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Phenotypic characterization of patients with early-onset high myopia due to mutations in *COL2A1* or *COL11A1*: Why not Stickler syndrome?

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Purpose: Our previous study reported that 5.5% of probands with early-onset high myopia (eoHM) had mutations in *COL2A1* or *COL11A1*. Why were the probands initially considered to have eoHM but not Stickler syndrome (STL)?
Methods: Probands and family members with eoHM and mutations in *COL2A1* or *COL11A1* were followed up and reexamined based on the criteria for STL. Further comprehensive examinations were conducted for patients with eoHM and mutations in *COL2A1* or *COL11A1* and controls with eoHM without mutations in *COL2A1* or *COL11A1*. We performed comparisons between probands, affected family members with mutations in *COL2A1* or *COL11A1,* and controls with eoHM without mutations in *COL2A1* or *COL11A1*.
Results: Twelve probands (8.91±4.03 years) and 14 affected family members (37.00±11.18 years) with eoHM and mutations in *COL2A1* or *COL11A1*, as well as 30 controls with eoHM but without mutations in *COL2A1* or *COL11A1*, were recruited. Among them, 25.0% of probands and 50.0% of affected family members met the diagnostic criteria for STL after reexamination. Posterior vitreous detachment/foveal hypoplasia (PVD/FH), hypermobility of the elbow joint (HJ), and vitreous opacity were more frequent in patients with eoHM with mutations in *COL2A1* or *COL11A1* than in the controls ($p = 1.40 \times 10^{-5}$, 3.72×10^{-4}, 2.30×10^{-3}, respectively). HJ was more common in the probands than in the affected family members (11/12 versus 3/14; $p = 3.42 \times 10^{-4}$), suggesting age-dependent manifestation. EoHM presented in all the probands and in 11/14 affected family members, suggesting that it is a more common indicator of STL than the previously described vitreoretinal abnormalities, especially in children. The rate of STL diagnosis could increase from 25.0% to 66.7% for probands and from 50.0% to 92.9% for affected family members if eoHM, PVD/FH, and HJ are added to the diagnostic criteria.
Conclusions: In summary, it is not easy to differentiate STL from eoHM with routine ocular examination in outpatient clinics. Awareness of atypical phenotypes and newly recognized signs may be of help in identifying atypical STL, especially in children at eye clinics.

Early-onset high myopia (eoHM), defined as a spherical refraction of less than or equal to −6.0 diopters (D) in each meridian [1] or an axial length of at least 26 mm in both eyes [2], occurs before 7 years of age [3-5]. Compared to other types of myopia, eoHM is more likely to be determined by genetic factors due to minimal effects of the environment [4,6,7], such as extensive near work, that plays an important role in common or late-onset high myopia [8,9]. Thus far, the genetic defects known to cause HM have been identified in only a small number of families, based on our previous studies [5,10-12]. However, mutations in the genes known to be responsible for retinal diseases were found in about one-fourth of probands with eoHM in a comprehensive analysis of whole-exome sequencing data from 298 families [4]. These findings were further confirmed with an analysis of whole-exome sequencing data from another eoHM cohort of 325 families [7]. For those families with eoHM and mutations in RetNet genes, approximately one-fifth (34 probands) had mutations in the genes responsible for Stickler syndrome (STL), including *COL2A1 (*Gene ID 1280, OMIM 120140) or *COL11A1* (Gene ID 1301, OMIM 120280). It is of interest to investigate the phenotypic characteristics of patients with eoHM with mutations in genes associated with STL.

STL is a group of genetic disorders involving the collagen of connective tissue, notable mainly in the face, joints, ears, and eyes; STL affects an estimated 1 in 7,500 to 9,000 newborns [11,13]. Marshall syndrome, caused by mutations in *COL11A1*, is considered a variant of STL [14-16]. STL can be transmitted as an autosomal dominant or autosomal recessive

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trait. The autosomal dominant form of STL is caused by mutations in *COL2A1* [17], *COL11A1* [18], or *COL11A2* (Gene ID 1302, OMIM 120290) [19], while the autosomal recessive form of STL is caused by mutations in *COL9A1* (Gene ID 12839, OMIM 120210) [20], *COL9A2* (Gene ID 1298, OMIM 120260) [21], *COL9A3* (Gene ID 1299, OMIM 120270) [22], or *LOXL3* (Gene ID 84695, OMIM 607163) [23,24]. STL type 1 (STL1), the most common subtype of STL, accounting for 80–90% of all STL cases, is caused by mutations in *COL2A1*. STL type 2 (STL2) is caused by mutations in *COL11A1*; it accounts for 10–20% of all STL cases [13]. Truncation mutations or missense mutations affecting glycine are the main class of the pathogenic mutations of *COL2A1* or *COL11A1* [4,25]. The manifestation of STL is multisystemic, and includes ocular findings of characteristic vitreous opacity, myopia, cataract, and retinal detachment, hearing loss, midfacial dysplasia and cleft palate (either alone or as part of the Robin sequence), mild spondyloepiphyseal dysplasia, and precocious arthritis [26,27]. The presence and severity of each sign may vary greatly from patient to patient and change over time [28,29]. Additionally, STL type 3, caused by mutations in *COL11A2,* may have no eye involvement [30,31]. Mutations in exon 2 of *COL2A1* have been suggested to affect mainly ocular phenotypes with minimal or the absence of systemic involvement [32-34]. The diagnosis of STL may not be easy even with the diagnostic criteria that were created for this syndrome in 2005 [27]. Previously, genotype–phenotype studies were based mainly on analyses of patients with STL. Extended genotype–phenotype analysis based on patients with individual major signs, such as eoHM [27], may detect patients with atypical phenotypes, but such studies have been rare.

