RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Spondylo-Epiphyseal Dysplasia, Maroteaux Type (Pseudo-Morquio Syndrome Type 2), and Parastremmatic Dysplasia are Caused by *TRPV4* Mutations

Gen Nishimura,[1] Jin Dai,[2,3] Ekkehart Lausch,[4] Sheila Unger,[4,5] André Megarbané,[6] Hiroshi Kitoh,[7] Ok Hwa Kim,[8] Tae-Joon Cho,[9] Francesca Bedeschi,[10] Francesco Benedicenti,[11] Roberto Mendoza-Londono,[12] Margherita Silengo,[13] Maren Schmidt-Rimpler,[4] Jurgen Spranger,[4] Bernhard Zabel,[4] Shiro Ikegawa,[2] and Andrea Superti-Furga[4]*

[1]Department of Radiology, Tokyo Metropolitan Kiyose Children's Hospital, Kiyose, Japan

[2]Laboratory for Bone and Joint Diseases, Center for Genomic Medicine, RIKEN, Minato-ku, Tokyo, Japan

[3]The Center of Diagnosis and Treatment for Joint Disease, Drum Tower Hospital Affiliated to Medical School of Nanjing University, Nanjing, China

[4]Centre for Pediatrics and Adolescent Medicine, Freiburg University Hospital, University of Freiburg, Freiburg, Germany

[5]Institute for Human Genetics, Freiburg University Hospital, University of Freiburg, Freiburg, Germany

[6]Unité de Génétique Médicale, Laboratoire de Biologie Moléculaire et Cytogénétique, Faculté de Médecine, Université Saint-Joseph, Beirut, Lebanon

[7]Department of Orthopaedic Surgery, Nagoya University School of Medicine, Nagoya, Japan

[8]Department of Radiology, Ajou University Hospital, Youngtong-gu, Suwon, Korea

[9]Department of Orthopedic Surgery, Seoul National University Children's Hospital, Seoul, South Korea, Korea

[10]Clinical Genetic Unit, Department of Obstetrics and Pediatrics, Fondazione Ospedale Maggiore Policlinico Mangiagalli e Regina Elena, Milano, Italy

[11]Clinical Genetics Service, Department of Pediatrics, General Regional Hospital, Bolzano, Italy

[12]Division of Clinical and Metabolic Genetics, The Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada

[13]Department of Pediatrics, Ospedale Infantile Regina Margherita, University of Torino, Torino, Italy

Received 5 January 2010; Accepted 24 February 2010

Recent discoveries have established the existence of a family of skeletal dysplasias caused by dominant mutations in *TRPV4*. This family comprises, in order of increasing severity, dominant brachyolmia, spondylo-metaphyseal dysplasia Kozlowski type, and metatropic dysplasia. We tested the hypothesis that a further condition, Spondylo-epiphyseal dysplasia (SED), Maroteaux type (MIM 184095; also known as pseudo-Morquio syndrome type 2), could be caused by *TRPV4* mutations. We analyzed six individuals with Maroteaux type SED, including three who had previously been reported. All six patients were found to have heterozygous *TRPV4* mutations; three patients had unreported mutations, while three patients had mutations previously described in association with metatropic dysplasia. In addition, we tested one individual with a distinct rare disorder, parastrem-

Grant sponsor: German Ministry for Education and Research; Grant sponsor: European Union; Grant sponsor: Ministry of Education, Culture, Sports, and Science of Japan; Grant number: 20390408; Grant sponsor: Research on Child Health and Development; Grant number: 20-S-3; Grant sponsor: Korea Healthcare technology R&D Project; Grant sponsor: Ministry for Health, Welfare and Family Affairs, Republic of Korea; Grant number: A080588; Grant sponsor: European Skeletal Dysplasia Network (ESDN); Grant sponsor: University of Freiburg; Grant sponsor: Deutsche Forschungsgemeinschaft; Grant number: La 1381/1-3.

Shiro Ikegawa and Andrea Superti-Furga are equally contributed to this work.

