


RESEARCH ARTICLE

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Next-generation sequencing reveals a new mutation in the *LTBP2* gene associated with microspherophakia in a Spanish family

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Abstract

Background: Microspherophakia is a rare autosomal recessive eye disorder characterized by small spherical lens. It may present as an isolated finding or in association with other ocular and/or systemic disorders. This clinical and genetic heterogeneity requires the study of large genes (*ADAMTSL4*, *FBN1*, *LTBP2*, *ADAMTSL-10* and *ADAMTSL17*). The purpose of the present study is to identify the genetic cause of this pathology in a consanguineous Spanish family.

Methods: A clinical exome sequencing experiment was executed by the *TruSight One® Sequencing Panel* (TSO) from Illumina©. Sanger sequencing was used to validate the NGS results.

Results: Only the insertion of an adenine in exon 36 of the *LTBP2* gene (c.5439_5440insA) was associated with pathogenicity. This new mutation was validated by Sanger sequencing and segregation analysis was also performed. Haplotype analyses using the polymorphic markers *D14S1025*, *D14S43* and *D14S999* close to the *LTBP2* gene indicated identity by descent in this family.

Conclusion: We describe the first case of a microspherophakia phenotype associated with a novel homozygous mutation in the *LTBP2* gene in a consanguineous Caucasian family by means of NGS technology.

Keywords: Microspherophakia, *LTBP2* gene, NGS, Clinical exome sequencing, TruSight one sequencing panel

Background

Microspherophakia (MSP, OMIM 251750) is a rare autosomal recessive (AR) eye disorder characterized by small spherical lens. It may present either as an isolated finding or in association with other ocular anomalies such as megalocornea, ectopia lentis and secondary glaucoma, or with hereditary systemic disorders such as Marfan syndrome and Weill-Marchesani syndrome. These two latter conditions are caused by mutations in the *FBN1* gene, whose protein product fibrillin-1 (FBN1) is a major structural component of the microfibrils. Three additional genes of the *ADAMTS* family (4, 10 and 17) have been associated with some of these conditions, from isolated ectopia lentis to Weill-Marchesani syndrome. In patients

with microspherophakia or other ocular anomalies, such as megalocornea, myopia, congenital primary glaucoma or secondary glaucoma, mutations have been found in the *LTBP2* gene. Isolated microspherophakia (IM), without any other ocular feature, has been recently been linked to the *LTBP2* gene [1]. This latent transforming growth factor beta binding protein 2 (*LTBP2*) gene is considered one of the major known causative genes for MSP.

The *FBN1* gene, with 65 exons extending over 200 kb of genomic DNA, codes for the main protein of extracellular microfibrils: Fibrillin-1. It is an extracellular matrix glycoprotein that serves as a structural component of calcium-binding microfibrils. These microfibrils provide force-bearing structural support in connective tissue. The *LTBP2* gene, 114 kb long and organized into 22 exons, is the largest member of the *LTBP* family. The coded protein shows strong structural homologues with the fibrillins. Because the C-terminal region of the *LTBP2* protein specifically binds to the N-terminal

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region of fibrillin-1, this protein may have a structural role in elastic-fiber architectural organization for LTBP2 [2]. The *ADAMTSL4* gene (22 exons/10 Kb of genomic DNA) [3], the *ADAMTSL10* gene (26 exons/30 Kb of genomic DNA) [4] and the *ADAMTSL17* gene (24 exons /370Kb) [5] belong to a family of extracellular matrix proteases. It has been postulated that these proteins play either a structural or a regulatory role in the microfibrillar network [6].

The present work describes for the first time the association of a mutation in the *LTBP2* gene (c.5439_5440insA) with an isolated microspherophakia phenotype in a consanguineous Caucasian family.

Methods

Clinical evaluation

We studied two siblings from a consanguineous Spanish family with microspherophakia (MSP) (Fig. 1). Both patients underwent a complete ophthalmic and systemic workup, including eco-cardiography and homocystinuria screening. Neither had any cardiovascular, metabolic or musculo skeletal abnormalities.

