Eye (2004) 18, 1258–1263

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CLINICAL STUDY

# The ocular manifestations of Weissenbacher–Zweymuller syndrome

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**Abstract**

*Purpose* **Weissenbacher–Zweymuller syndrome (WZS) is an autosomal recessive disorder of delayed skeletal maturation. Its characteristic features include rhizomelic dwarfism with metaphyseal and vertebral changes. It has been challenged whether WZS is a part of the spectrum of Stickler syndrome. We report ocular findings in the largest ever-presented series of patients with WZS.**
*Methods* **Patients underwent a paediatric examination, including assessment of growth and development, genetic work-up and X-ray of vertebra and long bones. All had a complete ophthalmic examination, cycloplegic refraction, and face and body photography.**
*Results* **All patients had hypertelorism and protruding eyes. Four patients had refractive errors necessitating optical correction ranging from +3 to –8 D. Two patients had strabismus. None had vitreoretinal degeneration, glaucoma, or cataract.**
*Conclusions* **Ocular manifestations of WZS differ from those in Stickler syndrome, indicating that the two likely represent distinct clinical entities. Strabismus and various refractive errors often accompany WZS. An ophthalmologist should follow children with this disorder from an early age to prevent amblyopia.**
*Eye* (2004) **18,** 1258–1263. doi:10.1038/sj.eye.6701386
Published online 26 March 2004

*Keywords:* Weissenbacher–Zweymuller syndrome; dwarfism; stickler syndrome

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Received: 4 August 2003
Accepted: 12 November 2003
Published online: 26 March 2004

## Introduction

Weissenbacher–Zweymuller syndrome (WZS) is an inherited disorder of delayed skeletal maturation. Its characteristic features include rhizomelic dwarfism (short limbs), metaphyseal widening of the long bones, and vertebral coronal clefts.[1] Regression of the bone changes is usual during a later childhood and most patients achieve normal or near-normal body proportions and normal radiographic appearance of the skeleton.[2] Other WZS features are microretrognathia with or without cleft palate, neonatal respiratory distress, nasal root depression and sensory neural deafness.

Since its first description by Weissenbacher and Zweymuller in 1964, this syndrome has been reported under several names, such as 'micrognathic dwarfism,' and 'Pierre–Robin with chondrodysplasia,' illustrating confusion regarding its delineation.[3–5] This condition has been lumped together with Stickler and Marshall syndromes, and has been called the neonatal form of Stickler syndrome.[6,7] Chemke *et al*,[2] along with Galil *et al*,[8] suggested that WZS is distinguishable clinically and radiographically from Stickler and Marshall syndromes and, as opposed to them, is inherited as an autosomal recessive trait. To the best of our knowledge, ocular presentation of WZS has not been systematically studied. We report herein the largest ever-presented series of eight WZS patients (four of them have been previously reported[2,8]) and describe their ocular manifestations. We show that ocular features in WZS differ from those in Stickler syndrome.

## Patients and methods

Children were assessed and followed up in a university-hospital inpatient and outpatient facilities. Eight patients with WZS were included, five female and three male patients aged 6 months to 18 years.

Patients underwent an examination by a paediatrician including assessment of growth

and development, as well as X-ray of vertebra and long bones, and genetic work-up. The diagnosis of WZS was based on clinical and radiological findings. The clinical features included rhizomelic short stature, microretrognathia, depressed nasal root, cleft palate (soft or/and hard), a history of a neonatal respiratory distress, and sensory neural deafness. The radiological findings included widening of the metaphyses of the long bones and coronal clefts of the lumbar vertebrae. All patients and their parents had karyotypes checked and family pedigrees were constructed.

All patients had a complete ophthalmic examination including orthoptic assessment and cycloplegic refraction, as well as photography of face and body. A best-corrected visual acuity was measured by methods commensurate with patient's age and cooperation. A presence of facial dysmorphism, refractive errors, strabismus, and structural ocular abnormalities was assessed. An examination of ocular alignment consisted of prism and Hirschberg measurements for distance and near fixation, as well as evaluation of ductions and versions. In patients with vertical deviations and sufficient cooperation, Bielschowsky head tilt test was also performed. Vitreoretinal changes were assessed by a slit-lamp biomicroscopy and indirect ophthalmoscopy carried out with dilated pupils. In addition, patients aged 12 years and older were examined with a Goldman's three-mirror lens.