*Correspondence to:
Prof. Andrea Superti-Furga, Centre for Pediatrics and Adolescent Medicine, Mathildenstrasse 1, Freiburg 79106, Germany.
E-mail: asuperti@uniklinik-freiburg.de

Published online 11 May 2010 in Wiley InterScience
(www.interscience.wiley.com)
DOI 10.1002/ajmg.a.33414

matic dysplasia (MIM 168400). This patient had a common, recurrent mutation seen in several patients with Kozlowski type spondylo-metaphyseal dysplasia. We conclude that SED Maroteaux type and parastremmatic dysplasia are part of the TRPV4 dysplasia family and that *TRPV4* mutations show considerable variability in phenotypic expression resulting in distinct clinical-radiographic phenotypes.

Key words: spondylo-epiphyseal dysplasia; skeletal dysplasia; Morquio; TRPV4; dominant inheritance

How to Cite this Article:
Nishimura G, Dai J, Lausch E, Unger S, Megarbané A, Kitoh H, Kim OH, Cho T-J, Bedeschi F, Benedicenti F, Mendoza-Londono R, Silengo M, Schmidt-Rimpler M, Spranger J, Zabel B, Ikegawa S, Superti-Furga A. 2010. Spondylo-epiphyseal dysplasia, Maroteaux type (pseudo-Morquio syndrome type 2) and parastremmatic dysplasia are caused by *TRPV4* mutations.
Am J Med Genet Part A 152A:1443–1449.

INTRODUCTION

In 1929, Luis Morquio reported a family in which four of five sibs had a familial osseous dystrophy characterized by predominant shortening of the trunk [reviewed in Morquio, 1935]. The description attracted much attention, similar patients were reported rapidly, and the Morquio syndrome became the prototype for skeletal dystrophies with short trunk. Maroteaux and Lamy [1961] wrote in their milestone monography on phenotypic chondrodystrophies, that there seemed to be variants of the so-called Morquio syndrome, but that they preferred to maintain Morquio disease as a single clinical entity. Maroteaux et al. [1968] formally distinguished Morquio syndrome (then known to be associated with increased mucopolysaccharide excretion) from two conditions that they called pseudo-Morquio type 1 and pseudo-Morquio type 2.

The relationship between Morquio and pseudo-Morquio disorder were unraveled over the years. The original Morquio syndrome was found to have two distinct biochemical variants; N-acetylgalactosamine 6-sulfatase deficiency (Morquio A; MIM 253000) and beta-galactosidase deficiency (Morquio B; MIM 253010). Pseudo-Morquio type 1, that included mental retardation as part of the phenotype, was recognized as akin to a condition first described by Dyggve et al. [1962] as Morquio-Ulrich's disease but that has since become known as *Dyggve–Melchior–Clausen dysplasia* (MIM 223800) and is now known to be a distinct entity associated with mutations in the *dymeclin* gene [Cohn et al., 2003; El Ghouzzi et al., 2003]. The second condition, pseudo-Morquio type 2 (MIM 184095), has been subsequently renamed to spondylo-epiphyseal dysplasia (SED), Maroteaux type [Doman et al., 1990] and then to spondylo-epimetaphyseal dysplasia, Maroteaux type [Megarbane et al., 2004]. An older patient report [Kochs, 1932] was considered to be an example of spondylo-epimetaphyseal dysplasia Maroteaux—pseudo-Morquio type 2 (SEDM-PM2). More examples of the disorder have been reported [Matteini et al., 1981; Doman et al., 1990; Nishimura et al., 2003; Megarbane et al., 2004]. Unlike Morquio syndrome and the other Morquio-like conditions reported so far, SEDM-PM2 is inherited as a dominant, rather than a recessive trait.

It was recently reported that mutations in *TRPV4*, that codes for a calcium-permeable cation channel, cause a spectrum of skeletal dysplasias that range from dominantly inherited brachyolmia (isolated shortening of the trunk; MIM 113500) to spondylometaphyseal dysplasia, Kozlowski type (SMDK; MIM 184252) and metatropic dysplasia (MD; MIM 156530) [Rock et al., 2008; Krakow et al., 2009]. These findings established a novel skeletal dysplasia family and highlighted the importance of TRPV4 in skeletal development.

