Significant ocular findings are a feature of heritable bone dysplasias resulting from defects in type II collagen

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Background/aims: The type II collagenopathies are a phenotypically diverse group of genetic skeletal disorders caused by a mutation in the gene coding for type II collagen. Reports published before the causative mutations were discovered suggest heritable bone dysplasias with skeletal malformations may be associated with a vitreoretinopathy.

Methods: A retrospective notes search of patients with a molecularly characterised type II collagenopathy chondrodysplasia who had been examined in the ophthalmology clinic was conducted.

Results: 13 of 14 patients had a highly abnormal vitreous appearance. One patient aged 11 presented with a total retinal detachment. Two other children aged 2 and 4 had bilateral flat multiple retinal tears on presentation. 10 of 12 patients refracted were myopic. Two patients had asymptomatic lens opacities: one associated with bilateral inferiorly subluxed lenses and the other with a zonule and lens coloboma.

Conclusion: Heritable skeletal disorders resulting from a mutation in the gene coding for type II collagen are associated with abnormal vitreous, myopia and peripheral cataract with lens subluxation. In bone dysplasias resulting from a defect of type II collagen there is likely to be a high risk of retinal detachment with a propensity to retinal tears at a young age.

The type II collagenopathies (MIM#120140) are a group of disorders caused by a mutation in the gene coding for type II collagen (COL2A1). Type I Stickler syndrome is one disorder that can result from a mutation in COL2A1. There is a high risk of ocular problems in Stickler syndrome. Other conditions resulting from COL2A1 mutations have a more pronounced skeletal phenotype than Stickler syndrome and are usually diagnosed in childhood. Diagnoses on the type II collagenopathy spectrum include achondrogenesis type 2, hypochondrogenesis, spondyloepiphyseal dysplasia (SEDC), spondyloepimetaphyseal dysplasia Strudwick type (SEMD), Kniest dysplasia, and spondyloperipheral dysplasia (SPD).¹

The heritable bone dysplasias caused by mutations in COL2A1 have common clinical and radiological manifestations but show a very wide variation in phenotype. Diagnosis relies heavily on the radiographic pattern described as axially centred retardation in ossification. The type II collagenopathy chondrodysplasias are distinguished from type I Stickler syndrome by the skeletal malformations and result in disproportionate dwarfism in more severely affected individuals (fig 1). In addition, cleft palate and hearing loss are known associations of all type II collagenopathies.²

Although several review articles have been written on the ocular features of Stickler syndrome,^{3,4} there is little in the medical literature regarding ocular phenotype in other type II collagenopathies. In a case series written before molecular genetics isolated the underlying mutation in COL2A1

Maumenee and Traboulsi reported vitreoretinal degeneration and congenital severe myopia in seven patients with a clinical diagnosis of Kniest dysplasia.⁵ There are also earlier, isolated reports of ocular manifestations in patients with chondrodysplasias that include cataracts, subluxed lens and blepharoptosis.^{6–8}

Here we present the ocular findings in 14 patients with a molecularly characterised bone dysplasia. This series clearly demonstrates the need for ophthalmological assessment in all individuals with a type II collagenopathy.

SUBJECTS AND METHODS

Fourteen patients with a chondrodysplasia other than Stickler syndrome, and known COL2A1 mutation were identified. Six cases had a clinical diagnosis of SEDC, five of Kniest dysplasia, two of SEMD and one with a diagnosis of SPD. In all cases the diagnosis was made before attending the eye department on the basis of typical systemic features and radiographic skeletal survey. The causative mutations are summarised in table 1.

All patients seen in the eye clinic had a full ophthalmological examination with slit-lamp biomicroscopy or indirect ophthalmoscopy either in clinic or as an examination under general anaesthesia.

RESULTS

The present series consists of 10 males and 4 females. Age at which the patients were first seen in the ophthalmology clinic ranged from 1 to 30 years old, with 10 patients younger than 7 years at first presentation. The clinical and radiographic features of the chondrodysplasias in this case series are summarised in table 2.

The ocular findings are summarised in table 3. A cycloplegic refraction was documented in all 10 patients who presented under the age of 10 years, with further refractions in two patients who presented to the eye clinic as adults. The majority were myopic, the exceptions being one child who was hypermetropic at +2.50 D (examined age 6) and one adult who was emmetropic. The documented myopia in the other 10 patients ranged from −0.50 to −15.00 D with a mean refractive error of −4.75 D. The highest cylindrical correction prescribed was 1.50 D and, in general, astigmatism was low or absent. In all cases the corneal examination was normal. Clear lens was documented in 12 of the 14 patients. One patient had bilateral and symmetrical, peripheral, quadrant lamellar lens opacities. This same patient (patient number 13) also had bilateral, inferiorly subluxed lenses. One other patient (patient number 4) had a lens opacity in the right eye associated with a nasal lens and zonule coloboma (seen on examination under anaesthesia).