## Results

Figures 1–4 show the pedigrees of our patients. Patients 1–6 were of Bedouin–Muslim origin and had consanguineous parents (Figures 1 and 2). Four of them (patients IV:1, IV:2, IV:9, IV:10) originated from one extended inbred family (Figure 1). Patients 1 and 2 (IV:1, IV:2, respectively in Figure 1) had a brother (IV:3) with

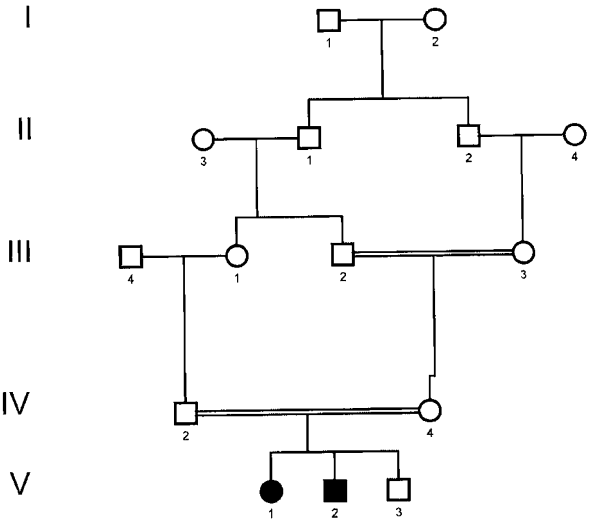


**Figure 2** Pedigree of patients 5 and 6. Note that both parents and maternal grandparents of patients 5 (V:1) and 6 (V:2) are consanguineous.

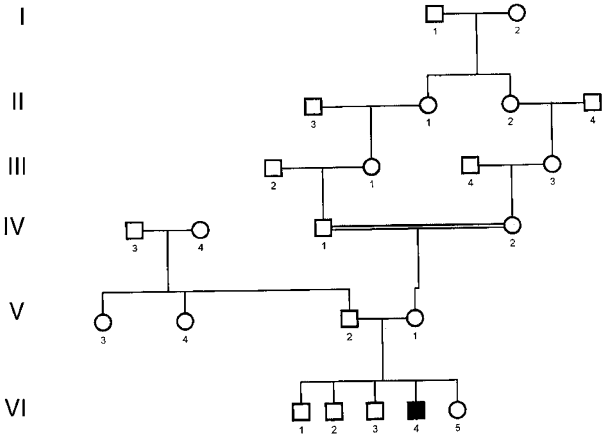


**Figure 3** Pedigree of patient 7. Although his parents are not related, the maternal grandparents are consanguineous.

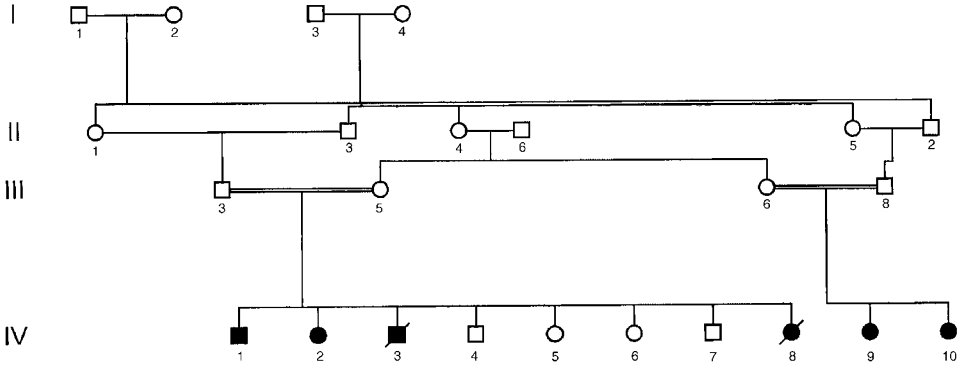


**Figure 1** Pedigree of patients 1–4. Note parental consanguinity. Individuals IV:1, IV:2, IV:9, IV:10 correspond to patients 1, 2, 3, 4, respectively. Individual IV:3 died of a neonatal respiratory distress, IV:8 corresponds to a pregnancy termination due to suspicion of WZS.