In this study, follow-up reexaminations were performed on probands and their affected family members with eoHM and mutations in *COL2A1* or *COL11A1* to reveal why these probands were initially considered to have eoHM but not STL. In addition, we wanted to know whether any specific ocular or systemic signs could warrant further examination of atypical STL in childhood with major presenting signs of eoHM.

METHODS

Participants: This study is part of our ongoing project on the genetics of eoHM. Based on whole-exome sequencing, potential pathogenic mutations were previously identified in 34 of the 623 probands with eoHM [4,7] in two of the six genes known to cause STL (i.e., *COL2A1* and *COL11A1*). Of the 34 families with mutations, 12 probands (Table 1) and 14 affected family members were available for follow-up reexamination in the present study. Meanwhile, 30 recently identified probands with eoHM without mutations in the six genes but with comparable clinical data were analyzed as controls. Written informed consent conforming to the tenets of the Declaration of Helsinki and adhering to the ARVO statement on human subjects was obtained from the participants or their guardians before the collection of blood samples and clinical data. This study was approved by the institutional review board of Zhongshan Ophthalmic Center, Sun Yat-Sen University, Guangzhou, China.

Clinical evaluation: The participants described above received ocular and systemic evaluations based on the diagnostic criteria for STL [27]. Refractive error was measured with an autorefractometer (Topcon KR-8000, Paramus, NJ) after mydriasis using compound tropicamide (Mydrin-P, Santen Pharmaceutical, Osaka, Japan). Axial length was measured using an optical biometer (IOL master V5.0, Carl Zeiss Meditec AG, Oberkohen, Germany). Photographs of the anterior vitreous opacity were taken with a photo slit-lamp microscope (LS-6, Chongqing, China). Fundus photographs were obtained using a digital retinal camera (CR-2 PLUS AF, Canon, Tokyo, Japan). The posterior vitreoretinal and macular regions were examined using optical coherence tomography (OCT; Topcon Corp, Oakland, NJ).

Examinations of the orofacial, auditory, and musculoskeletal systems were also performed. Pure-tone audiometry (GSI 61, GSI, Eden Prairie, MN), the air conduction threshold (0.25–8 kHz), and the angles of elbow and knee hypermobility were evaluated for all 12 probands and their 14 affected family members. X-ray examinations (Luminors Select, SIEMENS, Munich, Germany) were conducted on select individuals with complaints of discomfort in their joints or on individuals recommended for such examinations by professional physicians.

Overview of the genotype–phenotype: To understand the extent of phenotypic variation in eoHM associated with mutations in *COL2A1* and *COL11A1*, the reported phenotypes of STL caused by mutations in these two genes were reviewed and summarized based on the published literature [15,17,18,25,27-29,32,35-90], which were retrieved from PubMed, Web of Science, and Google Scholar (Appendix 1). The phenotypes of the present cases were discussed based on comparison with the reported overview phenotypes of STL.

Statistical analysis: Clinical data for patients with eoHM with or without mutations in *COL2A1* or *COL11A1* were compared first. For patients with eoHM with mutations in *COL2A1* or *COL11A1*, the clinical data for the probands were compared to the data for affected family members. A *t* test and Fisher's exact test were performed in SPSS 22.0 (SPSS, Inc., Chicago,

Table 1. Pathogenic mutations of *COL2A1* or *COL11A1* detected in the 12 probands with eoHM.

