the first row: "F" is the abbreviation of "Family" followed by two letters corresponding to the initials of the last and the first name. In the second row the numbers correspond to propositi and relatives as reported in the pedigrees (Figure 1). *FBN1* gene and protein mutations are reported in the last row.

ameter versus body surface area on previously published normograms [15]. MRI for DE was performed once every three to five years for a total of 10 years.

Biochemical analysis was performed to exclude homocystinuria [8] and genetic analysis to search for mutations in *FBN1*. All subjects gave their informed consent, and the study was approved by the local ethics committee and complies with the Declaration of Helsinki.

Procedures: Mutation screening analysis was performed on genomic DNA by polymerase chain reaction (PCR) amplification of each single exon of the 65 exons of *FBN1* containing the intron flanking sequences important for splicing by using synthetic oligonucleotides [16] with slight modifications [17], heteroduplex analysis of the amplified PCR DNA fragments by D-HPLC, and direct sequencing of heteroduplexes as described [18].

One mutation was further analyzed by seeding dermal fibroblasts obtained from skin biopsy as described [19]. Total RNA was extracted from confluent cells using RNeasy mini-Kit (Qiagen, Hilden, Germany) and subjected to reverse transcriptase to obtain a cDNA that was amplified in overlapping fragments by PCR amplification with the following oligonucleotides: CF 8S 5'-ACT GTG ATA TGG GCT ACT CC-3' and CF 8AS 5'-CCT GGA GTG TTG ACA CAG TT-3' [20].

The amplified fragment was directly sequenced using the same oligonucleotides used as primers for the PCR.

RESULTS

The detailed clinical and molecular features of four familial pedigrees, shown in Figure 1, and three sporadic cases are reported in Table 1 for 12 out of 14 patients and affected relatives (Family Fo. I-2 and II-2, affected by ectopia lentis, refused to come to our Centre). A clinical 5-10 year follow-up was performed for each patient.

Clinical features: The common clinical feature of all patients (eight females and six males) is the presence of ectopia lentis with an onset ranging between 2 and 52 years. Five index cases underwent eye surgery, one at the age of 11 and four between age 23-45. Three patients had retinal detachment. Three patients presented only skeletal manifestations while the others had two to four features among skeletal, cardiovascular, ocular, and skin features (Table 1) [7]. Patient F.Fa. II-2 was negative for all major criteria at the age of nine (Figure 1). Homocystinuria was excluded in all the probands and their affected relatives.

Genetic analysis: FBN1 genomic DNA mutation screening analysis allowed the detection of five novel mutations: four missense and one splicing mutations.

Family M. I-2 and her two sons (II-1 and II-2) carry a G>A substitution at nucleotide (nt) 8 in IVS35 causing the activation of a cryptic acceptor splice site with an insertion of 6 intronic nts in exon 36 cDNA (c.4459_4460insTTTTAG). The mutation caused an inframe insertion of two amino acids

Table 2. Marfan major clinical criteria onset in EL/Mild form of Marfan syndrome versus classic Marfan

A

		EL onset (yrs)	EL surgery (yrs)	Other manifestations	DE onset (yrs)	years §	TA dilat/aneurysm onset (yrs)
F.M.	**I-2**	3	11	ske	50	47	
	II-1	5	15	ske+sk+CVS			
	II-2	5	15	ske+sk+CVS			
F.Z.	**I-2**	6		ske	64	58	
	II-1	38		ske+sk+CVS	48	10	
	II-2	42		ske+sk	44	2	
F.Fo	**II-1**	8		ske+sk+CVS	40	32	
F.Fa	**I-1**	22	45	ske	58	36	
	II-1	25		ske+CVS+laxity			
CMT	**II-2**	3	32	ske+sk+CVS	52	49	
BV	**II-1**	7	23	ske+sk+CVS			
GP	**II-1**	5	42	ske+sk+CVS	45	40	47

B

	DE onset (yrs)	TA dilat/aneurysm onset (yrs)
EL/mild MFS	DE 40-64 Grade I	45
Classic MFS	DE 8-55 * Grade1(20 %)-3	Birth-50 **

A displays the major criteria onset in patients with EL/mild form of Marfan syndrome. **B** displays DE and TA dilatation in patients with EL/mild form of Marfan syndrome in contrast to classic Marfan syndrome.

(aas) inside the protein (p.Thr1486_Asp1487insValLeu). Sequence analysis of reverse-transcriptase polymerase chain reaction (RT-PCR) products confirmed the inframe insertion.

