

# Ophthalmic and molecular genetic findings in Kniest dysplasia

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CLINICAL STUDY

## Abstract

**Purpose** To study the variability of the ophthalmic phenotype in Kniest dysplasia. Kniest dysplasia is an inherited disorder associated with defects in type II collagen and characterised by short-trunked dwarfism, kyphoscoliosis, and enlarged joints with restricted mobility. Other features include marked hand arthropathy, cleft palate, hearing loss, and ocular abnormalities (myopia, abnormal vitreous, and high risk of developing retinal detachment).

**Methods** Data from eight unrelated individuals with a clinical and molecular diagnosis of Kniest dysplasia are reported. Clinical assessment included an audiogram and ophthalmological examination in all but one patient who died in the immediate postnatal period. Sanger sequencing of the *COL2A1* gene was performed.

**Results** Six of the seven patients tested were high myopes with one patient being an emmetrope. Bilateral quadrantic cataracts and subluxed lenses were noted in one subject. Variable but abnormal vitreous architecture was observed in all seven individuals tested. Six of the seven patients had significant hearing impairment and five of the seven patients exhibited clefting abnormalities. One patient had bilateral retinal detachments in his twenties. Six dominant disease-causing *COL2A1* variants were detected. In three cases, testing of parental samples revealed that the disease-causing variant was not present in either parent.

**Conclusion** The ophthalmic features in Kniest dysplasia are very similar to those in other disorders of type II collagen such as Stickler syndrome. It is likely that different type II collagenopathies have a similar level of ocular morbidity and regular ophthalmologic examination is recommended. Kniest dysplasia is associated

with heterozygous *COL2A1* mutations that are frequently *de novo*.

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## Introduction

All collagen molecules are composed of a triple helix consisting of three  $\alpha$ -chains. In the case of type II collagen, which is the major structural component of cartilaginous tissues and the vitreous, these chains are identical (forming a homotrimer) and are encoded by the *COL2A1* gene (MIM +120140).<sup>1,2</sup> Defects in this gene give rise to a phenotypically diverse group of disorders collectively termed type II collagenopathies (or *COL2A1*-related disorders).<sup>3</sup> These conditions are typically inherited in an autosomal dominant manner and present with a multisystem phenotype that may include skeletal, orofacial, auditory, and ocular features. Notably, type II collagenopathies span a wide range of clinical severity ranging from ‘ocular-only’ variants of Stickler syndrome (MIM #609508)<sup>2</sup> to perinatally lethal chondrodysplasias (for example, hypochondrogenesis (MIM #200610)).<sup>4</sup> In the middle of this spectrum lies a subgroup of disorders presenting with short stature at birth. The differential diagnosis of such type II collagenopathies causing short stature includes spondyloepiphyseal dysplasia congenita (SEDC (MIM #183900)), spondyloepimetaphyseal dysplasia (SEMD Strudwick type (MIM #184250)), spondyloperipheral dysplasia (MIM #271700), and Kniest dysplasia (MIM #156550).

Kniest dysplasia is a dominantly inherited *COL2A1*-related disorder, first described by Wilhelm Kniest in 1952.<sup>3,5</sup> Classically, it is characterised by short-trunked dwarfism (expected height 100–140 cm; <http://www.ksginfo.org/aboutus.html>,

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accessed on 27 September 2014), kyphoscoliosis, and short limbs with prominent joints that restrict mobility.<sup>6</sup> Major problems arise from progressive joint enlargement and contracture, especially affecting the metacarpophalangeal and interphalangeal joints.<sup>2</sup> Additional associated features of the syndrome, including orofacial abnormalities (cleft palate, small jaw, and flat mid-face), hearing loss (conductive, sensorineural, or mixed), and ocular abnormalities, are shared with the other type II collagenopathies.<sup>4</sup> In a case series of seven patients clinically diagnosed with Kniest dysplasia, Maumenee and Traboulsi<sup>7</sup> advocated the need for ophthalmologic assessment in all individuals with the disorder; they concluded that congenital non-progressive high myopia, abnormal vitreous on slit lamp examination, and an increased risk of retinal detachment are important features of the syndrome.