The vitreous was documented as abnormal in 13 of the 14 cases, and a membranous anomaly in the immediate retrolental

Abbreviations: SEDC, spondyloepiphyseal dysplasia; SEMD, spondyloepimetaphyseal dysplasia Strudwick type; SPD, spondyloperipheral dysplasia

Figure 1 Spondyloepiphyseal dysplasia (SEDC) in a 30-year-old man with a mutation in exon 27 of COL2A1 demonstrating short stature. Informed consent was obtained for publication of this figure.

space (as has been described in type I Stickler syndrome^{9 10}) was present in nine patients. In the cases without the membranous anomaly the gel was architecturally abnormal with reduced lamellae and a ‘mobile’, fibrillar cortex. Only one patient had a normal vitreous appearance and this was the

Table 1 Summary of clinical diagnosis and mutational analysis

Pt no	Diagnosis	Mutation – DNA	Mutation – amino acid	Effect of mutation
1	SEDC	Exon 27 c.1781G→A	p.G594E	Disruption to collagen helix
2	SEDC	Exon 34 c.2276G→A	p.G759D	Disruption to collagen helix
3	Kniest	Exon 14 c.905C→T	p.A102V	Mis-splicing
4	SEDC	Exon 19 c.1214G→A	p.G405D	Disruption to collagen helix
5	SEDC	Exon 27 c.1781G→A	p.G594E	Disruption to collagen helix
6	Kniest	IVS16 c.1023+1g→t		Probable exon skip
7	Kniest	IVS25 c.1681-1g→c		Probable exon skip
8	SPD	Exon 54 c.4357del C	Multiple amino acid changes	Frame shift
9	Kniest	Exon 46 c.3383G→T	p.G1128V	Disruption to collagen helix
10	SEDC	Exon 42 c.2761G→C	p.G921R	Disruption to collagen helix
11	SEMD	IVS29 c.1942-2a→g		Probable exon skip
12	SEMD	Exon 45 c.3121G→A	p.G1041S	Disruption to collagen helix
13	Kniest	Exon 14 c.905C→T	p.A102V	Mis-splicing
14	SEDC	Exon 27 c.1781G→A	p.G594E	Disruption to collagen helix

Exons are numbered 1–54. Mutations are numbered in relation to the reference cDNA sequence NM_001844.3. This sequence has 157bp of a 5' untranslated region. +1 corresponds to the A of the ATG translation initiation codon. Amino acids are numbered corresponding to the reference sequence NP_001835.2.

Table 2 Presence of radiographic and clinical features in the case series with a molecularly characterised type II collagenopathy chondrodysplasia

Pt no	Diagnosis	Radiographic observations					Clinical features				
		Platyspondyly	Metaphyseal widening	Delayed ossification	Coxa vara	Shortening of long bones	Hypoplastic mid-face	Kyphosis/scoliosis	Cleft palate	Abnormal audiogram	Chest signs
1	SEDC	+							+	+	Dextrocardia
2	SEDC	+	+	+	+			+	+	+	Wide chest
3	Kniest	+	+					+			
4	SEDC								+	+	
5	SEDC	+							+	+	
6	Kniest		+			+			+		
7	Kniest	+		+				+			
8	SPD	+	+					+	+		
9	Kniest		+						+		Atrial septal defect
10	SEDC	+	+			+		+		+	
11	SEMD	+	+		+						
12	SEMD		+	+	+			+			
13	Kniest	+						+	+		
14	SEDC								+	+	

In the radiographic observations + indicates the presence of the radiographic feature based on available radiographs and reported by one person (PB). A skeletal survey was not available for reporting in all. + in the clinical features indicates the clinical feature was recorded in the hospital notes. All patients were assessed for cleft palate and all had an audiogram.