Mutation analysis in families Z. and Fo., and sporadic cases (BV and GP), revealed four missense mutations all affecting conserved amino acids in cbEGF-like repeats: two out of four involved cysteine residues (p.Cys1526Ser, c.4577A>G and p.Cys1646Arg, c.4336T>C) and the other two involved asparagine residues (p.Asn589Ser, c.1766A>G and p.Asn1382Ile, c.4145A>T). In F.Z. the mutation was present in I-2, II-1, and II-2 and absent in II-5 (Figure 1), the healthy son carrying only mild scoliosis and myopia. One hundred controls analyzed did not carry any of the five mutations described above (data not shown). No mutation in *FBN1* was detected in patients F.Fa. I-1 and CMT (Table 1).

Clinical follow-up: In the MRI imaging analysis, 8 out of 12 patients, who underwent follow up, displayed the presence of dural ectasia (DE) grade 1 (Table 1). In our patients, DE developed after 2-58 years from the initial EL diagnosis [14]. In patient BV, dural ectasia was absent in 2001 and 2006.

Echocardiogram was performed once every two years. The thoracic aortic diameters resulted to be normal except for patient GP in whom we detected an initial thoracic aorta enlargement (at Valsalva Sinus) at the age of 45. A slight increase (0.2 mm) of the aortic diameter always within a normal range was found in patients F.Z. II-2 and F.Fa. I-1 (Table 1).

Patient F.Fa. II-1 displayed a mild bilateral lens subluxation in 2006 at the first examination. Since F.Fa I-1 displayed ED according to Ghent's diagnostic criteria, [8] we diagnosed both son II-1 and the father I-1 as Marfan syndrome (Table 1).

DISCUSSION

EL is considered a relatively mild disorder. An early diagnosis and a correct follow-up can avoid the risk of blindness. On the other hand, Marfan syndrome is a multisystemic disorder, which presents more than 80% of patients with cardiovascular involvement, thoracic aortic aneurysms/dissections, heart valves alterations, and arrhythmias,[10] causing increased morbidity and mortality. For this reason, it requires an accurate follow-up and prevention in younger generations of familial cases.

According to world panel experts, whose last report was presented in the Ghent nosology [8] and confirmed in recent reviews [9,21], EL is still considered a clinical entity distinct from Marfan syndrome. Nevertheless, the presence of dural ectasia would shift an ectopia lentis diagnosis into a Marfan syndrome. The hypothesis that EL is not a distinct clinical entity was proposed by others [7] but never investigated. Our