Gene	Patient	Position		Exon/	Nucleotide	Amino Acid	Status	Computational Prediction		dbSNP	Novel or
	ID	Chr	Position	Intron	variant	Change		PPH2/BDGP	SIFT		Reported
COL2A1	HM992	chr12	48,380,410	Exon 45	c.3138delT	p.P1046fs	Het	/	/	rs121912873	Novel
	HM304	chr12	48,380,792	IVS 44	c.3111+1G>A	/	Het	DL	/	None	Reported
	HM894	chr12	48,380,855	Exon 44	c.3049delG	p.G1017fs	Het	/	/	None	Novel
	HM862	chr12	48,372,481	Exon 42	c.2794C>T	p.R932*	Het	/	/	rs121912866	Reported
	HM918	chr12	48,375,892	Exon 33	c.2128C>T	p.R785*	Het	/	/	None	Reported
	HM842	chr12	48,377,504	Exon 30	c.1957C>T	p.R653*	Het	/	/	rs121912893	Reported
	HM951	chr12	48,377,504	Exon 30	c.1957C>T	p.R653*	Het	/	/	rs121912893	Reported
	HM849	chr12	48,378,777	IVS 27	c.1833+1G>A	/	Het	SSA	/	None	Reported
	HM1000	chr12	48,379,358	Exon 26	c.1693C>T	p.R565C	Het	PrD	D	rs121912884	Reported
	HM820	chr12	48,380,672	IVS 21	c.1366−1G>C	/	Het	SSA	/	None	Reported
COL11A1	HM813	chr01	103,355,027	Exon 59	c.4484G>A	p.G1495E	Het	PrD	D	None	Reported
	HM878	chr01	103,385,883	Exon 49	c.3782G>T	p.G1261V	Het	PrD	D	None	Reported

Note: these mutations were not present in the 1000G, EVS, or ExAC databases. Chr, chromosome; Het, heterozygous; PPH2, PolyPhen-2, not applicable for truncation mutations; DL, donor loss; SSA, splicing site abolished; PrD, probably damaging; D, damaging; PPH2, PolyPhen; BDGP; SIFT; 1000G; EVS.

IL). A p value of less than 0.05 was considered statistically significant (the hypothesis tests were two-sided).

RESULTS

Of the 34 eoHM families with mutations in *COL2A1* or *COL11A1*, 26 patients from 12 families received follow-up examinations, including 12 probands and 14 affected family members (Figure 1). Of the 26 patients, 23 were from ten families with mutations in *COL2A1,* and three were from two families with mutations in *COL11A1* (Table 1 and Appendix 2). No patients in this cohort had mutations in exon 2 of *COL2A1* (Table 1).

The medical records from the initial visits of the 12 probands with mutations in *COL2A1* or *COL11A1* did not