Table 3 Ocular findings in type II collagenopathy chondrodysplasias

Pt no	Diagnosis	Age at presentation	Sex	Refraction right eye	Refraction left eye	Lens findings	Vitreous description	Retinal findings
1	SEDC	1	M	-1.00	-1.00	Clear	Abnormal with membranous anomaly	Normal
2	SEDC	1	M	-2.75/ -0.75	-4.50	Clear	Abnormal with membranous anomaly	Normal
3	Kniest	2	F	-6.50/ -1.50	-7.00/ -1.00	Clear	Abnormal with membranous anomaly	Normal
4	SEDC	2	M	-1.00	-1.00	Unilateral lens and zonule coloboma with lamellar lens opacity	Abnormal, very mobile with strands	Bilateral multiple flat retinal breaks
5	SEDC	3	M	-3.25/ -0.75	-2.75/ -0.75	Clear	Abnormal with membranous anomaly	Normal
6	Kniest	3	M	-14.00	-15.00	Clear	Abnormal with membranous anomaly	Normal
7	Kniest	3	F	-9.50	-9.50	Clear	Abnormal with membranous anomaly	Normal
8	SPD	4	M	-5.50	-6.00/ -1.00	Clear	Abnormal with membranous anomaly	Bilateral multiple flat retinal tears
9	Kniest	4	M	-0.5	-0.5	Clear	Highly abnormal, mobile	Normal
10	SEDC	6	M	+2.50	+2.50	Clear	Normal	Normal
11	SEMD	11	M			Clear	Abnormal with membranous anomaly	Unilateral total retinal detachment
12	SEMD	20	F	-1.00/ -0.25	-1.25/ -0.25	Clear	Highly abnormal	Normal
13	Kniest	21	F			Bilateral symmetrical cataract and subluxed lenses	Abnormal, fibrillar	Widespread paravascular lattice
14	SEDC	30	M	plano	plano	Clear	Abnormal with membranous anomaly	Normal

same patient who was hypermetropic (patient number 10). At presentation one patient had a total retinal detachment and two had multiple flat tears in the periphery of both retinas. Paravascular lattice was documented in only one patient. All others had a normal retinal appearance.

DISCUSSION

Type II collagen is the major structural component of secondary vitreous, comprising 70% of the total protein content.¹¹ As vitreous is largely inert and detected at an early stage of embryogenesis, COL2A1 mutations might be expected to produce congenital and permanent abnormalities of the vitreous gel. The findings of the present report would support this with 13 of 14 cases having a highly abnormal vitreous appearance. In those patients exhibiting the membranous anomaly on slit-lamp examination the vitreous changes were indistinguishable from those seen in type I Stickler syndrome. Different diagnoses on the type II collagenopathy spectrum cannot be separated on the basis of ophthalmoscopy.

The exception to the finding of abnormal vitreous with a COL2A1 mutation was also unusual for being the only child who was hypermetropic rather than myopic (patient number 10). This mutation did not appear to result in a milder systemic phenotype (table 2). A possible explanation in this individual is mosaicism resulting in a characteristic skeletal phenotype for a type II collagenopathy and with expression of the mutated allele in peripheral blood cells from which the mutation was identified, but normal COL2A1 expression in ocular tissue. When investigating sporadic cases it is difficult to ascertain the presence of mosaicism and this could also be an explanation for the lack of a membranous anomaly in some of the cases with an abnormal appearance to the vitreous.

We have found the degree of myopia associated with bone dysplasias resulting from a COL2A1 mutation to be moderate and not associated with significant astigmatism. This is in contrast to the higher myopia (mean -15.00 D) described in

the other case series of Kniest dysplasia⁵ and the typically high myopia that is associated with type I Stickler syndrome.³ Two cases of Kniest dysplasia associated with high myopia have been reported in which axial length was abnormally long.¹² The reason why a COL2A1 mutation should cause myopia has not yet been ascertained. Type II collagen has not been found in human sclera or cornea but may yet be found to have a structural role in ocular tissues.¹³⁻¹⁵ Alternatively, there is some evidence that the vitreous body plays a role in the early regulation of eye size¹⁶ and the development of myopia may be related to the abnormalities of the vitreous humour.

An association between chondrodysplasias and lens changes, specifically cataract and inferior dislocation of the lens, has been suggested in isolated case reports.^{7,8} These case reports were published before advances in molecular genetics identified causative mutations in the heritable bone dysplasias so it is not known if they are applicable to type II collagenopathies. However, we have also described two cases with lens opacities, one associated with a zonule coloboma and the other with inferiorly subluxed lenses (patient numbers 4 and 13). Both of these cases also had retinal changes consisting of multiple retinal breaks and paravascular lattice, respectively. Interestingly the specific mutation in the case of bilateral cataracts with subluxation was identical to that found in another unrelated case with normal lens and retina (patient numbers 13 and 3). This is in keeping with the general difficulty of predicting phenotype from genotype in the type II collagenopathies.¹⁷

The level of ocular morbidity related to retinal detachment in type I Stickler syndrome is high with a 60–80% lifetime risk of retinal detachment.¹⁸ Maumenee and Traboulsi report rhegmatogenous retinal detachment in 4 of 7 patients with Kniest dysplasia.⁵ In the present report of 14 patients with a molecularly characterised type II collagenopathy chondrodysplasia one had a total retinal detachment by age 11 and two required prophylactic treatment for multiple bilateral retinal tears on presentation to ophthalmology at age 2 and 4 (table 3). The flat

tears were an incidental finding on examination in both cases. The three cases presenting with retinal breaks have diverse causative mutations and clinical diagnoses (patient numbers 4, 8 and 11; table 1). It would seem sensible to assume any condition that results from a mutation in COL2A1 may have a level of ocular morbidity similar to that reported for type I Stickler syndrome.

