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*Clinical Report*

# Czech Dysplasia: Report of a Large Family and Further Delineation of the Phenotype

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Czech dysplasia (OMIM 609162) is a recently delineated COL2A1 disorder characterized by early-onset progressive pseudorheumatoid arthritis, platyspondyly, short third and fourth metatarsals, normal height, and the absence of ophthalmological problems or cleft palate. Czech dysplasia is caused by a specific missense mutation (R275C, c.823C > T) in the triple helical domain of the *COL2A1* gene. We report on a large family with 11 patients with typical Czech dysplasia and sensorineural hearing loss. Hearing loss has hitherto not been considered as a major manifestation of Czech dysplasia. Mutation analysis documented the *COL2A1* c.823C > T (R275C) mutation in all affected individuals. Thus, Czech dysplasia is possibly caused exclusively by the R275C mutation, which is a unique situation among the COL2A1 disorders. The family provides further evidence for the remarkably uniform manifestation of the clinical and radiological abnormalities and adds hearing loss to the list of major anomalies of Czech dysplasia. © 2008 Wiley-Liss, Inc.

**Key words:** COL2A1; Czech dysplasia; deafness; sensorineural hearing loss; arthritis; spondyloepiphyseal osteoarthritis

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## INTRODUCTION

Czech dysplasia (OMIM 609162) is an autosomal dominant skeletal dysplasia characterized by early-onset, progressive pseudorheumatoid arthritis, platyspondyly and short third and fourth toes [Kozlowski et al., 2004; Marik et al., 2004]. Recently, a specific missense mutation (R275C, c.823C > T) in the triple helical domain of the *COL2A1* gene was identified in five unrelated patients with Czech dysplasia [Hoornaert et al., 2007]. The identical mutation had been reported before in patients from five other families whose condition was, in hindsight, compatible with Czech dysplasia [Williams et al., 1993; Reginato et al., 1994; Bleasel et al., 1995, 1996; Lopponen et al., 2004; Hoornaert et al., 2006]. (R275C corresponds to R75C in the older publications where the numbering of the amino acid residues started at the first glycine of the triple helical domain of the pro-α1(II) collagen chain. The new codon numbering of COL2A1 starts at the first methionine, i.e. the start codon of translation [Hoornaert et al., 2007].)

Extraskeletal defects appear to be rare in patients with Czech dysplasia; in particular, no eye problems or cleft palate have been reported to date. Hearing deficits have only been reported in two families [Bleasel et al., 1995; Lopponen et al., 2004].

Here, we report on a large German family in which Czech dysplasia was associated with hearing loss in all affected relatives, and the detection of a R275C mutation.

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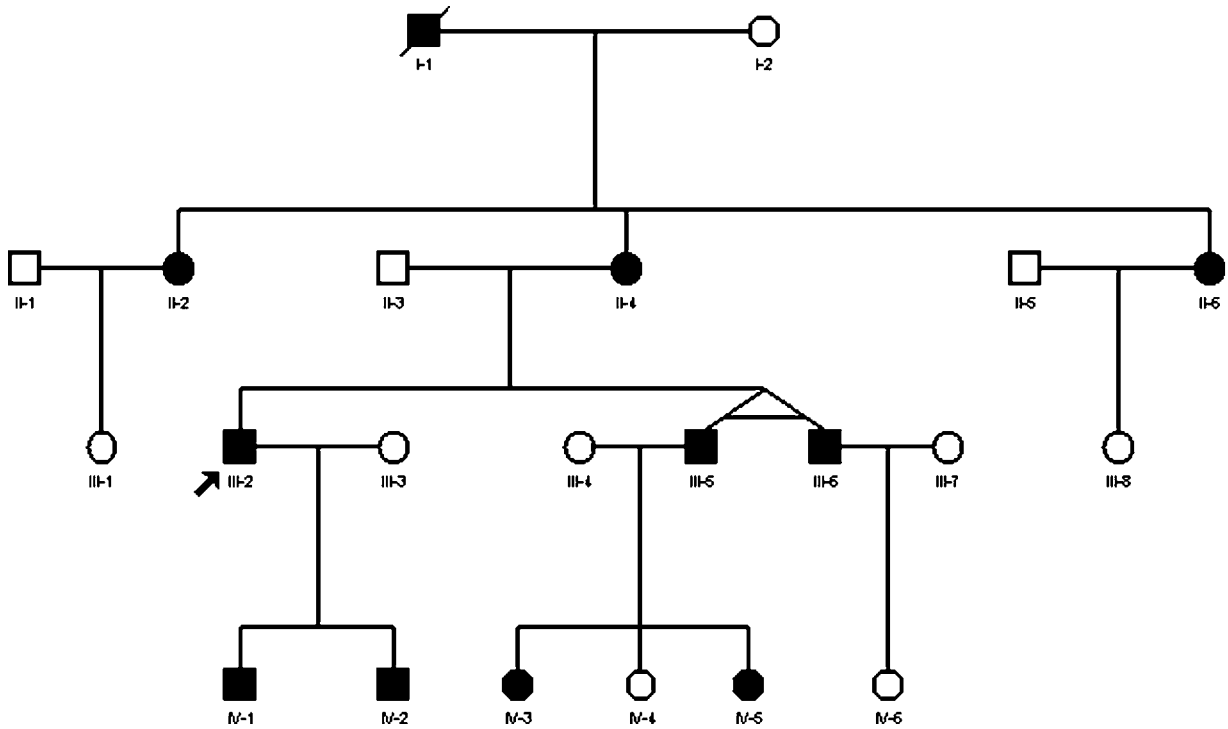