Herein, we report the findings in eight patients with a clinical diagnosis and molecular confirmation of Kniest dysplasia. Variability in the ophthalmic phenotype is described and *COL2A1* allelic heterogeneity is discussed.

### Materials and methods

Eight individuals (median age: 11 years old) with clinical and radiographic features of Kniest dysplasia (including short stature and prominent joints with reduced mobility) and heterozygous likely disease-causing variants in *COL2A1* were ascertained from the Vitreoretinal Service at Addenbrooke's Hospital, Cambridge, UK. The local research ethics committee approved the study, and all investigations were conducted in accordance with the principles of the Declaration of Helsinki; informed consent was obtained from all participating individuals. Six of the cases have been partially described in previous reports (Table 1).<sup>8,9</sup>

Clinical assessment included a detailed history and palatal, audiological, and ophthalmological examination in all but one patient who died in the immediate postnatal period owing to respiratory distress associated with the condition (subject KN1). Cycloplegic refraction was undertaken in two patients (subjects KN2 and KN3; aged 4 and 7 years, respectively) and subjective refraction was performed in four patients (subjects KN4–KN7; aged 11–29 years). Vitreous architecture was assessed on slit lamp biomicroscopy by at least one clinician (MPS) in seven of the subjects studied (it was not possible to test subject KN1).

Screening of the *COL2A1* gene was performed according to previously described methods;<sup>10</sup> all eight patients and, where possible, parental DNA samples were tested. Genomic DNA was extracted from the peripheral blood lymphocytes of the donated blood samples. The *COL2A1* coding region and intron–exon

boundaries of exons 1–54 (NCBI reference sequence NG\_008072.1; transcript NM\_001844.4) were amplified and sequenced. To predict whether the missense changes associated with Kniest dysplasia affect exonic splice regulatory sequences and/or generate a cryptic splice site within *COL2A1*, the wild-type and mutant sequences of the corresponding exons were analysed using Alamut version 2.3 (Interactive Biosoftware, Rouen, France, accessed on 31 May 2014). The splicing prediction tools within Alamut include MaxEntScan ([http://genes.mit.edu/burgelab/maxent/XmaxentScan\\_scoreseq.html](http://genes.mit.edu/burgelab/maxent/XmaxentScan_scoreseq.html)), NNsplice ([http://www.fruitfly.org/seq\\_tools/splice.html](http://www.fruitfly.org/seq_tools/splice.html)), human splicing finder (<http://www.umd.be/HSF/>), ESE finder (<http://rulai.cshl.edu/cgi-bin/tools/ESE3/esefinder.cgi?process=home>), and Rescue-ESE (<http://genes.mit.edu/burgelab/rescue-ese/>). All variants are described according to the Human Genome Variation Society (HGVS) guidelines based on reference sequence NM\_001844.4 (*COL2A1*).

### Results

The clinical features and *COL2A1* screening results of the eight study participants are summarised in Table 1. Patients were examined by an ophthalmologist within the first year of life. Typical skeletal manifestations and radiographic features were observed in all the cases (Figure 1). Five of the seven tested patients exhibited palatal clefting abnormalities that required formal surgical repair; six of the seven patients had significant hearing impairment, which was either due to conductive or sensorineural loss, or a combination of both.

Visual acuity ranged from  $-0.100$  to  $+2.000$  logarithm of the minimum angle of resolution (LogMAR) units (median  $+0.175$ ). Six of the seven tested patients were high myopes; the documented refractive error ranged from plano to  $-14.50$  dioptres (median spherical equivalent refraction  $-11.00$  dioptres). Low astigmatism was observed in most cases, with the highest identified cylindrical correction being 3.00 dioptres. Bilateral quadratic lamellar lens opacities, in addition to bilateral inferiorly subluxed lenses, were noted in one patient (subject KN4).