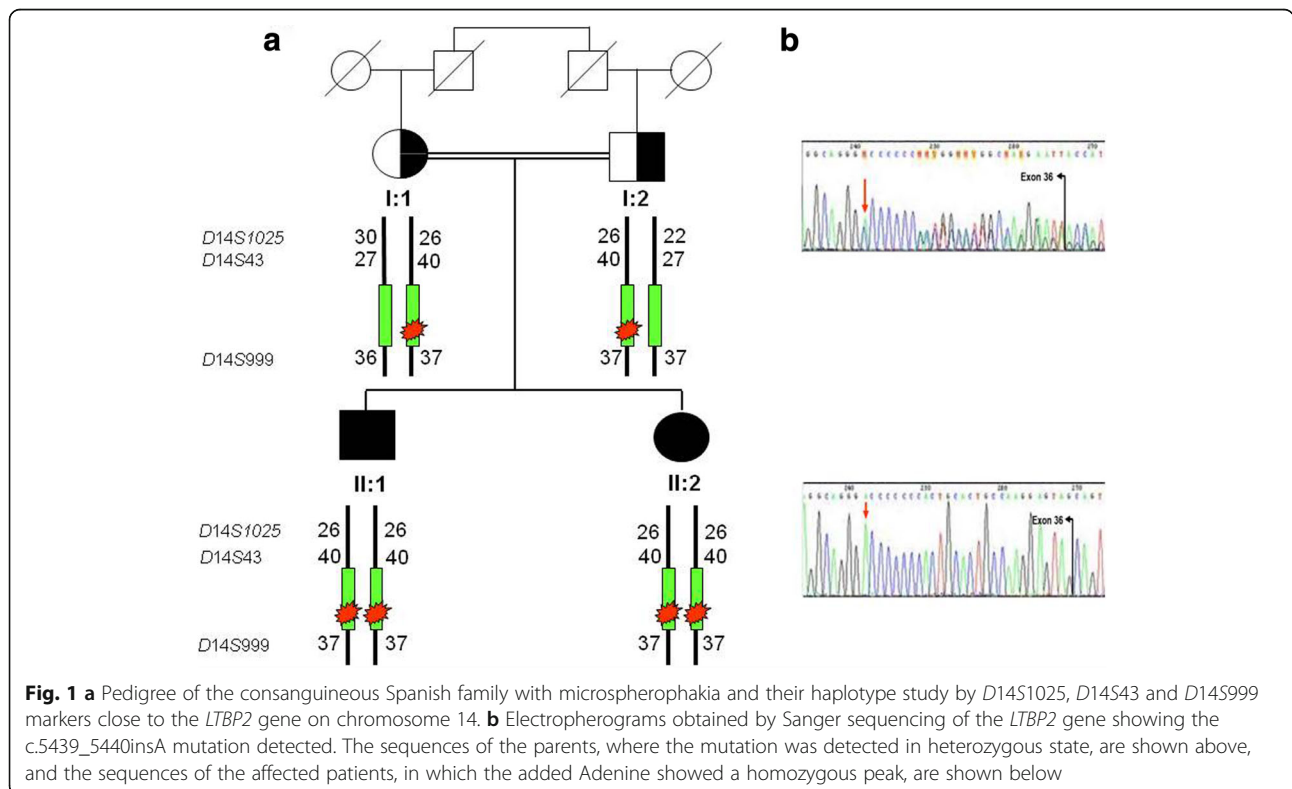
Bilateral slit lamp biomicroscopy, intraocular pressure (IOP) measurement with Goldmann applanation tonometer, gonioscopy and fundus examination (through a dilated pupil and using +90D Volk lens) were performed. In both siblings, the slit-lamp biomicroscopy revealed that lenses were smaller and more spherical than normal (MSP). The

absence of enlarged cornea, buphthalmos, abnormal angle structures or increased IOP excluded primary congenital glaucoma. The diagnosis of isolated MSP was confirmed by ultrasound biomicroscopy (UBM, Sonomed Inc., New York, USA).