FIG. 1. Pedigree of the family. Full symbols denote patients with Czech dysplasia.

## CLINICAL REPORTS

The pedigree of this German family is shown in Figure 1, and the clinical details of the affected relatives are listed in Table I. The index patient (III-2, Fig. 2a+b) had been suffering from hip pain since the age of 12 years. He underwent hip replacement at the age of 26 and 28 years, respectively. On examination at the age of 42 years, he had difficulties turning his head or to move his shoulders. He suffered from pain in the lower back and the knee joints after slight exercise and used analgetics (ibuprofen, cox-2-inhibitors) regularly. He had bilateral shortness of the third and fourth toes (Fig. 3a). X-ray investigations showed mild platyspondyly with irregular end plates, synovial osteochondromatosis lesions of the knees and short metacarpals III and IV (Fig. 4a–c and Fig. 5a–c). Hearing problems had been noticed for the first time at the age of 16 years, and the patient needed hearing aids by the age of 39 years. Audiologic investigations revealed sensorineural hearing loss particularly of higher frequencies.

The manifestations and the course of the disease in the other affected adult relatives were remarkably

TABLE I. Clinical and Radiographic Findings of the Individual Patients and Review of Published Cases

| Manifestations | Patients | | | | | | | | | | | Literature (n = 10)[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pedigree nr | I-1 | II-2 | II-4 | II-6 | III-2 | III-5 | III-6 | IV-1 | IV-2 | IV-3 | IV-5 | |
| Age (years) | Died aged 76 | 71 | 63 | 61 | 42 | 35 | 35 | 11 | 5 | 13 | 3 | |
| Normal height | + | + | + | + | + | + | + | + | + | + | + | 10/10 |
| Short toes (III + IV) | + | + | + | + | + | + | + | − | − | + | − | 10/10 |
| Hearing loss | + | + | + | + | + | + | + | − | − | − | − | 2/10 |
| Hip replacement | − | + | + | + | − | − | + | − | − | − | − | 7/10 |
| Limited joint mobility | + | + | + | + | + | + | + | − | − | + | − | 10/10 |
| Radiographic traits | | | | | | | | | | | | |
| Platyspondyly | ND | + | + | + | + | + | + | ND | ND | + | ND | 10/10 |
| Irregular vertebral plates | ND | + | + | + | + | + | + | ND | ND | + | ND | 10/10 |
| Short metatarsals III + IV | ND | + | + | + | + | + | + | ND | ND | + | ND | 10/10 |
| Osteoarthrosis | ND | + | + | + | + | + | + | ND | ND | + | ND | 10/10 |
| Osteochondromatosis | ND | + | + | + | + | + | + | ND | ND | − | ND | 7/10 |

ND, not determined.

[a]Williams et al. [1993], Bleasel et al. [1995, 1996], Lopponen et al. [2004], Hoornaert et al. [2006, 2007].