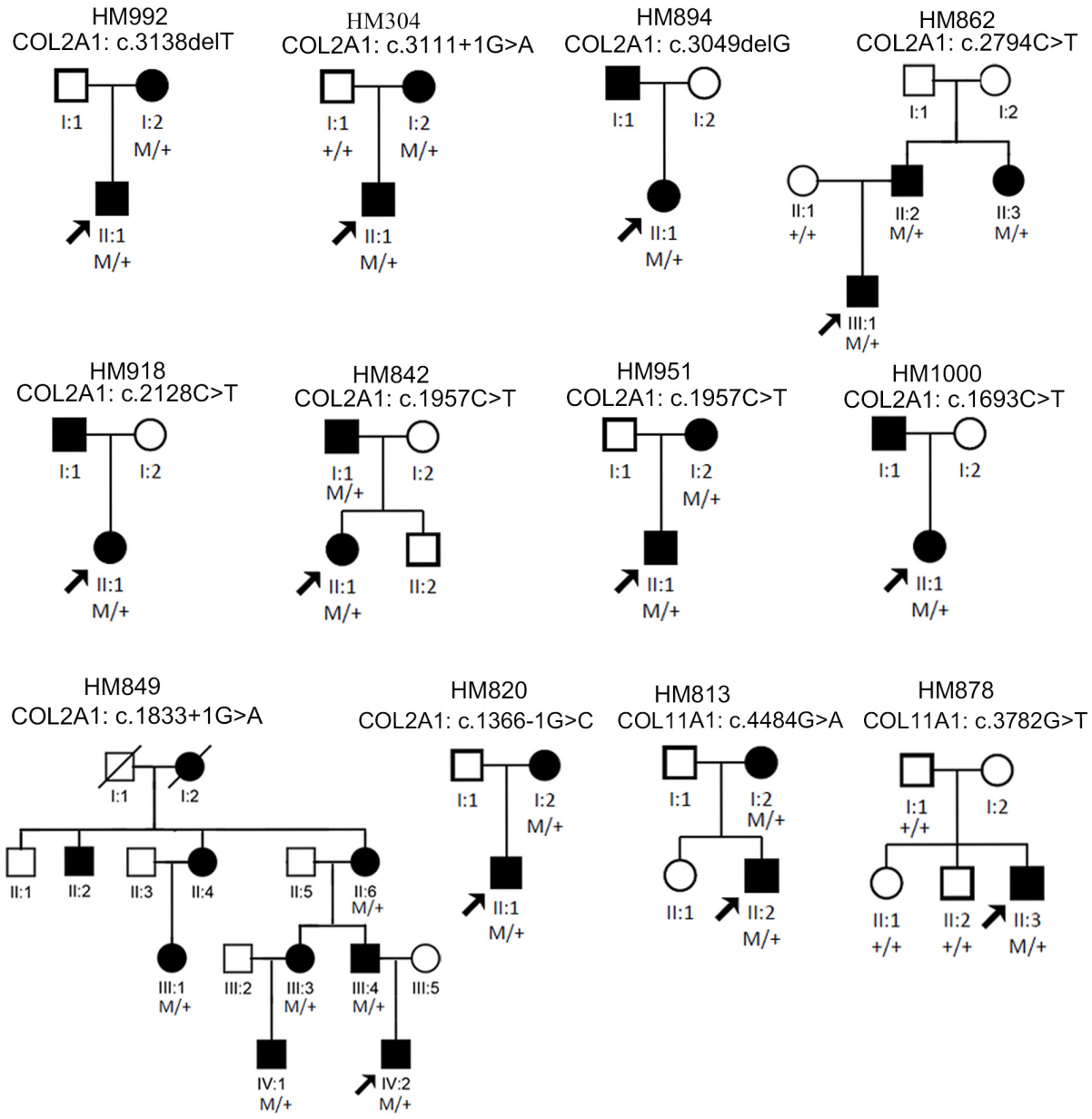

Figure 1. Pedigrees of 12 families with mutations and cosegregation results for those mutations. The family members and their corresponding mutations are shown just above the pedigrees (M, mutated allele; +, wild-type allele). Squares indicate male individuals, and circles indicate female individuals. The patients with arrows were the probands in these families.

mention specific signs that could lead to a diagnosis of STL rather than eoHM. However, comprehensive follow-up reexaminations, based on STL diagnostic criteria [27], identified additional ocular and systemic signs in some of the probands and their affected family members (Appendix 2). Based on clinical data obtained in the reexaminations, a diagnosis of STL could be made in 25.0% (3/12) of the probands and 50% (7/14) of the affected family members, following the reported diagnostic criteria [27] (Figure 2 and Figure 3; Appendix 2).

Comparing the 26 patients with eoHM harboring mutations in *COL2A1* or *COL11A1* with the 30 patients with eoHM without mutations in *COL2A1* or *COL11A1* (Table 2 and Appendix 2), there were statistically significant differences in posterior vitreous detachment and/or foveal hypoplasia (PVD/FH; 22/26 versus 8/30; $p = 1.40 \times 10^{-5}$; Figure 2), hypermobility of the elbow joints (HJ; 16/26 versus 3/30; $p = 3.72 \times 10^{-4}$), and vitreous opacity (9/26 vs. 1/30, $p = 2.30 \times 10^{-3}$). For all patients less than 14 years old, hypermobility of the elbow joints (Figure 3) was present in all 12 patients with eoHM with mutations in *COL2A1* or *COL11A1* but in only three of the 18 patients with eoHM without mutations in *COL2A1* or *COL11A1* ($p = 8.00 \times 10^{-6}$). Between the two cohorts, there were no significant differences in the presence of HM, the degree of refractive error, the axial length,