Genetic studies

Genomic DNA was automatically extracted from peripheral leukocytes using the salting out procedure (Autopure, Qiagen). To screen for the presence of mutations in the *ADAMTSL4* gene, we sequenced all 20 exons and exon-intron boundaries of the gene (BigDye v1.1 Terminator Reaction Kit on an ABI Prism [®] 3500 Dx Capillary DNA Sequencer unit according to manufacturer’s protocol, Life Technologies Corporation). The sequences of primers, annealing temperatures and PCR conditions were adapted from the literature [7].

To perform NGS analyses we used a clinical exome sequencing panel called *TruSight One[®] Sequencing Panel* (TSO) from Illumina[®]. This panel focuses on exonic regions harboring 4813 disease-causing variants. We included all genes that have been associated to date to isolated ectopia lentis (*ADAMTSL4*, *FBN1*, *LTBP2*, *ADAMTSL10*, *ADAMTSL17*) in the clinical exome panel. Amplified samples following the TSO protocol were loaded onto the MiSeq instrument according to the manufacturer’s instructions (Illumina[®]). VariantStudio software[®] (Illumina[®]) allowed us to analyze the files



from the experiment. Sanger sequencing was used to validate the NGS results.

To investigate whether IBD (identity by descent) occurs in the studied family, we performed haplotype analysis of the region containing the *LTBP2* gene. We studied three polymorphic markers (*D14S1025*, *D14S43* and *D14S999*) located on the 5' up-stream region of the gene. The fragments amplified by dye-labelled primers of the *D14S1025*, *D14S43* and *D14S999* markers were analyzed on an ABI Prism® 3500 Dx Capillary DNA Sequencer (Life Technologies Corporation®). Genotypes were determined using the GeneScan® software package (Perkin Elmer-Applied Biosystems®).

All mutations and genetic variants were numbered according to the first translated base of the sequenced genes (GenBank entry NT_006713) and variant sequences were designated according to standard nomenclature guidelines [8].

In silico studies

To investigate the functional impact of the genomic variations found in the present study, we used the ALAMUT® VISUAL software. This software uses the following relevant prediction tools: i) Splice Site Finder-like, MaxEntScan, NNSPLICE, GeneSplicer, Human Splicing Finder and ESE for splicing prediction ii) Align GVGD, SIFT, MutationTaster, PolyPhen-2 and KD4v for missense prediction.

To check all the variants detected in this study the ExAc, the 1000 Genomes Project and the CSVS (Collaborative Spanish Variant Server) databases were consulted.

Results

Clinical results

Figure 1 shows the pedigree of the family studied. Patient II:1 was a 42-year-old man who was referred to our department for progressive visual loss and high lenticular myopia. His medical history was unremarkable. Visual acuity was 20/50 in both eyes. Refractive error was $-22.00/-0.75 \times 78^0$ (OD) and $-21.00/-0.50 \times 100^0$ (OS).

Intraocular pressure was 19 mmHg and 20 mmHg in OD and OS, respectively. Gonioscopy examination showed open angle grade IV 360°. Ophthalmic examination findings were compatible with MSP. The lens had a central nuclear cataract with notable phacodonesis but without subluxation in either eye (Fig. 2). Ultrasound biomicroscopy showed that the equatorial lens diameter was small with an increased antero-posterior diameter, consistent with microspherophakia. UBM also detected the presence of missing and stretched zonular fibers which were compatible with clinical phacodonesis (Fig. 3). A fundoscopic exam showed that optic disk appearance was normal and no pathology was observed. The patient underwent bilateral lensectomy with posterior iris claw intraocular lens implantation that restored vision to 20/20 in both eyes.

Patient II:2 was an asymptomatic 39-year-old woman and the proband's younger sister. Her visual acuity was normal and IOP was 18 mmHg in both eyes. Gonioscopy examination showed open angle grade IV bilaterally. The ophthalmic examination showed microspherophakia without cataracts or lens dislocation. The fundoscopic exam of the posterior segment was unremarkable and the cup-disk ratio was within normal limits in both eyes.

Genetic results

Taking into account that the *ADAMTSL4* gene is considered responsible for most cases of isolated ectopia lentis in the European population [9], we started the present study by sequencing all 20 exons and exon-intron boundaries of this gene. We identified several variants from the reference sequence (Table 1), but none met the requirements to be considered as the molecular cause of the disease in the consanguineous family studied.