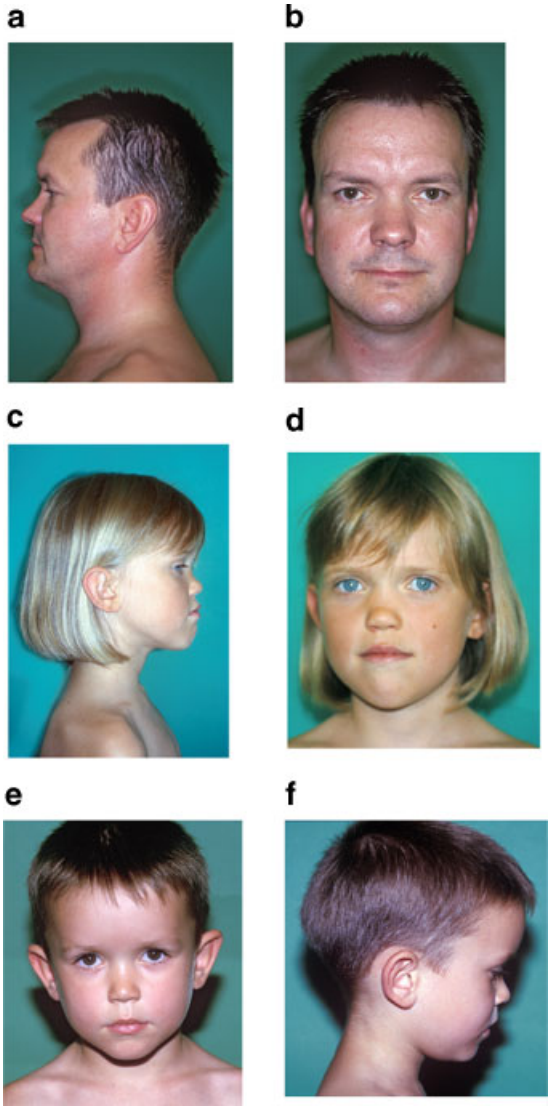


FIG. 2. Facial appearance of patients III-2 (**a** + **b**), IV-3 (**c** + **d**), and IV-1 (**e** + **f**). Note: Depressed nasal bridge, which is more pronounced in the young patients. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

similar: they had hip replacements before the age of 40 years, the older patients also had replacements of the knees; all had hearing impairments, and all had short third and fourth toes. No patient suffered from ocular problems or cleft palate. Facial appearance was unremarkable except for a mildly flattened nasal bridge. This finding was more clearly visible in childhood and tended to normalize with age (Fig. 2a–f). Patient I-1 had died at the age of 76 years. He was reported to be wheelchair-bound and nearly deaf in his last years.

The two sons of the index patient (IV-1 and IV-2) had no clinical problems on examination at the age of 11 and 5 years, respectively. However, the parents emphasized the "broad knees" of both children (a similar observation had been made in IV-3 and IV-5) and therefore suspected them to be affected, which was later confirmed by the molecular tests, and in the older child IV-3 also by the clinical course. Importantly, all toes were still of normal length at that age, and in IV-3 the shortness of the third and fourth toes only became apparent at about 12 years.

## MATERIALS AND METHODS

DNA of the patients and healthy relatives was extracted from peripheral blood after informed consent. Mutation analysis of the *COL2A1* coding region was performed using the MegaBACE 1000 Sequencing System (Molecular Dynamics/Amersham Biosciences, Piscataway, NJ). Details of the PCR and sequencing reactions are available upon request. Sequencing results were compared to the wild-type *COL2A1* sequence (GenBank accession no. NM_001844). For cDNA numbering, +1 corresponds to the A of the ATG translation initiation codon 1 in the reference sequence. Amino-acid residues were numbered according to GenBank accession no. L10347 starting from the translation initiation codon.

## RESULTS

Mutation analysis of the index patient (III-2) revealed a heterozygous mutation in *COL2A1* exon 13: c.823C > T which is predicted to change arginine to cysteine at codon 275 (p.R275C). This mutation was also identified in the other affected family members (II-2; II-4; II-6; III-5; III-6; IV-3) and in the children IV-1, IV-2, and IV-5. The healthy individuals III-1, III-8, IV-4, and IV-6 did not carry this mutation.

## DISCUSSION

The family reported here included 11 patients with Czech dysplasia (OMIM 609162, progressive pseudorheumatoid dysplasia with hypoplastic toes) associated with an R275C mutation in the *COL2A1* gene. The disorder was fully penetrant and showed a remarkably uniform phenotypic expression. Main manifestations were osteoarthrosis of hips, knees, shoulders and spine with onset in adolescence, osteochondromatosis particularly of knees, short metatarsals III and IV that became clinically visible as short 3rd and 4th toes by late childhood, vertebral abnormalities (mild platyspondyly, irregular end plates, reduced intervertebral distances), hearing loss starting in early adulthood, and normal height.