WZS who died at the age of 1 month from a respiratory distress. Termination of a pregnancy due to a suspicion of another foetus with WZS (according to a prenatal ultrasound scan) was also performed in this family. Patients 7 (VI:4 in Figure 3) and 8 (II:1 in Figure 4) were of Jewish Sephardic origin, each originated from a small segregated community (Bukharan and Georgian, respectively). Their parents were not consanguineous, but patient 7 had consanguineous maternal grandparents (Figures 3 and 4). Patient 8 (II:1 in Figure 4) had a brother who was presumably affected and died at the age of 6 weeks following repeated episodes of aspirations and pulmonary infections (Figure 4).

Clinical and radiological data of the eight patients are shown in Table 1. All patients had typical WZS signs, including short limbs, micrognathia, cleft palate, depressed nasal root, vertebral clefts, and wide methaphyses (Figures 5 and 6). All experienced a sensory neural hearing loss of variable degree and had a history of a neonatal respiratory distress (Figure 6). Patients' follow-up period ranged from 6 months to 18 years, with three patients (1, 7, 8) followed-up for at least 12 years. At the end of the follow-up, all patients aged 3–18 years, achieved height above the fifth percentile, while those aged 2 years or less (patients 3, 5, 6), were still below the third percentile and too young to assess a catch-up growth. All patients and their parents had normal karyotypes. A detailed clinical evaluation of the parents of our patients showed normal phenotypes.

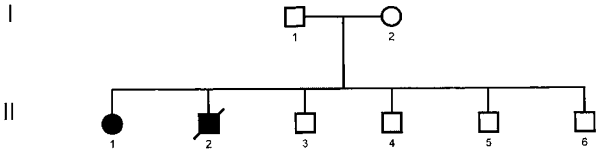


**Figure 4** Pedigree of patient 8. A prematurely born brother (II:2) of patient 8 (II:1) died of a neonatal respiratory distress.

The ocular findings of the eight patients are summarized in Table 2. All patients had a variable degree of hypertelorism and protruding eyes (Figure 5). Four

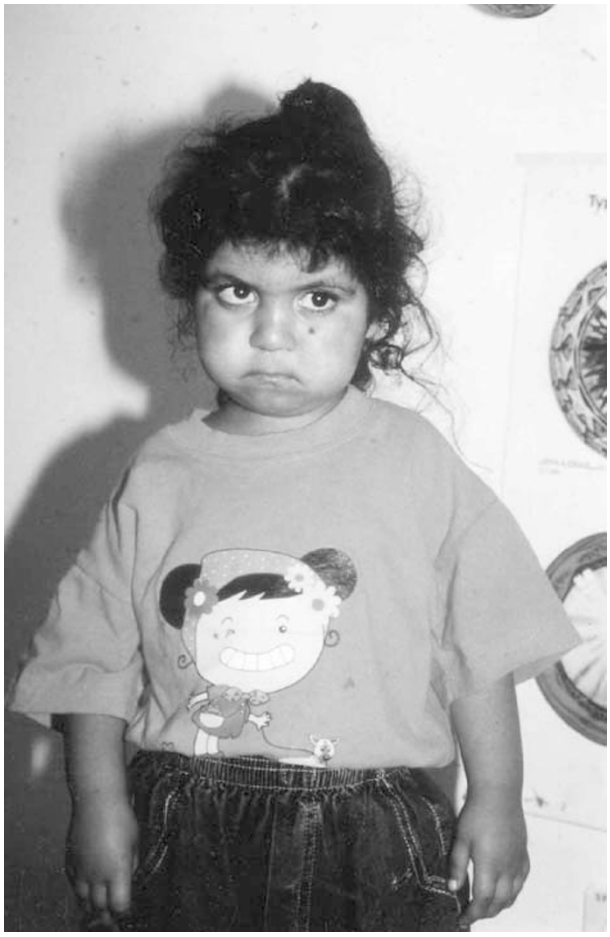

**Figure 5** Colour photograph of patient 5 showing a rhizomelic dwarfism (short limbs), microretrognathia, mild hypertelorism, and depressed nasal root. She had had surgery for esotropia, but there is still right hypertropia, with right inferior oblique overaction, and left head tilt.