We noted clinical and radiographic features in common among SEDM-PM2, SMDK, and MD and tested the hypothesis that SEDM -PM2 was caused by *TRPV4* mutations. We also tested another girl whose clinical and radiographic features best fit the condition of parastremmatic dysplasia [Langer et al., 1970]; this latter condition is very rare and has not been included in the nosology of genetic skeletal disorders.

CLINICAL REPORTS

Patient Ascertainment and Diagnostic Criteria

The diagnostic criteria for SEDM-PM2 were: short stature with marked, progressive shortening of the trunk but absence of significant scoliosis; presence of brachydactyly; and absence of facial deformities, ocular changes, and neurodevelopmental abnormalities [Doman et al., 1990; Nishimura et al., 2003; Megarbane et al., 2004]. None of the patients included here had clinically significant hypoacusis. Radiographic criteria were marked but uniform platyspondyly without anterior tongue formation, broad pelvis with dysplastic changes at the femoral neck, and generalized shortening of metacarpals and phalanges. Genetic data included dominant inheritance in one family, as well as exclusion of *COL2A1* mutations in three individuals (data not shown).

Subjects

Three of the individuals included have been published as examples of SEDM-PM2: patient 1 (multiplex) and patient 2 (simplex): [Nishimura et al., 2003]; patient 3 (simplex): [Megarbane et al., 2004], and detailed clinical and radiographic descriptions are given in those articles.

Patient 4 was part of a multiplex family. The proband was born at 40 weeks of gestation with normal weight and length. He came to medical attention at age at 1 year and 6 months because of bowed legs. When referred to one of us (HK) at age 2 years and 1 month, physical findings included mild bowed legs, mild brachydactyly, and increased lumbar lordosis. The face and body proportions were normal. At 5 years and 5 months, his height was 105.3 cm (−1.4

SD). Other than mild brachydactyly, he was healthy. At age 6 years and 6 months, his height was 111 cm (−1.5 SD). The patient came from a family with dominantly inherited short stature. The mother showed mild restriction of the elbow and interphalangeal joints. The interphalangeal joints were enlarged and there was moderate brachydactyly. She had painful knee and ankle joints. At age 28 years, her height was 144 cm (−2.7 SD). The maternal grandfather and grand-grandmother are similarly affected with height of 157 cm (−2.2 SD) and 136 cm (−4.4 SD), respectively.

Patients 5–7 were simplex patients. Patient 5 (Fig. 1) was born full-term with BW of 7lb 2oz and length of 21 in. (90th centile). At age 2.5 years he was noted to have short stature and metaphyseal thickening of his distal femurs. At 4 years of age he had discoid cartilages removed from his knees. On examination at age 7 years, his height was 95.5 cm (approximately −5 SD) and his weight was 16.5 kg. The chest was described as flattened from side to side and had a prominent sternum. There was a wider diameter of his wrists, elbows and IP joints, fingers and knees, and bilateral cubitus valgus. The fingers appeared short. The radiographic findings were interpreted as SED with areas of metaphyseal involvement. Urinary mucopolysaccharide excretion and leucocyte beta-galactosidase and N-acetylgalactosamine sulfate sulfatase activities were normal. At age 15 years, he had bilateral wedge resection of the tibia followed by wedge resection of the femur. At the age of 38 years, his height was 118 cm (<3rd centile), weight 40 kg (<3rd centile), HC 55.8 cm (25–50th centile), and arm span 120 cm (<3rd centile). The impression was that of short stature with shortening of both the limbs and the trunk. There was bilateral cubitus valgus, marked