All the genes associated with ectopia lentis phenotypes to date, (*ADAMTSL4*, *FBN1*, *LTBP2*, *ADAMTSL10*, *ADAMTSL17*) included in the clinical exome employed, revealed several genetic variants in these genes. We analyzed their sequences using VariantStudio software.

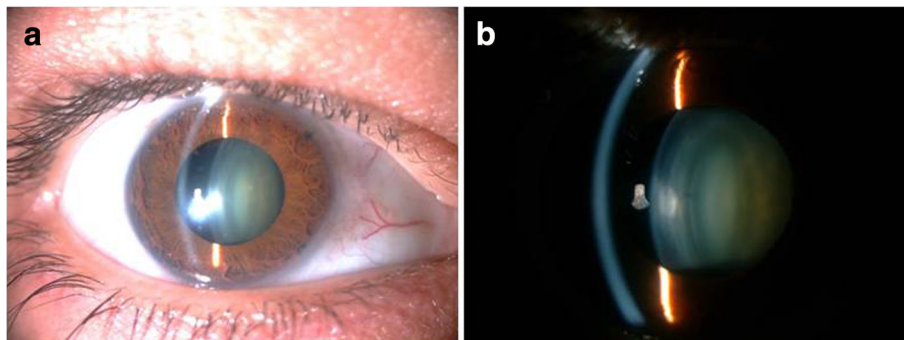


Fig. 2 a Slit lamp photography. b A left eye section performed in patient II:1. shows a small nuclear cataract. The lens is small in diameter and spherical in shape

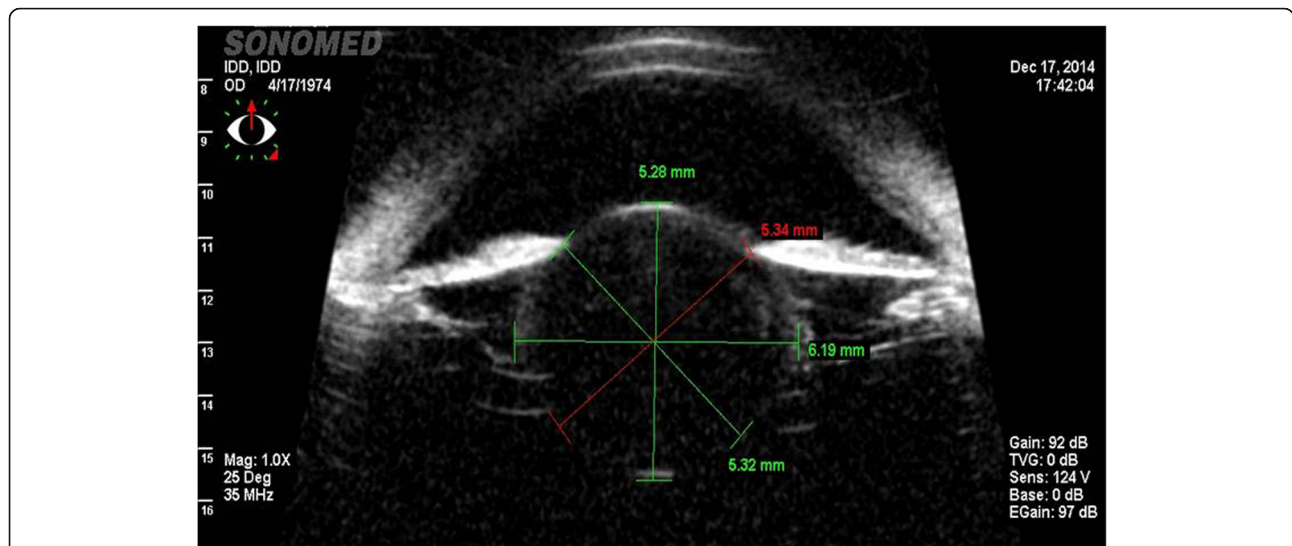


Fig. 3 Ultrasound biomicroscopy performed in patient II:1. The analysis showed a thickness of 5,32 mm (OD) and 5,35 mm (OS), respectively, and evidence of missing and stretched zonular fibres