Abnormal vitreous architecture, visible on slit lamp biomicroscopy, was documented in all the seven examined patients. In five cases this was consistent with a membranous vitreous anomaly in the immediate retrolental space (identical to that seen in type I Stickler syndrome);<sup>11</sup> the remaining two cases had a hypoplastic vitreous with reduced lamellae and a fibrillar cortex. One patient (subject KN8) had bilateral rhegmatogenous retinal detachments at ages 26 and 27. The right eye had a macula-on detachment and was treated with a 360° buckle and laser retinopexy (acuity after surgery 0.175 LogMAR), whereas the left eye had recurrent

**Table 1** Ophthalmic and molecular genetic findings in patients with Kniest dysplasia

Patient ID	COL2A1 variant (heterozygous)	Age at most recent review	Sex	Right eye refraction (LogMAR acuity)	Left eye refraction (LogMAR acuity)	Vitreous appearance	Additional features	Family history	References
KN1	c.1366G>C; p.Gly456Arg	Post-mortem radiological diagnosis	M	Not examined	Not examined	Not examined	Immediate postnatal death.	Father is a somatic mosaic, <sup>9</sup> diagnosed with type I Stickler syndrome.	9
KN2	c.1023+1G>T	4	M	-14.00 DS (0.300)	-15.00 DS (0.175)	Membranous anomaly	Bilateral prophylactic cryotherapy, age 4. Binaural hearing aids. Cleft palate surgical repair. Odontoid hypoplasia.	Two unaffected siblings.	8
KN3	c.1681-1G>C	7	F	-14.50/-0.75 × 80 (0.480)	-11.50/-0.50 × 30 (0.300)	Membranous anomaly	Bilateral prophylactic cryotherapy, age 5. Odontoid hypoplasia.	Two unaffected siblings. No parental mutation detected.	8
KN4	c.905C>T; p.Ala302Val	11	F	-9.00/-3.00 × 150 (0.175)	-9.00/-2.00 × 10 (0.175)	Hypoplastic	Bilateral cataracts and subluxed lenses. Binaural hearing aids. Cleft palate surgical repair.	One unaffected sibling. No parental mutation detected.	8
KN5	c.905C>T; p.Ala302Val	11	F	-10.75/-1.50 × 25 (0.175)	-8.25/-1.75 × 155 (0.000)	Membranous anomaly	Bilateral prophylactic cryotherapy, age 4. Binaural hearing aids. Cleft palate surgical repair.	One unaffected sibling.	8
KN6	c.905C>T; p.Ala302Val	12	M	-8.50/-1.00 × 30 (0.700)	-7.00/-1.75 × 145 (0.200)	Membranous anomaly	Binaural hearing aids.	One unaffected sibling.	This study
KN7	c.3383G>T; p.Gly1128Val	13	M	Emmetropic (-0.100)	Emmetropic (-0.100)	Hypoplastic	Binaural hearing aids. Cleft palate surgical repair.	Three unaffected siblings. No parental mutation detected.	8
KN8	c.1448G>A; p.Gly483Glu	29	M	High myope (0.175)	High myope (2.000)	Membranous anomaly	Bilateral retinal detachments at age 26 and 27. Binaural hearing aids. Cleft palate surgical repair.	No other affected family members.	This study