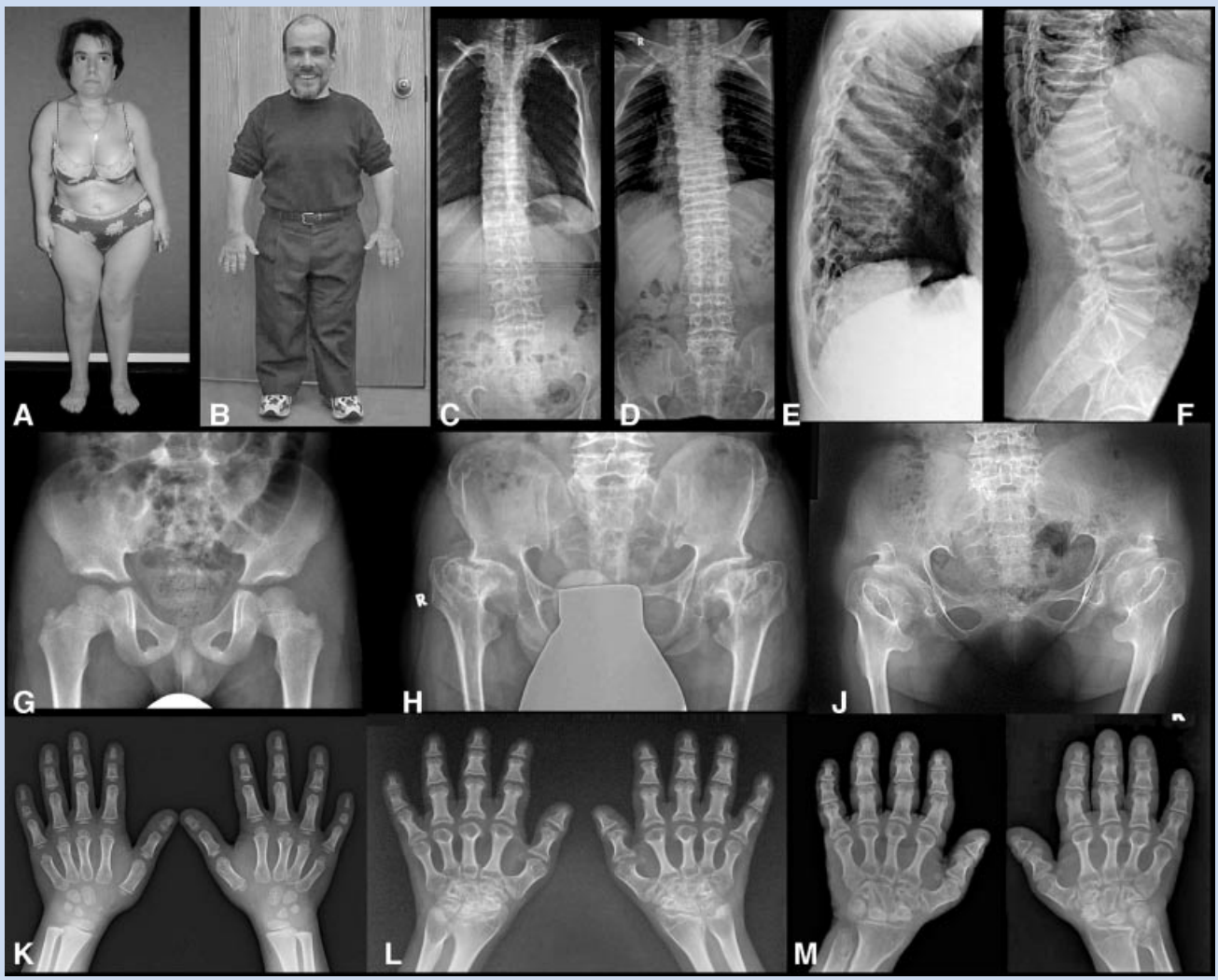

FIG. 1. Clinical appearance and radiographic features of SEDM-PM2. Patients 1, 2, and 3 have been reported previously (see text). Shown are patient 6 (panels A, C, E, H, and L), patient 5 (panels B, D, F, J, and M), and patient 4 (panels G and K). The body proportions were those of predominant trunk shortening with less pronounced limb shortening but marked brachydactyly. The radiographs show platyspondyly without anterior tongue formation, marked dysplasia of the proximal femoral metaphyses and epiphyses, as well as flaring of the iliac wings with a marked notch just above the acetabulum (the shape of the ilia being reminiscent of the blade of a halberd), and generalized brachyphalangy.