In conclusion the heritable bone dysplasias resulting from a defect of type II collagen are associated with an abnormal vitreous appearance, myopia and, more rarely, cataract and subluxation of the lens. There is likely to be an increased risk of retinal detachment with a propensity to retinal tears at a young age. Type II collagen disorders with a significant skeletal phenotype are unlikely to present initially to an eye department but ophthalmology has an important role as part of the multidisciplinary approach to the management of all disorders which result from a mutation in COL2A1.

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REFERENCES

- 1 **Superti-Furga A**, Unger S. Nosology and classification of genetic skeletal disorders: 2006 revision. *Am J Med Genet A*, 2007;**143**:1–18.
- 2 **Spranger J**, Winterpacht A, Zabel B. The type II collagenopathies: a spectrum of chondrodysplasias. *Eur J Pediatr* 1994;**153**:56–65.
- 3 **Snead MP**, Yates JR. Clinical and molecular genetics of Stickler syndrome. *J Med Genet* 1999;**36**:353–9.
- 4 **Donoso LA**, Edwards AO, Frost AT, *et al*. Clinical variability of Stickler syndrome: role of exon 2 of the collagen COL2A1 gene. *Surv Ophthalmol* 2003;**48**:191–203.
- 5 **Maumenee IH**, Traboulsi EI. The ocular findings in Kniest dysplasia. *Am J Ophthalmol* 1985;**100**:155–60.
- 6 **Bardelli AM**, Lasorella G, Barberi L, *et al*. Ocular manifestations in Kniest syndrome, Smith-Lemli-Opitz syndrome, Hallermann-Streiff-Francois syndrome, Rubinstein-Taybi syndrome and median cleft face syndrome. *Ophthalmic Paediatr Genet* 1985;**6**:343–7.
- 7 **Kim HJ**, Beratis NG, Brill P, *et al*. Kniest syndrome with dominant inheritance and mucopolysacchariduria. *Am J Hum Genet* 1975;**27**:755.
- 8 **Langer LO**, Gonzalez-Ramos M, Chen H, *et al*. A severe infantile micromelic chondrodysplasia which resembles Kniest disease. *Eur J Paediatr* 1976;**123**:29.
- 9 **Snead MP**, Payne SJ, Barton DE, *et al*. Stickler syndrome: correlation between vitreoretinal phenotypes and linkage to COL2A1. *Eye* 1994;**8**:609–14.
- 10 **Rose PS**, Levy HP, Liberfarb RM, *et al*. Stickler syndrome: clinical characteristics and diagnostic criteria. *Am J Med Genet* 2005;**138A**:199–207.
- 11 **Bishop P**. The biochemical structure of mammalian vitreous. *Eye* 1996;**10**:664–70.
- 12 **Kagotani Y**, Takao K, Nomura K, *et al*. Two cases of kniest dysplasia – ocular manifestations. *Nippon Ganka Gakkai Zasshi* 1995;**99**:376–83.
- 13 **Keeley RW**, Morin JD, Vesely S. Characterization of collagen from normal human sclera. *Exp Eye Res* 1984;**39**:533–42.
- 14 **BenEzra D**, Foidart JM. Collagens and non collagenous proteins in the human eye. I. Corneal stroma in vivo and keratocyte production in vitro. *Curr Eye Res* 1981;**1**:101–10.
- 15 **Ben-Zvi A**, Rodrigues MM, Krachmer JH, *et al*. Immunohistochemical characterization of extracellular matrix in the developing human cornea. *Curr Eye Res* 1986;**39**:533–42.
- 16 **Halfier W**, Winzen U, Bishop PN, *et al*. Regulation of eye size by the retinal basement membrane and vitreous body. *IOVS* 2006;**47**:3586–94.
- 17 **Nishimura G**, Haga N, Kitoh H, *et al*. The phenotypic spectrum of COL2A1 mutations. *Hum Mutat* 2005;**26**:1–8.
- 18 **Stickler GB**, Hughes W, Houchin P. Clinical features of hereditary progressive arthro-ophthalmopathy (Stickler syndrome): a survey. *Genet Med* 2001;**3**:192–6.