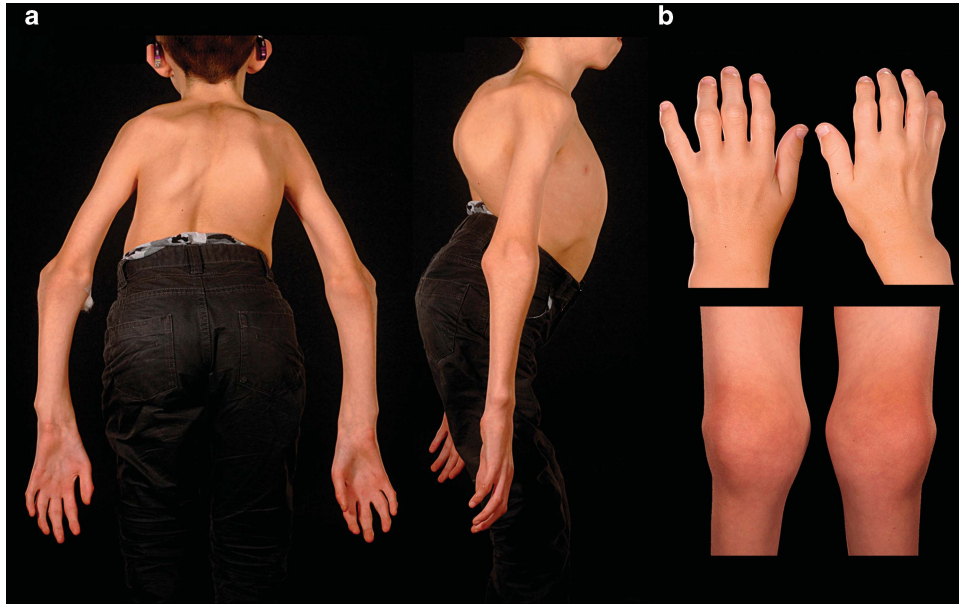
detachments that were complicated by proliferative vitreoretinopathy; there was silicone oil *in situ* in his left pseudophakic eye and the left acuity was 2.000 LogMAR. None of the other examined study subjects (mean age 11) had a retinal break at presentation, and the posterior hyaloid membrane was attached in all their eyes. Three patients had bilateral 360° prophylactic cryoretinopexy according to a standardised protocol (<http://www.vitreoretinalservice.org/ProphylacticCryotherapyProtocol.html>, accessed on 27 September 2014). This protocol was designed to prevent the retinal detachment secondary to giant retinal tears and has been previously shown to be safe and to substantially reduce (but not eliminate) the risk of detachment in individuals with type I Stickler syndrome.<sup>12</sup>

Six different likely disease-causing DNA variants in *COL2A1* were detected in eight alleles of the eight patients. These included four missense (c.1366G>C, p.Gly456Arg; c.1448G>A, p.Gly483Glu; c.3383G>T, p.Gly1128Val, and c.905C>T, p.Ala302Val) and two splice site (c.1023+1G>T and c.1681-1G>C) changes (Tables 1 and 2). In three cases, parental testing revealed the disease-causing variant to be not present in either parent (subjects KN3, KN4, and KN7). The father of subject KN1 was a somatic mosaic for the c.1366G>C, p.Gly456Arg mutation and had an existing diagnosis of type I Stickler syndrome, as previously reported.<sup>9</sup> Parental samples were not available for segregation analysis in the four remaining study subjects (KN2, KN5, KN6, and KN8).

## Discussion

To date, over 400 likely disease-causing variants have been described in the *COL2A1* gene (HGMD, Human Gene Disease Mutation Database, <http://www.hgmd.cf.ac.uk/>, accessed on 27 September 2014). Of these, 25 have been associated with Kniest dysplasia (Table 2). Here, we discuss allelic heterogeneity in Kniest dysplasia and report the ophthalmic phenotype in this type II collagenopathy.

The diagnosis of a type II collagenopathy has important implications as it can highlight the existing problems that have been overlooked and allow the prediction of future complications. On the basis of the severity of skeletal, radiographic, and extraskelatal manifestations, type II collagenopathies have been classically viewed as a mixture of distinct conditions (for example, Stickler syndrome, SEDC, and Kniest dysplasia). Such categorisation often has no obvious mechanistic basis and is often confounded by the phenotypic variability (family of subject KN1<sup>9,13</sup>) and by the presence of age-dependent phenotypic transitions.<sup>13-15</sup> Therefore, clinical suspicion for all



**Figure 1** Colour photos of subject KN6 (a) and subject KN2 (b) showing kyphoscoliosis, short trunk, prominent large joints, flexion contractures of hips and fingers, and interphalangeal joint enlargement.

manifestations of type II collagenopathies is advised when managing cases of Kniest dysplasia. Some relatively common and important systemic features of the disorder identified here and elsewhere include a narrow chest (subject KN1<sup>16,17</sup>), laryngotracheomalacia (subject KN1<sup>18</sup>), odontoid hypoplasia resulting in cervical instability (subjects KN4 and KN5<sup>19,20</sup>), and hearing impairment (subject KN2, KN3, KN5, KN6, KN7, and KN8<sup>8</sup>).