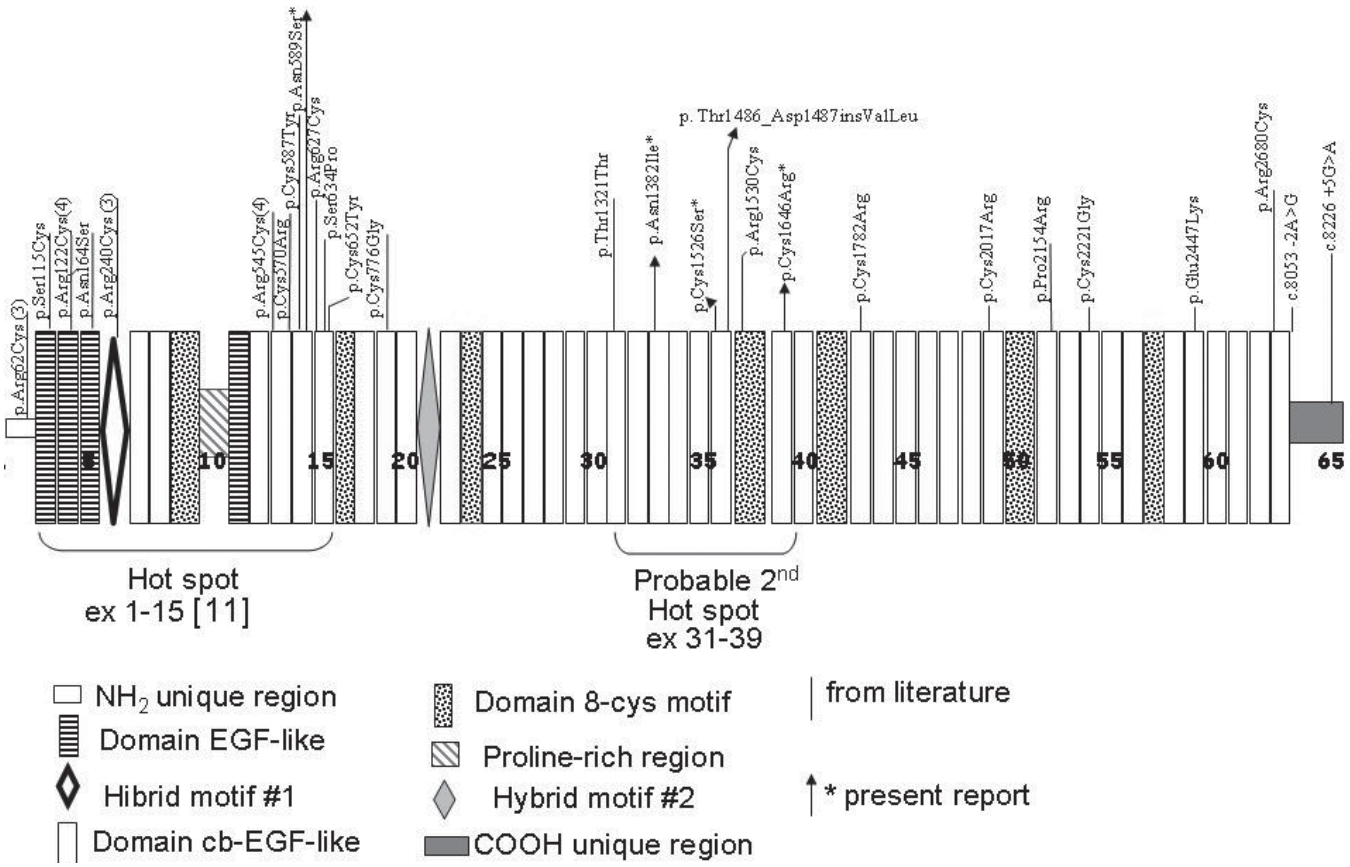

Figure 2. Distribution of fibrillin 1 mutations in patients with ectopia lentis/mild form of Marfan syndrome. Schematic representation of the protein domains. The numbers in bold correspond to *FBN1* exons. Most mutations detected in EL/mild form of MFS appear to cluster in two hot spots.

study by means of a long-term follow-up (mean range 8±2 years) needed to detect the late onset of central nervous system and cardiovascular system manifestations in our patients. Due to the fact that MRI has only recently become part of routine imaging analyses, the long-term follow-up allowed us to demonstrate that in some cases EL is a mild phenotypic expression of MFS.

At present, only patient BV (29 years) does not show other major criteria of Marfan syndrome. Noteworthy, the age of BV is lower than the age range at which the other patients displayed the onset of dural ectasia or aortic dilatation (Table 2). Moreover, some of our patients seem to be developing dural ectasia grade 1 and aortic dilatation at a later age (32-64 years) than that of patients with classic Marfan syndrome. According to what has previously been reported, only 20% of Marfan patients present dural ectasia grade 1, the remaining 80% has more severe manifestation (60% grade 2 and 20% grade 3; Table 2) [14]. GP also developed initial thoracic aortic dilatation at age 45, which is later than the usual age-range in Marfan patients (Table 2) [22]. F.Fa. I-1 (58 years) and F.Z. II-2 (44 years) showed a slight increase in aortic diameter although it was still within the normal range (Table 1).

Mutations in *FBN1* were detected in five out of seven patients. They are four novel missense mutations and one splicing mutation already reported in a patient with classic Marfan syndrome [23]. Only one of the missense mutations is inside exons 1-15, the hot spot area of *FBN1* where 10 out of 11 mutations affecting patients with ectopia lentis were reported (Figure 2) [13]. The other four mutations detected in the present study are located between exons 33 and 39. Another mutation in EL patient was reported in exon 31 [13]. We believe that the group of mutations between exons 31 and 39 may represent a second hot spot area (Figure 2). In an attempt to perform genotype-phenotype correlation in our patients, the only two cysteine substitutions in two cbEGF-like domains (exons 36 and 39) seem to correlate to a more severe phenotype with the two patients presenting an earlier onset of DE and the onset of aortic dilatation in one of them. The arginine substitution (the most frequent amino acid mutated in EL) in exon 14 (Figure 2) correlates instead with the mildest phenotype (Table 2). Both the type of amino acid mutated and its domain localization probably influence the severity of the phenotype expression.

Here, we demonstrate that six out of seven (86%) patients with ectopia lentis are affected by a milder form of Marfan syndrome that causes the development of dural ectasia and aortic dilatation later in life. This is also in agreement with the fact that mutations in the same gene are associated with both diseases [8] and with the presence of a continuum clinical phenotype already reported for other inherited connective tissue disorders[24]. Alternatively, it may be that both of these disorders present dural ectasia but differentiate in that there is a severe and rapid progression of aortic dilatation in MFS and a slight progression or stability in EL. For the first time, our data provide a significant clinical clue on long-term follow-up of the disease, specifically for cardiovascular manifestations. In fact, monitoring patients affected by ectopia lentis may save them from sudden death from aneurysms or dissections or heart valve problems due to aging. Moreover, patients who develop cardiovascular manifestations such as atherosclerosis, which also affect vessels with aging, will predispose them to abdominal aortic aneuryms due to the altered structure of the vessel walls.

Overall, these data suggest that EL and MFS represent a continuum clinical phenotype, and we speculate that in the near future, other disorders in differential diagnosis with Marfan syndrome and due to mutations in *FBN1* could turn out to represent mild or variant forms of Marfan syndrome.

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