Two different filters were applied to the NGS panel: a) genetic variants detected in the genes described in the literature causing isolated ectopia lentis; and b) genetic variants detected in any of the 4813 genes analyzed by the panel causing a frameshift or a nonsense mutation. Table 2 shows the genetic variants identified. Only one of them has been associated with a pathogenic effect; the insertion of an adenine in the g.74967613 position of the chromosome 14 (NM_000428: c.5439_5440insA)

would cause the appearance of a premature stop codon 30 aminoacids later (p.Pro1814ThrfsX30). This frameshift mutation (c.5439_5440insA) in the *LTBP2* gene has not been previously reported.

The presence of the c.5439_5440insA mutation in exon 36 of the *LTBP2* gene was identified in all four family members by Sanger sequencing. As expected, the two patients were homozygous for the mutation while their parents showed this mutation in a heterozygous

Table 1 *ADAMTSL4* genetic variants detected in the IEL patients by Sanger sequencing of this gene

	Exon/Intron	DNA variant	cDNA	Protein	SNP	MAF	State
Patient 1	exon 6	g.150526044 G > C	c.577G > C	p.Ala193Pro	rs41317515	0,443	Het
	intron 8	g.150527292 G > A	c.1303 + 182G > A		rs9659061	0,452	Het
	intron 8	g.150527294 C > T	c.1303 + 184C > T		rs12124948	0,338	Het
	intron 8	g.150527703_150527704 ins TCAT	c.1304-202_1304-201insTCAT				Het
	intron 11	g.150529323_150529324 ins TT	c.1818 + 54_1818 + 55insTT				Het
	exon 16	g.150558532 T > C	c.2511 T > C	p.Asn837Asn	rs1088382	0,156	Hom
	exon 16	g.150558574 G > A	c.2553G > A	p.Pro851Pro	rs10749657	0,118	Het
Patient 2	intron 16	g.150558694 C > T	c.2628 + 45C > T		rs10749658	0,065	Hom
	exon 6	g.150526044 G > C	c.577G > C	p.Ala193Pro	rs41317515	0,443	Het
	intron 8	g.150527292 G > A	c.1303 + 182G > A		rs9659061	0,452	Het
	intron 8	g.150527294 C > T	c.1303 + 184C > T		rs12124948	0,338	Het
	intron 8	g.150527703_150527704insTCAT	c.1304-202_1304-201insTCAT				Het
	intron 11	g.150529323_150529324insTT	c.1818 + 54_1818 + 55insTT				Het
	exon 16	g.150558532 T > C	c.2511 T > C	p.Asn837Asn	rs1088382	0,156	Hom
	exon 16	g.150558574 G > A	c.2553G > A	p.Pro851Pro	rs10749657	0,118	Het
	intron 16	g.150558694 C > T	c.2628 + 45C > T		rs10749658	0,065	Hom
	intron 16	g.150531380 T > C	c.2629-58 T > C		rs11204664	0,452	Het

Het Heterozygous state, Hom Homozygous state

Table 2 Results of the analyses of the TruSight One Panel using VariantStudio software