All examined patients in the present cohort had congenitally abnormal vitreous gel architecture; five of the seven patients exhibited the membranous type I vitreous anomaly seen in type I Stickler syndrome. Notably, although abnormal vitreous architecture appears to be a consistent finding among type II collagenopathies, cases with normal vitreous have previously been reported.<sup>8</sup> Myopia was present in six of the seven examined patients in this series, with the remaining study subject being found to be emmetropic (subject KN7). This reinforces the notion that although congenital myopia is an important feature of *COL2A1*-related disease, it is not a reliable screening tool for exclusion.<sup>2</sup> In addition to abnormal vitreous and myopia, patients with Kniest dysplasia have been reported to have a high risk of developing rhegmatogenous retinal detachment.<sup>7</sup> Maumenee and Traboulsi<sup>7</sup> reported the occurrence of retinal detachment (during the first or second decade of life) in four of seven cases with Kniest dysplasia. None of the participants in this study had suffered a retinal detachment during their childhood, but

one case (subject KN8) developed retinal detachments in his twenties. Although a case of retinal dialysis has been previously reported in a patient with Kniest dysplasia,<sup>7</sup> given the similarities in the vitreoretinal phenotype with other type II collagenopathies (including type I Stickler syndrome), we speculate that retinal tears are more likely to be the main cause of detachment in these patients.<sup>2,21</sup> Therefore, after informed consent, three study subjects had prophylactic retinopexy designed and positioned to prevent retinal detachment arising from giant retinal tears. Importantly, the efficacy of such an approach has not been demonstrated in Kniest dysplasia but a significant reduction in the risk of retinal detachment has been shown in type I Stickler syndrome.<sup>12</sup>

Most mutations associated with Kniest dysplasia are in-frame deletions and/or presumed to disrupt normal *COL2A1* pre-mRNA splicing (Table 2). Notably, six missense changes have been previously reported (c.905C>T, p.Ala302Val; c.908G>A, p.Gly303Asp; c.980G>A, p.Gly327Asp; c.1366G>C, p.Gly456Arg; c.1375G>C, p.Gly459Arg; c.3383G>T, p.Gly1128Val). The c.905C>T, p.Ala302Val change, which appears to be the commonest cause of Kniest dysplasia in both the present cohort and the literature (Table 2), has been previously shown to create a cryptic splice-donor site within exon 14.<sup>22,23</sup> The effect of the remaining five missense changes on splicing has not been studied to date; we have used online bioinformatics tools to make predictions and the results are presented in Table 2. It is not uncommon in human disease that coding point