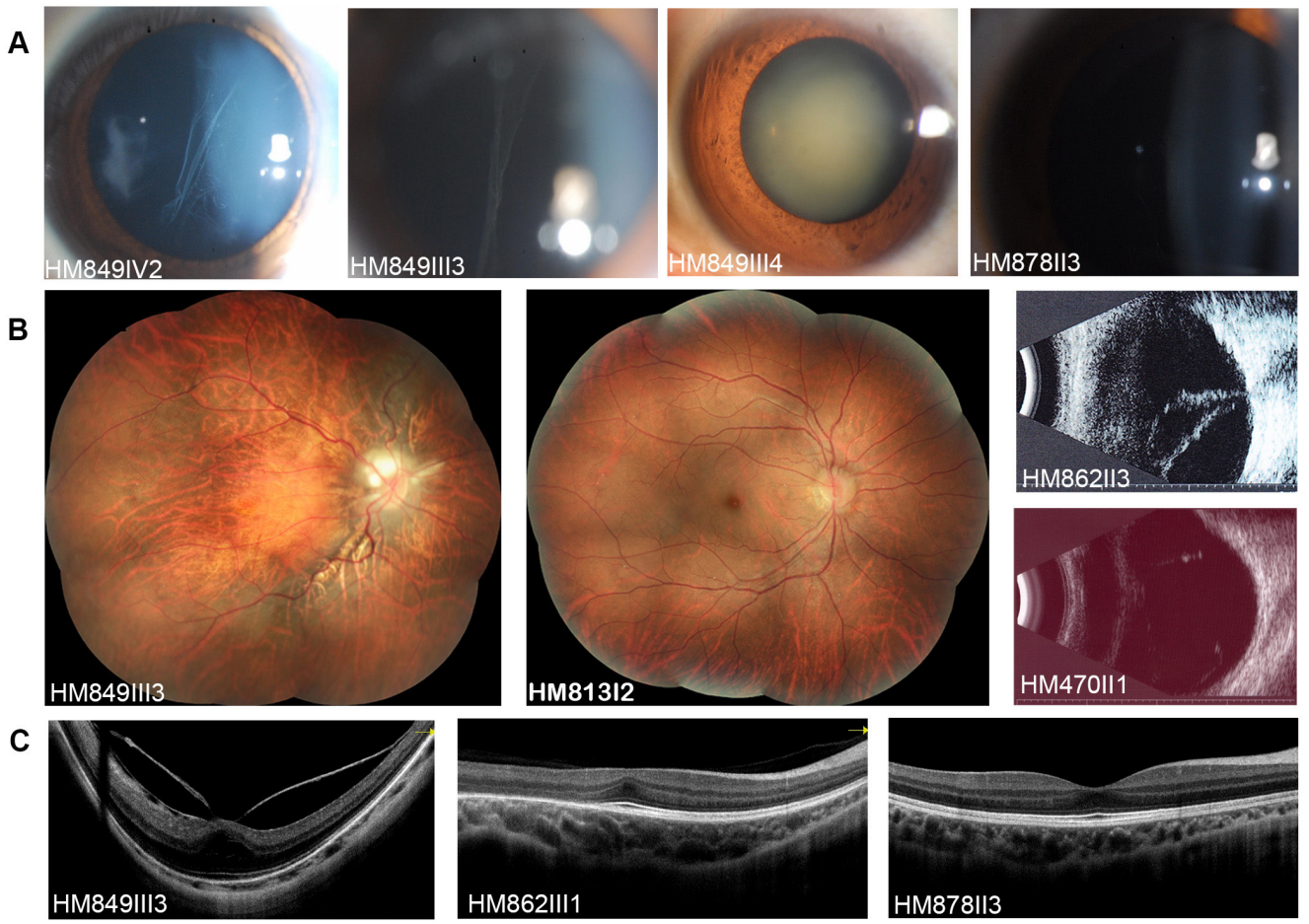

Figure 2. Ocular manifestations of patients with mutations in *COL2A1* or *COL11A1*. **A**: Photographs of the anterior segments of HM849IV2, HM849III3, HM849III4, and HM878II3. Membrane and beaded vitreous opacity and cataracts can be seen in HM849IV2, and membrane vitreous opacity can be seen in HM849III3. Cataracts can be seen in HM849IV2 and HM849III4, while HM878II3 is normal. **B**: Multidirectional wide-field color photographs of HM849III3 and HM813I2, and B-scans of the left eyes of HM862II3 and HM470II1. Retinal degeneration can be seen in HM849III3, but not in HM813I2. On the B-scans of HM862II3 and HM470II1, retinal detachment and vitreous opacity, respectively, can be seen. **C**: OCT scans of HM849III3, HM862III1, and HM878II3. Posterior vitreous detachment and foveal hypoplasia (the remaining layers in the central fovea of the macula, including the inner limiting membrane, the nerve fiber layer, the ganglion plexiform layer, the inner plexiform layer, and the inner nuclear layer) can be detected in HM849III3 and HM862III1. The macular structure of HM878II3 was normal.