With the exception of hearing loss, these anomalies had also been observed in all 10 previously reported patients or families with the R275C mutation of *COL2A1* (Table I). Thus, the family reported here provides further evidence that the recently delineated "Czech dysplasia" is clinically distinguishable from other COL2A1 disorders, and that Czech dysplasia is probably caused exclusively by the R275C mutation.


FIG. 3. Feet of patients III-2 (**a**), IV-1 (**b**), IV-2 (**c**), II-4 (**d**), IV-3 (**e**), III-5 (**f**), and III-6 (**g**). Note: Shortness of 3rd and 4th toes is not yet visible in patients IV-1 and IV-2. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

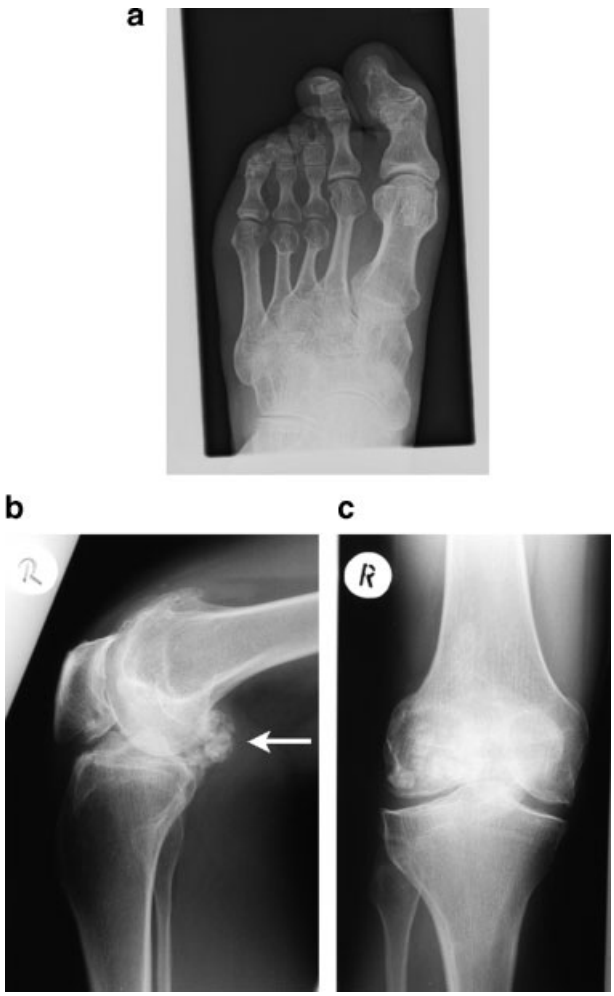


FIG. 4. Radiographs of patient III-2: (**a**) Left foot. Note: Short metatarsals III and IV. (**b**+**c**) Right knee. Note: Arthritic changes and osteochondromatosis lesions (arrow) at age 36 years.

Sensorineural hearing loss was present in all adult patients of this family and necessitated hearing aids by the end of the fourth decade. Subclinical hearing impairment for high frequencies was already detected at the age of 6 years by a pre-school test in patient IV-3. The auditory problems are similar to those reported in type I Stickler syndrome which are, however, less severe and not progressive [Szymko-Bennett et al., 2001]. Type II collagen is expressed in the cochlea, and structural alterations could affect sound mechano-transduction or lead to hair cell degeneration by abnormal mechanical stress forces [Slepecky et al., 1992; Thalmann, 1993]. Hearing loss was also present in the families reported by Bleasel et al. [1995] and Lopponen et al. [2004], but was not reported in the other eight families with R275C mutations (Table I). This suggests that hearing loss is a variable finding in Czech dysplasia, as it is in Stickler syndrome. On the other hand, no auditory tests had been performed in these families, and it is conceivable that some patients (many of whom were children or young adults) may have had subtle changes that did not (or not yet) need any treatment. Alternatively, we cannot exclude that the hearing problems in this family may have been caused by a different defect independent from the *COL2A1* mutation.

Though Czech dysplasia is characterized by a unique combination of clinical problems, it shares several characteristics with other COL2A1 disorders. Auditory problems and osteoarthrosis are also part of type I Stickler syndrome (OMIM 108300), but neither the ocular signs nor cleft palate that are characteristic of Stickler syndrome have been reported in patients with Czech dysplasia.