**Table 1** Clinical and radiological data

| *Pt. No.* | *Pedigree location* | *Gender* | *Age (years)* | *Parental consanguinity* | *Previous respiratory distress* | *Short limbs* | *Micrognathia* | *Cleft palate* | *Nasal Root depression* | *Vertebral clefts* | *Wide metaphyses* | *Catch up growth* | *Sensory neural deafness* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Figure 1 (IV:1) | M | 14 | + | + | + | + | + | + | + | + | + | + |
| 2 | Figure 1 (IV:2) | F | 7 | + | + | + | + | + | + | + | + | + | + |
| 3 | Figure 1 (IV:9) | F | 2 | + | + | + | + | +a | + | + | + | NA | + |
| 4 | Figure 1 (IV:10) | F | 3 | + | + | + | + | +a | + | + | + | + | + |
| 5 | Figure 2 (V:1) | F | 2 | + | + | + | + | + | + | + | + | NA | + |
| 6 | Figure 2 (V:2) | M | 0.5 | + | + | + | + | + | + | + | + | NA | + |
| 7 | Figure 3 (VI:4) | M | 18 | − | + | + | + | +a | + | + | + | + | + |
| 8 | Figure 4 (II:1) | F | 12.5 | − | + | + | + | +b | + | + | + | + | + |

[a]Submucosal.
[b]Bifid uvula.
NA = nonapplicable because of young patient age.

patients (1, 2, 7, 8) had visual acuity measured by a Snellen chart. All had a near-normal acuity in both eyes. The other four patients (3–6), whose visual acuity could not be measured because of their young age, were able to fix and follow with each eye. Refractive errors ranged from moderate hyperopia to high myopia (Table 2). Patients 7 and 8 had myopia ranging from 1.25 to 8 D with astigmatism of 1–4 D. Patients 1–6 were hyperopic from 1.5 to 3 D. Spectacles were prescribed to four of the eight children (patients 1, 5, 7, 8). Patients 1 and 5 had strabismus. Patient 1 had an intermittent alternating exotropia, left hypertropia with overaction of the left inferior oblique muscle and head tilt to the right. He had a negative Bielschowsky head tilt test and no evidence of superior oblique muscle weakness. Patient 5 had an alternating esotropia with right inferior oblique muscle overaction, right superior oblique underaction, right hypertropia, and head tilt to the left (Figure 5). Owing to of the insufficient cooperation, it was not possible to perform a Bielschowsky head tilt test. The patient was diagnosed with infantile esotropia and possible congenital right fourth cranial nerve palsy, and underwent a strabismus surgery. The ocular media was clear and no vitreoretinal pathology was found in any eye. There was no history of retinal detachment in any of the patients.

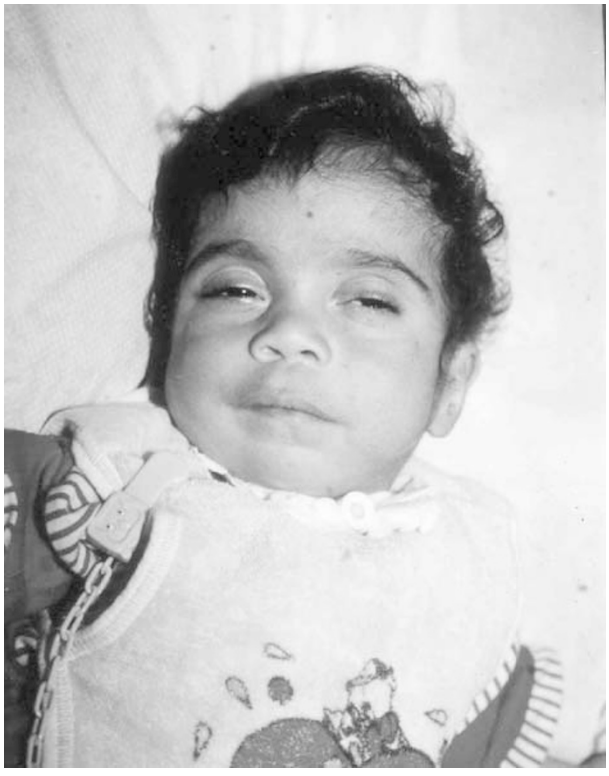

**Figure 6** Colour photograph of patient 6. Note microretrognathia and a tracheostomy tube inserted due to recurrent episodes of respiratory distress.