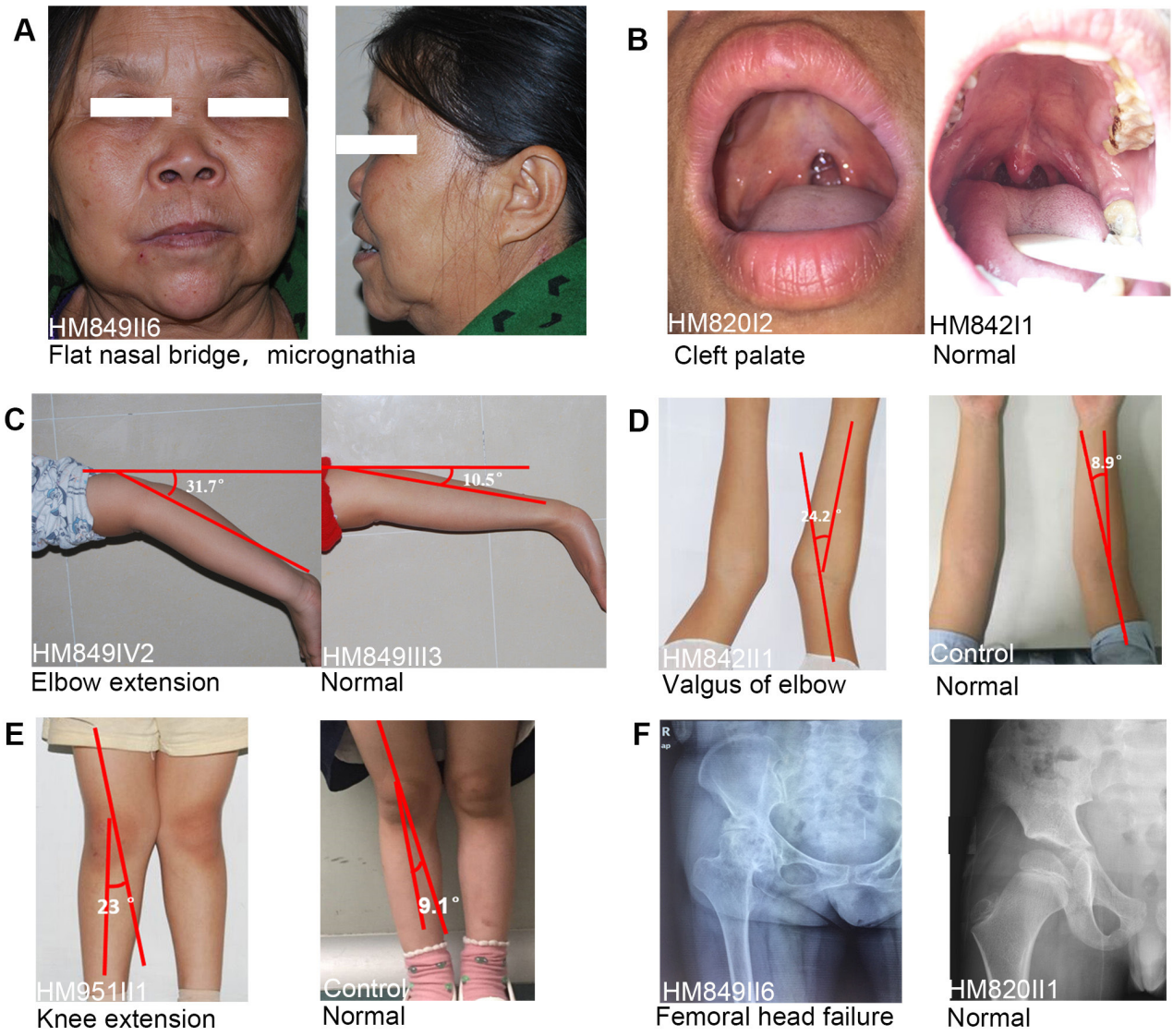

Figure 3. Systemic manifestations of patients with mutations in *COL2A1* or *COL11A1*. **A**: Frontal and profile facial images of HM849II6. A flat midface with a depressed nasal bridge, a short nose, and micrognathia can be seen in HM849II6. **B**: Oral photographs of HM820I2 and HM842I1. A cleft palate can be seen in HM820I2, while HM842I1 is normal. **C**: Hypermobility of the elbow. Hyperextension of the elbow joint can be seen in HM849IV2, while HM849III3 is normal. **D**: Valgus of the elbow. Valgus of the elbow can be detected in HM842II1 with a normal control beside it. **E**: Valgus of the knee can be seen in HM951II1 with a normal control beside it. **F**: Hip-joint X-rays of HM849II6 and HM820II1. The X-ray of HM849II6 shows femoral head necrosis, while the hip joint of HM820II1 is normal.

retinal abnormalities (i.e., lattice degeneration, retinal holes, or retinal detachment), and cleft palate (Table 2).

To test whether there were age-dependent differences for clinical signs associated with mutations in *COL2A1* or *COL11A1*, comparisons of clinical data were also performed between the probands and their affected family members. There were statistically significant differences in age ($p = 1.80 \times 10^{-8}$), HJ (11/12 versus 3/14; $p = 3.42 \times 10\text{-}^{4}$) and retinal abnormalities ($p = 0.02$). In addition, older patients had a higher frequency of vitreous opacity, retinal abnormalities (lattice degeneration, retinal holes, and retinal detachment), and musculoskeletal abnormalities, as seen in the family members (Table 3). However, these diagnostic signs were either absent or not obvious in early childhood, as in most probands.

PVD/FH and HJ are frequent specific signs in children with eoHM and mutations in *COL2A1* or *COL11A1*; therefore, these two signs may be considered early suggestive signs for

Table 2. Comparisons of clinical data eoHM patients with mutations compared to eoHM controls without mutations.

	NO. (%)†		
Parameter	**Patients with mutations n=26**	**Controls without mutations n=30**	**Comparison**
Age (Y)	24.04±16.46	17.53±13.18	0.10
eoHM	23 (88.5)	30 (100.0)	0.06
Refractive error	-10.92±6.94	-9.08±4.32	0.23
Axial length	27.06±2.25	27.12±2.64	0.93
PVD/FH	22 (84.6)	8 (26.7)	1.40E-05
Vitreous opacity	9 (34.62)	1 (3.3)	2.30E-03
Retinal abnormility	5 (19.2)	2 (6.7)	0.16
Cleft palate	3 (11.5)	0 (0)	0.06
HJ	14 (53.8)	3 (10.0)	3.72E-04
HJ (<16Y)	12/12 (100.0)	3/18 (16.7)	8.00E-06

NO., number; Y, years; PVD, posterior vitreous detachment; FH, foveal hypoplasia; HJ, hypermobility of the elbow joint;† Percentages are based on the total number of the individuals.