brachydactyly with enlarged joints, marked ligamentous laxity of the hands and fingers, and distal phalangeal shortening with lenticulate shape of the nails. The knee joints were enlarged with limited mobility and fixed flexion of 15–20°. There were no corneal clouding or dysmorphic features. Mucopolysaccharides in the urine were again negative and a blood smear examination for lysosomal inclusions was negative. The radiographic findings are shown in Figure 1. Since a diagnosis of SED within Morquio disease was not supported by the biochemical findings, the diagnosis was changed to SEDM-PM2 with a differential diagnosis of metatropic variant and DNA was stored for future studies.

Patient 6 (Fig. 1) was an adult woman who came for genetic counseling and prenatal diagnosis. She had been born at term and with normal size. At age 2 months, a narrow thorax was noticed and a diagnosis of Jeune asphyxiating thoracic dystrophy was entertained but subsequently rejected. At age 10 years, osteotomies were done for genua valga, and at age 13 years, a diagnosis of SED, unspecified type was made. She was ascertained through the European Skeletal Dysplasia Network, where the diagnosis of SEDM-PM2 was made. Her clinical features at that time included short stature with short trunk and brachydactyly. There was mild thoracic kyphosis, but no scoliosis. Her adult height was measured as 130 cm at age 27 years and 125 cm at age 31 years (both markedly below the 3rd centile). Because no molecular confirmation was possible at that time, she sought a new diagnostic workup 2 years later and was evaluated by two of us (F. Bedeschi and F. Benedicenti) at two different centers and subsequently submitted to the diagnostic group Skeldys-Italia, where—unaware of the previous diagnosis—the same diagnosis of SEDM-PM2 was made. Before molecular diagnosis was obtained, she became pregnant; after an uncomplicated pregnancy, a caesarean was performed at week 33 and a healthy baby was delivered who had normal intrauterine growth parameters and no signs of skeletal dysplasia.

Patient 7 was a 7-year-old girl referred from the Cabo Verde islands for diagnostic opinion. Her family history was unremarkable, the parents were unaffected and of average height, and her two elder brothers were unaffected. Her parents reported birth weight of 2.2 kg and birth length of 46 cm (both under P3 for newborn girls at term), but no medical records are available and she may have been born preterm. She is said to have walked only at age 4 years. When she was seen by one of us (MCS) at age 7 years, she manifested short stature (101 cm; approximately −4 SD for Italian children) and her legs showed marked windswept deformity combined with flexion at the knee joint (Fig. 2A). Her fingers and toes were long. Her mental development was apparently normal, ophthalmologic evaluation was normal, and her hearing was apparently normal. She had marked platyspondyly with a thoracolumbar scoliosis and diffuse metaphyseal changes. Her hand X-rays showed no brachydactyly but her carpal maturation was apparently retarded. Both the distal femoral metaphyses and the proximal tibial metaphyses had a flaky appearance consistent with diffuse enchondromatosis (Fig. 2B–D). The combination of windswept and flexural deformity of the legs, scoliosis, platyspondyly, and flaky metaphyses fit well with parastremmatic dysplasia [Langer et al., 1970]. Her phenotype was similar to that of a prior report of parastremmatic dysplasia [Sensenbrenner et al., 1974], particularly taking into account the younger age of the present patient.