Gene	Quality	Variant	Chr	Genotype	HGVSc	Alt Variant Freq	Consequence	Allele Freq Global Minor	SIFT	Polyphen
ADAMTS17	64313	G>G/A	15	het	NM_139057.2:c.1875C>T	44,1	Synonymous_variant	0,69		
ADAMTS17	147285	T>G/G	15	hom	NM_139057.2:c.1696A>C	100	Synonymous_variant	0,37		
ADAMTS17	93299	A>A/G	15	het	NM_139057.2:c.1445T>C	55,1	Missense_variant	13,23	Tolerated (0,71)	Benign (0)
ADAMTS17	131323	C>T/T	15	hom	NM_139057.2:c.1053G>A	100	Synonymous_variant	21,38		
ADAMTS17	71773	G>A/A	15	hom	NM_139057.2:c.1017C>T	100	Synonymous_variant	34,2		
ADAMTS17	147995	G>A/A	15	hom	NM_139057.2:c.718+8C>T	100	Splice_region_variant; intron_variant	29,03		
ADAMTS17	146211	G>A/A	15	hom	NM_139057.2:c.756C>T	100	Synonymous_variant	44,87		
ADAMTS17	200582	G>A/A	15	hom	NM_139057.2:c.647C>T	100	Missense_variant	43,86	Tolerated (0,32)	Benign (0,066)
ADAMTSL4	196134	G>G/C	1	het	NM_019032.4:c.577G>C	52,3	Missense_variant	44,28	Tolerated (0,53)	Benign (0)
ADAMTSL4	105948	T>C/C	1	hom	NM_019032.4:c.2442T>C	100	Synonymous_variant	15,57		
ADAMTSL4	73613	G>G/A	1	het	NM_019032.4:c.2484G>A	63,6	Synonymous_variant	11,77		
ADAMTSL4	123578	C>T/T	1	hom	NM_019032.4:c.2559+45C>T	100	Intron_variant	6,5		
FBN1	171496	C>T/T	15	hom	NM_000138.4:c.1415G>A	100	missense_variant	0		
FBN1	810	T>T/G	15	het	NM_000138.4:c.1293A>C	19	synonymous_variant	0		
LTBP2	239973	G>GT/GT	14	hom	NM_00428.2:c.5439_5440insA	98,2	Frameshift_variant	0		
LTBP2	58188	A>G/G	14	hom	NM_00428.2:c.2502T>C	100	Synonymous_variant	28,71		

Genetic variants detected in the genes described in the literature as responsible for the IEL disease (*ADAMTSL4*, *FBN1*, *LTBP2*, *ADAMTS10*, *ADAMTS17*) with a missense, a frameshift or a nonsense mutation. The frameshift c.5439_5440insA mutation in exon 36 of the *LTBP2* gene, reported for the first time in this work, is indicated in red. In the "Genotype" column: Hom should read homozygous and Het should read heterozygous

state. The study of the polymorphic markers (*D14S1025*, *D14S43* and *D14S999*) located next to the *LTBP2* gene demonstrated that identity by descent (IBD) occurred in this family (Fig. 1).

Finally, we ruled out the presence of the c.5439_5440insA mutation in DNA samples of a Spanish control population ($n = 100$ blood donors) by Sanger Sequencing. Furthermore, c.5439_5440insA had not been previously reported in the ExAc, the 1000 Genomes Project or the CSVS databases.

Discussion

The present work reports the clinical and genetic study of a Spanish consanguineous family with two cases of isolated microspherophakia. We identified the presence of a novel mutation in the *LTBP2* gene: c.5439_5440insA in the two affected siblings. A mutation in this gene causing isolated microspherophakia in Caucasian patients has not been reported previously.

The latest technological advances allow us to obtain NGS results of thousands of unrelated individuals. There are several databases that include the results of many different projects. All this information has allowed us to obtain an amazing statistical power, especially in the research on rare diseases. We have checked that the c.5439_5440insA mutation has not been reported in any of the databases consulted (ExAc, 1000 Genomes Project or CSVS). Thus, the presence of this mutation was not only excluded in the 100 control individuals sequenced

during this study, but we were also able to exclude it in more than 67,000 unrelated individuals from the ExAc database (which includes the results of the 1000 genomes project) and in more than 1582 unrelated Spanish individuals from CSVS.

To date, mutations in the *LTBP2* gene have been associated with several types of glaucoma. In primary congenital glaucoma (PCG), null mutations in *LTBP2* were reported in four consanguineous families of Gypsy ethnicity from Pakistan [2], in three unrelated Iranian families [10], and, more recently, two novel mutations in consanguineous families of Pakistani ancestry were identified using WES [11]. In primary open angle glaucoma, five putative disease-contributing or risk factor mutations in *LTBP2* were observed in 42 Iranian patients [12]. All these findings will contribute to the understanding of the genotype-phenotype correlation in patients with *LTBP2* mutations.

Recently, in three consanguineous Saudi families with congenital megalocornea with zonular weakness and childhood lens-related secondary glaucoma it was found that ocular anomaly segregated with homozygous *LTBP2* mutations [13]. In two families of Moroccan and Macedonian descent, biallelic null *LTBP2* mutations were identified in patients with megalocornea, spherophakia, and secondary glaucoma [14].