**Table 2** Kniest dysplasia associated COL2A1 variants reported here and elsewhere

COL2A1 sequence variant	Number of unrelated patients (comment)	Likely effect on COL2A1 mRNA and/or protein	References
c.905C>T, p.Ala302Val	7 (mutation not identified in either parent in 2 cases)		8,22,23, 30–32
c.906_924+9delGGGTCTCTGGTGTGAAGGTGAGAGGC	2 (mother of one of these patients is somatic mosaic and has milder disease)	Creation of a cryptic splice-donor site within exon 14 leading to a 21-bp deletion, <sup>22,23</sup> skipping of exon 14, <sup>29</sup> 28-bp deletion containing junction of exon 14 and intron 14 leading to exon skipping and a 54-bp deletion, <sup>3</sup> Predicted not to have a clear effect on splicing. <sup>34</sup>	3,7,16,33
c.908G>A, p.Gly303Asp	1 (mutation not identified in either parent) (patient reported to later develop a SEDC phenotype) <sup>15</sup>		35
c.980G>A, p.Gly327Asp	1 (case only mentioned as 'unpublished work')	Predicted to alter a splice enhancer element in exon 16. <sup>34</sup>	35,36
c.1023+1C>T	1	Mislicing of exon 16. <sup>8</sup>	8
c.1023+1_1023+4delGTGA	1	Skipping of exon 16 leading to an 18-bp deletion. <sup>16</sup>	16
c.1023+2T>G	1	Mislicing of exon 16. <sup>13</sup>	13
c.1024-2A>C	1 (mutation not identified in either parent)	Skipping of exon 17. <sup>37</sup>	37
c.1068+1C>A	1 (severe disease; patient died at week 2)	Skipping of exon 17 leading to a 45-bp deletion. <sup>36</sup>	36
c.1076_1096delTCCGCTCCTCTGGTGGCTCCTG	1 (severe disease; patient died at 13 months)	21-bp deletion in exon 18. <sup>16</sup>	16
c.1250_1256delGAGCCAAinsTGTGAGTGTGTGTGTG	1	Out-of-frame insertion-deletion in exon 20. <sup>13</sup>	13
c.1266+1G>C	1	Mislicing of exon 20. <sup>20</sup>	20
c.1266+1delG	1	Skipping of exon 20. <sup>15</sup>	15
c.1279_1296delATTGCTGGTGTCTCTCTGGC	1	18-bp deletion in exon 21. <sup>16</sup>	16
c.1366G>C, p.Gly456Arg	1 (patient's father is somatic mosaic and has milder disease) (severe disease; patient died at day 1) (p.Gly456Ala is associated with SEDC) <sup>27</sup>	Affects the first nucleotide of exon 22 and predicted to alter its splice acceptor site. <sup>34</sup>	9
c.1375G>C, p.Gly459Arg	1 (severe disease; patient died at day 2) (c.1376G>T, p.Gly459Asp is associated with hypochondrogenesis) <sup>13</sup>	Predicted to alter a splice enhancer and creates a splice silencer element in exon 22. <sup>34</sup>	38
c.1419+3_1419+6delGAGT	1 (severe disease; patient died at 3 months)	Mislicing of exon 22. <sup>16</sup>	16
c.1419+5G>A	1 (c.1419+5G>T is associated with an SEDC phenotype) <sup>26</sup>	Skipping of exon 22 leading to a 54-bp deletion. <sup>21</sup>	21
c.1420-2A>G	1 (patient's father is somatic mosaic and has milder disease)	Alternative splicing of exon 23 leading to an 18-bp deletion. <sup>39</sup>	33,39
c.1448G>A, p.Gly483Glu	1 (also associated with SEDC) <sup>13</sup>	Affects an amino acid in exon 23.	This study
c.1581+1C>A	1 (mutation not identified in either parent) (severe disease; patient died at 5 months)	Skipping of exon 24 leading to a 54-bp deletion. <sup>40</sup>	40
c.1681-1G>C	1 (mutation not identified in either parent)	Mislicing of exon 26. <sup>8</sup>	8
c.1734+5G>A	1 (severe disease; patient died at day 10)	Skipping of exon 26 leading to a 54-bp deletion. <sup>17</sup>	17,35,39
Not reported	1 (case only mentioned as 'unpublished work')	18-bp deletion in exon 36. <sup>15,41</sup>	15,41
c.3383G>T, p.Gly1128Val	1 (mutation not identified in either parent)	Predicted to alter a splice enhancer element in exon 48. <sup>34</sup>	8
c.3627_3644delTCTCCAGGTCCTCCCTGG	1 (mutation not identified in either parent)	18-bp deletion in exon 51. <sup>41</sup>	41

All variants are described according to the Human Genome Variation Society guidelines based on reference sequence NM\_001844.4 (COL2A1). SEDC corresponds to spondyloepiphyseal dysplasia congenita (MIM #183900), another COL2A1-related disorder with a significant skeletal phenotype.

mutations have an unexpected effect on splicing,<sup>24,25</sup> and mRNA experiments are expected to provide further insight.