STL. In addition, as eoHM is easily recognizable and more frequent than vitreous opacity and retinal abnormalities in young patients, eoHM might be an earlier suggestive sign for STL. The proportion of patients carrying eoHM and HJ to patients carrying all signs (eoHM, HJ, and PVD/FH) was statistically significantly higher in younger probands than in family members with mutations in *COL2A1* or *COL11A1* (11/12 versus 3/14, $p = 3.42 \times 10^{-4}$; 9/12 versus 3/14, $p = 6.32 \times 10^{-3}$) and controls with eoHM without mutations in *COL2A1* or *COL11A1* (11/12 versus 3/30, $p = 3.94 \times 10^{-7}$; 9/12 versus 0/30, $p = 8.73 \times 10^{-7}$; Table 4). This further supports the idea that eoHM, HJ, and PVD/FH are important clues for STL,

Table 3. Comparisons of clinical data between probands and affected family members with mutations.

	NO. (%)†		
Parameter	**Probands n=12**	**Family members n=14**	**Comparison**
Age (Y)	8.91±4.03	37.00±11.18	1.80E-08
eoHM‡	12 (100.0)	11 (78.6)	0.09
Refractive error	-9.53±7.14	-13.60±6.17	0.13
Axial length	27.72±1.88	26.35±2.40	0.12
PVD/FH‡	9 (75.0)	13 (92.9)	0.21
Vitreous opacity	2 (16.7)	7 (50.0)	0.08
Retinal abnormility	0 (0.0)	5 (35.7)	0.02
HJ‡	11 (91.7)	3 (21.4)	3.42E-04
HJ (<16Y)	11/11 (100.0)	1/1 (100.0)	1.00
Other signs of STL diagnostic criteria			
Orofacial abnormality	10 (83.3)	10 (71.4)	0.47
Musculoskeletal abnormality	3 (25.0)	8 (57.1)	0.10
Hearing loss	5 (41.7)§	7 (50.0)	0.67
Diagnosis of STL after follow-up exam	**3 (25.0)**	**7 (50.0)**	**0.19**
Diagnosis of STL if new signs added‡	**8 (66.7)**	**13 (92.9)**	**0.09**

NO., number; Y, years; PVD, posterior vitreous detachment; FH, foveal hypoplasia; HJ, hypermobility of the elbow joint; † Percentages are based on the total number of the individuals. ‡ eoHM, PVD/FH and HJ were added as one point each in the suggested criteria. § One proband was too young to undergo an auditory examination, and the data were not available.

Table 4. Comparison of suggested signs among probands, family members, and eoHM controls.

Parameter	Probands	Family members	Controls eoHM
	n=12	n=14	n=30
eoHM	12	11	30
HJ	11	3	3
PVD/FH	9	13	8
First two signs (*p*)	11	3 (3.42E-4)¶	3 (3.94E-7)Σ
All three signs (*p*)	9	3 (6.32E-3)¶	0 (8.73E-7)Σ

HJ, hypermobility of the elbow joint; PVD, posterior vitreous detachment; FH, foveal hypoplasia;¶ indicates the p value in the bracket was obtained by using Chi-square test based on comparison of the two signs (eoHM and HJ) or three signs (eoHM, HJ, and PVD/FH) between probands and affected family members; Σ indicates the p value in the bracket was obtained by using Chi-square test based on comparison of the two signs (eoHM and HJ) or three signs (eoHM, HJ, and PVD/FH) between probands and eoHM controls.

and eoHM together with HJ might be especially indicative of STL in childhood. In our case series, the rate of diagnosis for STL could be further increased if eoHM, HJ, and PVD/FH could be added as new suggestive signs (from 3/12 to 8/12 for probands and from 7/14 to 13/14 for affected family members; Table 3 and Appendix 2).

As for the phenotypic overview, clinical data from 595 patients were retrieved from the literature, including 380 patients with STL1 caused by mutations in *COL2A1* (except the mutations in exon 2 in *COL2A1*), 52 patients with ocular-only STL1 with mutations in exon 2 of *COL2A1*, 111 patients with STL2 caused by mutations in *COL11A1*, and 52 patients with Marshall syndrome caused by mutations in *COL11A1* [15,17,18,25,27-29,32,35-90]. The phenotypic overview of the 595 patients with *COL2A1* or *COL11A1* mutations is summarized in Appendix 1. The overview showed that myopia and orofacial abnormality are the most common signs, affecting 71.4% (425/595) and 60.0% (357/595) of patients, respectively. Vitreous opacity, hearing loss, and musculoskeletal abnormality were reported in 38.3% (228/595), 36.1% (215/595), and 30.9% (184/595) of patients, respectively. For those four subtypes of STL (STL1, ocular-only STL1, STL2, and Marshall syndrome), systemic signs are less frequent in ocular-only STL1 compared to the other three subtypes. The incidence of hearing loss in STL2 is higher than in STL1, as mentioned in a previous review [91]. Membranous and beaded vitreous abnormality might be a clue for distinguishing STL1 from STL2 [13], but few reports have clarified the type of vitreous abnormality. The prevalence of hearing loss, orofacial abnormality, hypertelorism, and short stature is higher in Marshall syndrome than in STL1 and STL2. However, hypertelorism and short stature might be rarely recognized as specific signs for certain populations. The pattern of major signs seen in the 14 adults in the present study was comparable to that of STL1 in an overview, while vitreous abnormality, hearing loss, and skeletal abnormality were more common in adults than in children with eoHM and STL mutations in the present study (Appendix 1). The overview of the phenotype might assist clinicians in identifying patients whose condition may be caused by mutations in *COL2A1* or *COL11A1*.