Involvement of *LTBP2* mutations in hereditary systemic disorders, such as Marfan or Weill-Marchesani syndromes, has also been studied. In a meeting abstract, Mathews et al. reported a missense mutation in the *LTBP2* gene in a

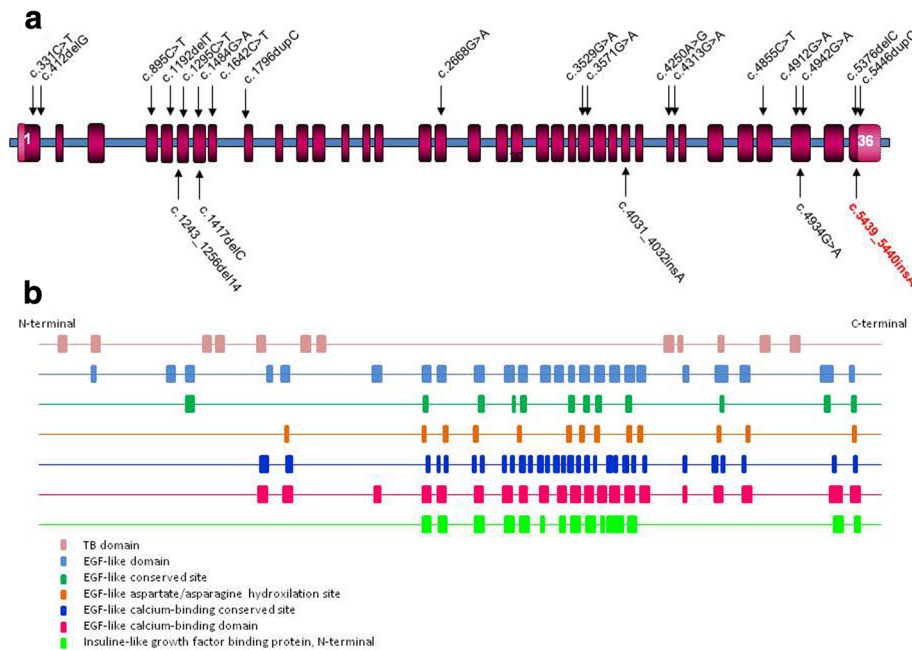


Fig. 4 **a** Schematic representation of the mutations reported along the *LTBP2* gene. The novel c.5439_5440insA mutation in exon 36 at the end of this gene is shown in red. **b** Schematic representation of the functional domains in the *LTBP2* protein

patient with an atypical MFS. More recently, in their study of Iranian patients, Haji-Seyed-Javadi et al. showed that *LTBP2* is a causative gene for Weill-Marchesani syndrome and suggested it plays a role in some clinical features observed in Marfan syndrome patients [15].

Figure 4 schematizes the location of all the *LTBP2* mutations published. The correlation between the localization of the mutations and their clinical manifestations has not yet been clearly established. However, it is reasonable to speculate with the intervention of regulatory sequences or other genes with a phenotype-modifying effect, especially

in those syndromic phenotype diseases. Nonetheless, the two mutations associated only with microspherophakia, c.5446dupC and c.5439_5440insA are located in the last exon of the *LTBP2* gene. In silico studies predict that both frameshift mutations would elongate their respective mutant proteins, producing changes in the amino acid composition of the C-terminal domain of the native protein. Because the interaction between the *LTBP2* and the Fibrillin-1 proteins is close to this *LTBP2* C-terminal region, we could speculate that the instability of the zonular fibers characteristic in microspherophakia is due to the