Short metatarsalia III and IV have also been observed in patients with platyspondylic skeletal

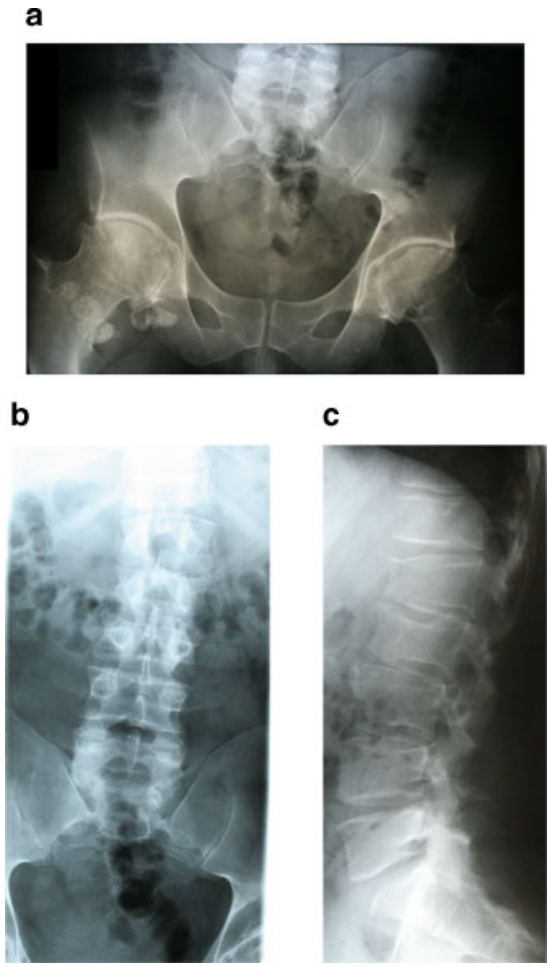


FIG. 5. Radiographs of patient III-5: (**a**) Note: Arthritic changes of the hip joints and osteochondromatosis lesions (age 25 years). (**b**+**c**) Note: Mild platyspondyly and irregular shape of vertebral bodies.

dysplasia type Torrance (OMIM 151210) [Neumann et al., 2003; Zankl et al., 2005]. In contrast to Czech dysplasia, Torrance type dysplasia is characterized by short stature, short limbs, short ribs and variable platyspondyly, and most patients die perinatally [Nishimura et al., 2004].

Brachydactyly of hands and feet is also present in spondyloperipheral dysplasia (OMIM 271700); but, in contrast to Czech dysplasia, this is not restricted to metatarsals III/IV [Zankl et al., 2004]. Other manifestations of spondyloperipheral dysplasia are short stature, clubfeet, platyspondyly, midface hypoplasia, myopia and epiphyseal dysplasia. Sensorineural hearing loss was reported in one patient [Sorge et al., 1995]. Spondyloperipheral dysplasia is probably the syndrome with the greatest clinical similarity to Czech dysplasia; indeed, one of the patients who had originally been included in the delineation of Czech dysplasia (Patient 3 in Kozlowski et al. [2004]), but who also had disproportionate short stature, was reclassified as spondyloperipheral dysplasia after the detection of a Y1391C mutation [Hoornaert et al., 2007].

Osteoarthritis, the most debilitating aspect of Czech dysplasia, is also a problem of Stickler dysplasia, spondyloperipheral dysplasia, osteoarthritis with mild chondroplasia (OMIM 604864) and Kniest dysplasia (OMIM 156550). Clinically, the joint problems can resemble rheumatoid arthritis (hence the alternative term "pseudorheumatoid dysplasia" for Czech dysplasia). Patient IV-3 of this family and both patients of the family reported by Lopponen et al. [2004] had been diagnosed as juvenile rheumatoid arthritis before.

In conclusion, patients with Czech dysplasia have a remarkably uniform intra- and interfamilial clinical manifestation and course of the disease. The first clinical signs in childhood are broad knees and flat nasal bridge, followed in late childhood and adolescence by short 3rd and 4th toes, joint pain in knees and hips and later osteoarthritis of the spine and shoulder. Hip replacement is usually necessary before the end of the 4th decade. Hearing loss had hitherto not been appreciated as a major trait but was a problem in all adult patients of this family. We propose that auditory tests should be performed in all patients with Czech dysplasia as part of the diagnostic work-up.

Czech dysplasia is the only *COL2A1* disorder that appears to be caused exclusively by a single mutation (R275C). To date it is unclear whether this mutation arose independently in all 11 families since none of the reported mutations was shown to be de novo. Since all families were (at least partially) of European descent, it is tempting to speculate about an ancient single origin of the R275C mutation. Future studies will also be needed to elucidate the precise structural and functional consequences of this arginine-to-glycine exchange, and why this mutant form of type II collagen determines such a specific clinical phenotype.

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