## Discussion

Several studies reported myopia in children suspected of having WZS.[6,9–11] Foveal or optic nerve hypoplasia, congenital glaucoma, and poor vision were also described in some of them.[9–11] Conversely, no myopia or other ocular manifestations were reported in WZS patients by Haller *et al*,[12] Cortina *et al*,[13] and Maroteaux *et al*.[12–14] In agreement with them, in the

**Table 2** Ocular findings

| *Patient no.* | *Age (years)* | *BCVA* | *Refractive error* | *Strabismus (PD)* |
|---|---|---|---|---|
| 1 | 14 | OD 6/9<br>OS 6/9 | OU + 3.00 | Intermittent AXT: D-30, N-18<br>Left IOOA, LHT 5<br>Right head tilt |
| 2 | 7 | OD 6/9<br>OS 6/9 | OD + 1.50 + 0.50 × 180<br>OS + 1.50 + 1.00 × 180 | None |
| 3 | 2 | F&F | OD + 2.50<br>OS + 2.00 | None |
| 4 | 3 | F&F | OD + 1.50 + 1.50 × 90<br>OS + 1.50 + 1.50X90 | None |
| 5 | 2 | F&F | OD + 2.50-1.00 × 30<br>OS + 2.00 | AET 60, Right IOOA, RHT 25 Left head tilt |
| 6 | 0.5 | F&F | OD + 2.50 + 1.00 × 90<br>OS + 2.50 + 1.00 × 90 | None |
| 7 | 18 | OD 6/9<br>OS 6/9 | OD −6.00–2.75 × 20<br>OS −8.25–4.00 × 160 | None |
| 8 | 12.5 | OD 6/9<br>OS 6/9 | OD −1.25–2.75 × 170<br>OS −2.00–1.00 × 10 | None |

AET = alternating esotropia; AXT = alternating exotropia; BCVA = best-corrected visual acuity; D = deviation for distant fixation; F&F = fixes and follows with each eye; IOOA = inferior oblique muscle overaction; LHT = left hypertropia; N = deviation for near fixation; RHT = right hypertropia.

present study, the corrected visual acuity was in the near-normal range for all patients who cooperated with acuity testing, and no structural ocular abnormalities were found. Only two of our patients had myopia, which indicates that myopia does not necessarily accompany WZS.

Kelly *et al*[6] and Winter *et al*[7] suggested that WZS is a neonatal form of Stickler syndrome and is caused by the same mutation as Marshall and Stickler syndromes. Conversely, Ayme and Preus[15] performed a cluster analysis of the published cases and concluded that WZS and Stickler syndrome are separate entities. Similarly, Chemke *et al*[2] studied five patients in three families with WZS, none of whom had symptoms compatible with Stickler syndrome. They concluded that WZS is a distinct disorder of delayed skeletal maturation, which, unlike the dominant Stickler syndrome, is inherited as an autosomal recessive trait.[2] The ocular findings in our patients, who had neither high myopia with vitreoretinal degeneration, nor glaucoma or cataract, characteristic of Stickler syndrome, support this opinion. The history of consanguinity in the families of most of our patients' also indicates a recessive inheritance. In agreement with that, WZS has been recently found to have a distinct genetic basis from that of Stickler syndrome. Pihlajamaa *et al*[16] analysed DNA from the original patient reported by Weissenbacher and Zweymuller[1] and found a mutation in COL11A2 gene. No mutations were found in the COL2A1 gene, responsible for the classical Stickler syndrome type 1. Based on these findings, the authors suggested that WZS is a nonocular Stickler syndrome.[16] The absence of vitreoretinal abnormalities in WZS patients could probably be accounted for by the lack of expression of COL11A2 gene in the mammalian vitreous, where it is replaced by COL5A2 gene.[17] Thus, COL11A2 mutations should not cause vitreoretinal anomalies, as opposed to the mutations in COL2A1 and COL11A1 genes, which are expressed in the vitreous and are responsible for Stickler syndrome types 1 and 2, respectively.[18]

We have shown, however, that WZS patients might also have ocular involvement, albeit different from Stickler syndrome. Significant refractive errors necessitating spectacle correction were found in half of our patients. Two patients had strabismus, both horizontal and vertical, which has not been previously reported in patients with WZS. Children with WZS, who survive a neonatal respiratory distress, usually have a good general prognosis due to a catch-up growth and normal, or almost normal, psychomotor development.[2,8] They suffer, however, from a hearing loss, and any visual impairment would significantly jeopardize their functional ability. Therefore, a complete ophthalmic examination, including cycloplegic refraction and orthoptic assessment, is warranted at an early age, in order to prevent amblyopia.