The p.Gly483Glu change identified in subject KN8, a 29-year-old male with radiographic findings consistent with Kniest dysplasia, has not been previously associated with the condition but was reported in a patient with SEDC.<sup>13</sup> It is of interest that the base pair substitutions of c.1419 + 5G have also been associated with both Kniest dysplasia (c.1419 + 5G > A)<sup>21</sup> and SEDC (c.1419 + 5G > T).<sup>26</sup> Furthermore, amino-acid substitutions of p.Gly456 and p.Gly459 have been reported in cases of Kniest dysplasia and other related phenotypes: SEDC (c.1367G > C, p.Gly456Ala)<sup>27</sup> and hypochondrogenesis (c.1376G > A, p.Gly459Asp).<sup>13</sup> This may reflect (i) a differential clinical diagnosis, (ii) a different effect of the substitution upon the collagen molecule, or (iii) a subtle difference that the nucleotide change has on pre-mRNA processing. When comparing the different glycine substitutions in collagen molecules, and their resulting phenotypic outcome, the latter is often overlooked. It may be significant that the mutations p.Gly456Arg and p.Gly459Arg resulting in Kniest dysplasia are also predicted to subtly alter the splicing signals, whereas those resulting in SEDC (c.1367G > C, p.Gly456Ala) or hypochondrogenesis (c.1376G > A, p.Gly459Asp) do not.

Despite the fact that Kniest dysplasia is associated with dominant mutations, most reports in the literature describe simplex cases. Exceptions to this include (i) a pair of identical twins with Kniest dysplasia,<sup>7</sup> (ii) a female patient with type 1 Stickler syndrome giving birth to a child with Kniest dysplasia,<sup>3</sup> (iii) a male patient with a mild SEDC-like phenotype having a child with Kniest dysplasia, and (iv) subject KN1 (father with Stickler syndrome, child with Kniest dysplasia).<sup>9</sup> This 'paradox' of a condition inherited in an autosomal dominant pattern manifesting clinically as sporadic disease with unaffected parents is also observed in other type I (for example, (MIM #166210)) and II (for example, (MIM #200610)) collagenopathies, and can be partially explained by *de novo* mutational events (somatic and germline mosaicism).<sup>9,28</sup> Such biological phenomena have been demonstrated in many families with Kniest dysplasia (Table 2), and mosaicism has been demonstrated or presumed in at least four of the eight families in the present study (subjects KN1, KN3, KN4, and KN7). The recognition that parental mosaicism may be present in cases of Kniest dysplasia makes the recurrence risk estimation challenging. Recent advances in genomic technologies are expected to enhance both our understanding of the molecular pathology of this disorder and our ability to detect it prenatally.

The ophthalmopathy associated with Kniest dysplasia has similarities with the other type II collagenopathies<sup>2,8</sup> and is characterised by abnormal vitreous on slit lamp biomicroscopy, myopia, and a high risk of developing retinal detachment at a young age. The ophthalmologist is an important member of the multidisciplinary team required to manage these patients and regular ophthalmic examinations are recommended. Most *COL2A1* variants associated with Kniest dysplasia are unlike classical loss-of-function mutations (Table 2) and cause a more severe phenotype than that of type I Stickler syndrome, which is often due to heterozygous nonsense or frameshifting *COL2A1* changes.<sup>2,14</sup> Therefore, it can be speculated that a dominant negative effect is exhibited in Kniest dysplasia with the product of the mutant allele not only being non-functional but also interfering with the function of the remaining normal allele. The frequency of *de novo* mutational events is high in this autosomal dominant disorder and this has implications with regards to genetic counselling.

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## Summary

### What was known before

- Disorders of type II collagen including Kniest dysplasia and Stickler syndrome are often associated with a specific ophthalmopathy. Retinal detachment at a young age can be a feature of Kniest dysplasia and there is a need for ophthalmological assessment in all individuals with the disorder.
- Although Kniest dysplasia is inherited in an autosomal dominant pattern it can manifest clinically as sporadic disease. This can be partially explained by *de novo* mutations in *COL2A1*.

### What this study adds

- Abnormal vitreous architecture is a consistent feature in molecularly confirmed cases of Kniest dysplasia.
  - A case of Kniest dysplasia with bilateral retinal detachments in his twenties is discussed.
  - The p.Gly483Glu mutation in *COL2A1* can cause both Kniest dysplasia and spondyloepiphyseal dysplasia congenita. This suggests that current categorisation of type II collagenopathies often has no obvious mechanistic basis.
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## Conflict of interest

The authors declare no conflict of interest.

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