DISCUSSION

In this study, follow-up examinations were performed on 12 probands and 14 affected family members with eoHM and mutations in *COL2A1 or COL11A1*. The resulting clinical data were compared with 30 patients with eoHM without mutations in *COL2A1* or *COL11A1*. None of the 12 probands met the diagnostic criteria for STL [27] based on a review of their medical records from their initial visits. Even after comprehensive follow-up reexaminations based on the diagnostic criteria for STL, the clinical data for most of the 26 patients (16/26 for all, 9/12 for probands, 7/14 for affected family members) still did not meet the diagnostic criteria for STL. These results suggest that a diagnosis of STL based on previous criteria is still challenging in routine clinical practice. This is especially true for children presenting with HM in an eye clinic, even after follow-up examinations with reference to the diagnostic criteria of STL and after the identification of the causative mutations in *COL2A1* or *COL11A1*.

Some of the previously described signs, such as flat or broad and round facial features, are commonly seen in the general population living in Southeast Asia [47,92,93]. Therefore, certain characteristic facial features, such as malar hypoplasia, a broad or flat nasal bridge, and micrognathia or retrognathia, might be not considered diagnostic signs of STL in such a population [47]. Other additional easily recognizable clues may help ophthalmologists identify STL without typical phenotypes.

Comparing the 26 patients harboring *COL2A1* or *COL11A1* mutations to 30 patients with eoHM without

mutations revealed suggestive signs that could be helpful in warning a patient about a potential diagnosis of STL. EoHM seemed to be present in all the probands with mutations in *COL2A1* or *COL11A1*, but this study demonstrated that mutations in STL-related genes are the most common cause of eoHM. This finding is identical to the overview of the phenotype of patients with mutations in *COL2A1* or *COL11A1* (Appendix 1). EoHM is the earliest presenting and most easily recognizable sign for children with potential STL. Specific ocular signs of STL, including characteristic vitreous changes or retinal abnormalities (lattice degeneration, retinal hole, retinal detachment, or retinal tear), were rarely present in children with eoHM and mutation in *COL2A1* or *COL11A1* in this cohort (Table 3 and Appendix 2). Therefore, keeping eoHM in mind as a common presenting sign of STL could facilitate the identification of children with potential STL at eye clinics.

Two additional new signs were frequently observed in probands with eoHM with mutations in *COL2A1* or *COL11A1*, that is, PVD/FH and HJ. A child with eoHM plus HJ is highly likely to have STL when compared to controls without STL with eoHM (Table 4). HJ can be easily observed in a routine clinic without any instruments or additional fees. HJ is an age-dependent sign that usually presents in affected children but rarely in affected adults. In addition, PVD/FH based on an OCT scan may provide additional evidence for STL (Table 4), which supports recently reported findings [94]. Thus, adding these three signs as new diagnostic clues may facilitate the clinical diagnosis of STL (Table 3).

The present study is limited by the lack of auditory and comprehensive musculoskeletal data from controls with eoHM without mutations in *COL2A1* or *COL11A1*. As an eye hospital without facilities for auditory examination, we are unable to refer patients for auditory tests at other hospitals if the patients do not present related signs or symptoms. Additionally, we are unable to refer patients for X-rays if the patients do not present related signs or symptoms.

In summary, some patients with STL may present as having eoHM at the clinic, and a considerable proportion of patients are actually patients with STL with atypical phenotypes. This further supports the great phenotypic variation of STL [18,26,28,29]. Mutations in exon 2 of *COL2A1* have been suggested to cause nonsyndromic ocular STL, even when systemic features are mild or even absent [34]. Mutations in other regions of *COL2A1* may also cause atypical STL with mainly ocular phenotypes [72], especially in the early stage. Nevertheless, HJ and PVD/FH, in addition to eoHM, may provide additional evidence suggestive of atypical STL in an eye clinic. Gene tests on suspected cases may provide a firm diagnosis of STL. Tests of suspected cases with other atypical signs may expand our knowledge of the phenotypic variation of STL, as well as the prevalence of STL in the general population, which might be greatly underestimated.

APPENDIX 1. SUPPLEMENTAL FIGURE 1.

A: Comparisons of the phenotypes between patients in our study and previous studies (STL1, ocular-only STL, STL2, and Marshall Syndrome). B: Comparisons of the phenotypes between children and adults with eoHM harboring STL mutations. VO, vitreous opacity; RD, retinal detachment; HL, hearing loss; Skel, skeletal abnormality; HJ, joint hypermobility. To access the data, click or select the words "Appendix 1."

APPENDIX 2. SUPPLEMENTAL TABLE 1.

Clinical data of the 12 probands and 14 affected family members from follow-up examination after identification of mutations. To access the data, click or select the words "Appendix 2."

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