## References

1 Weissenbacher G, Zweymuller E. Gleichzeitiges vorkommeneines syndroms von Pierre Robin und einer fetalen chondrodysplasie. *Monatsschr Kinderhwek* 1964; **112**: 315–317.
2 Chemke J, Carmi R, Galil A, Bar-Ziv J, Ben-Ytzhak I, Zurkowski L. Weissenbacher–Zweymuller syndrome: a distinct autosomal recessive skeletal dysplasia. *Am J Med Genet* 1992; **43**: 989–995.
3 Rolland JC, Laugier J, Greiner B, Desbuquois G. Nanisme chondrodystrophique et division palatine chez un nouveaune. *Ann Pediatr (Paris)* 1972; **19**: 139–143.
4 Dinno ND, Shearer L, Weisskopf B. Chondrodysplastic dwarfism, cleft palate and micrognathia in aneonatse, a new syndrome? *Eur J Pediatr* 1976; **123**: 39–42.
5 Ducas P, Roux C, Maroteaux P, Gelbert J. Nanisme micromilique non-achondroplastique associe a un syndrome de Pieere Robin. *Arch Fr Pediatr* 1967; **24**: 481–482.
6 Kelly TE, Wells HH, Tuck KB. The Weissenbacher–Zweymuller syndrome: possible neonatal expression of the Stickler syndrome. *Am J Med Genet* 1982; **11**: 113–119.
7 Winter RM, Baraitser M, Laurence KM, Donnai D, Hall CM. The Weissenbacher–Zweymuller, Stickler, and Marshall syndromes: further evidence for their identity. *Am J Med Genet* 1983; **16**: 189–199.
8 Galil A, Carmi R, Goldstein E, Porter B, Bar-Ziv J, Chemke J. Weissenbacher–Zweymuller syndrome: long term follow up of growth and psychomotor development. *Dev Med Child Neurol* 1991; **33**: 1104–1109.
9 Ramer JC, Eggli K, Rogan PK, Ladda RL. Identical twins with Weissenbacher–Zweymuller syndrome and neural tube defect. *Am J Med Genet* 1993; **45**: 614–618.
10 Moore SJ, Ladda RL, Mowrey PN, Mascari MJ, Ramer JC. Weissenbacher–Zweymuller syndrome in monozygous twins with neural defects and septo-optic dysplasia (Abstract). *Am J Hum Genet* 1989; **45**(Suppl): A56.
11 Scribanu N, O'Neill J, Rimoin D. The Weissenbacher–Zweymuller phenotype in the neonatal period as an expression in the continuum of manifestation of the hereditary arthro-ophthalmopathies. *Ophthalmic Paediatr Genet* 1987; **8**(3): 159–163.
12 Haller JO, Berdon WE, Robinow M, Slovis TL, Baker DH, Johnson GF. The Weissenbacher–Zweymuller syndrome of micrognathia and rhizomelic chondrodysplasia at birth with subsequent normal growth. *Am J Roentgenol Radium Ther Nucl Med* 1975; **125**: 936–943.
13 Cortina H, Aparici R, Beltram J, Alberto C. The Weissenbacher–Zweymuller syndrome. *Pediar Radiol* 1977; **6**: 109–111.
14 Maroteaux P, Roux C, Fruchter Z. Le nanisme micrognathe. *Press Med* 1970; **78**: 2371–2374.
15 Ayme S, Preus M. The Mashall and the Stickler syndromes: objective rejection of lumping. *J Med Genet* 1984; **21**: 34–38.
16 Pihlajamaa T, Prockop DJ, Faber J, Winterpacht A, Zabel B, Giedion A *et al.* Heterozygous glycine substitution in the COL11A2 gene in the original patient with the Weissenbacher–Zweymuller syndrome demonstrates its

identity with heterozygous OSMED (non ocular Stickler syndrome). *Am J Med Genet* 1998; **80**: 115–120.
17 Mayne R, Brewton RG, Mayne PM, Baker JR. Isolation and characterization of the chains of type V/type XÉ collagen present in bovine vitreous. *J Biol Chem* 1993; **268**: 9381–9386.
18 Richards AJ, Yates JRW, Williams R, Payne SJ, Pope FM, Scott JD *et al*. A family with Stickler syndrome type 2 has a mutation in the COL11A1 gene resulting in the substitution of glycine 97 by valine in α1(XI) collagen. *Hum Mol Genet* 1996; **5**: 1339–1343.