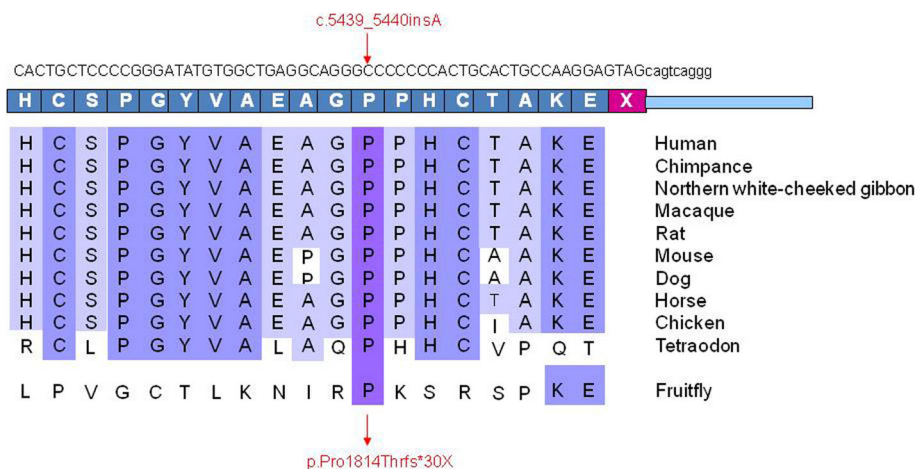


Fig. 5 Conservation analysis across the species of a fragment from exon 36 of the *LTBP2* gene where the c.5439_5440insA mutation is located. The genetic region that encompasses the altered amino acid remains highly conserved between species

loss of the association between these two proteins. It has been postulated that the LTBP2 interaction with some members of the TGF-beta family could regulate microfibril storage in the extracellular matrix. An altered regulation due to the presence of an abnormal LTBP2 protein might thus prevent normal growth of the lenses, characteristic of the microspherophakia phenotype [12]. Furthermore, the alignment of the sequences from different species depicted in Fig. 5 shows that the c.5439_5440insA mutation is located in highly conserved residues, indicating its importance for the functionality of the LTBP2 protein.

All previously known cases with mutations in the *LTBP2* gene were of Arab ethnicity. The present work describes an isolated microspherophakia phenotype due to a new homozygous mutation in the *LTBP2* gene in a Spanish consanguineous family. These new data highlight the value of investigating the involvement of the *LTBP2* gene in cases with an isolated microspherophakia phenotype.

The present work reinforces the fact that the new technologies of exome sequencing are becoming a common molecular diagnostic test for rare genetic disorders. Indeed, clinical exome sequencing proved to be an effective tool to identify the causative mutation in the family studied.

Conclusions

We describe a consanguineous Caucasian family showing a microspherophakia phenotype. Next-generation sequencing detected a homozygous novel frameshift mutation in the *LTBP2* gene present in the two affected patients. This is the first report of the association of a mutation in the *LTBP2* gene and isolated microspherophakia in Caucasians.

Abbreviations

AR: Autosomal recessive; CSVS: Collaborative Spanish Variant Server; FBN1: Fibrillin-1; IBD: Identity by descent; IM: Isolated microspherophakia; IOP: Intraocular pressure measurement; MFS: Marfan syndrome; MSP: Microspherophakia; NGS: Next-generation sequencing; OD: Oculus dexter (the right eye); OS: Oculus sinister (the left eye); PCG: Primary congenital glaucoma; TSO: *TruSight One*[®] Sequencing Panel; UBM: Ultrasound biomicroscopy

Acknowledgments

We wish to thank the consenting patients and parents who made this study possible.

Availability of data and materials

We do not wish to share data originating from our database in order to protect the anonymity of subjects included in this. Permission has not been obtained to share data widely with other investigators and would require individual consent.

Authors' contributions

JC received and diagnosed the patients and wrote the clinical data of the manuscript. LA designed and processed the study, interpreted the data, drafted the initial manuscript and approved the final manuscript as submitted. LGQ supported and interpreted the technique and results of the NGS. JT contributed to diagnosis and clinical follow-up of the patients. EM was the MiSeq technician. SB and PG provided overall supervision of the study from conception to completion. JC, LG, EM, SB and PG reviewed and revised the initial draft and approved the final draft. LA acts as the guarantor. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Informed written consent was obtained from all the patients involved in this study. This study was approved by the Ethics Committee of the Hospital de la Santa Creu i Sant Pau.

Consent for publication

The patients participating in this study signed their consent for the publication of the results obtained. This statement was approved by the Ethics Committee of the Hospital de la Santa Creu i Sant Pau.

Competing interests

The authors declare that they have no competing interests.

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