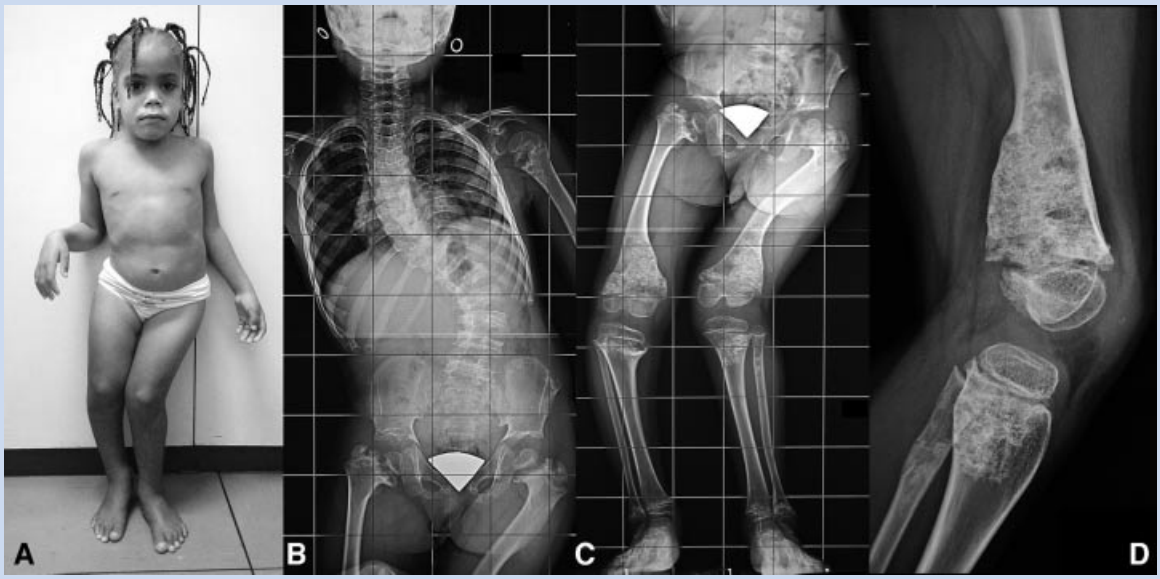

FIG. 2. Appearance and radiographic features of patient 7 with parastremmatic dysplasia. There was shortening of the trunk because of platyspondyly and scoliosis, as well as flexum deformity in both knees (left more than right) as well as windswept deformity with right genu varum and left genu valgum (panel A). Radiographs show platyspondyly with scoliosis (panel B) and marked metaphyseal changes in the long bones with popcorn appearance in the distal femur and proximal tibia consistent with extensive enchondromatosis (panels C and D). Compare these images with that of the patient report of parastremmatic dysplasia reported by Sensenbrenner et al. [1974].

METHODS

Molecular Analysis

Genomic DNA was extracted by standard procedures from peripheral blood. The exon sequences of *TRPV4* and their flanking intronic sequences were amplified by PCR from genomic DNA. PCR products were directly sequenced using an ABI 310 or ABI Prism 3700 automated sequencer (PE Biosystems). For confirmation of novel mutations in non-familial patients, genomic DNA from the unaffected parents was sequenced for the corresponding regions when parents' samples were available. The molecular analysis was performed independently in the two laboratories in Tokyo and in Freiburg; in both laboratories, over 200 control chromosomes from European or Asian origin have been sequenced within a collaborative genotype–phenotype analysis project [Dai et al., 2010]. Primer sequences are specified in the online supplemental material. The PCR reaction was done with standard protocols with annealing temperature of 60°C. The GenBank reference sequence for *TRPV4* is NM_021625.3.

RESULTS

All individuals with SEDM-PM2, whether published previously or ascertained for this study, were found to have heterozygous mutations in *TRPV4*. The mutations are listed in Table I. Briefly, patient 1 was found to have a heterozygous deletion c.2396_2412del17, which predicts p. Pro799Lfs63X. Patients 2 and 4 were heterozygous for mutations c.547G>A (Glu 183Lys) in exon 3 and c.1805A>G (Tyr6O2Cys) in exon 11, respectively. The unrelated patients 3 and 5 were both found to have the p.Pro799Leu mutation in exon 15; this mutation has been identified in several patients with metatropic dysplasia [Krakow et al., 2009; Dai et al., 2010]. Patient 6 had the substitution p.Glu797Lys in exon 15; we have observed this mutation, situated two amino acid residues upstream the p.Pro799Leu mutation, once before in an individual diagnosed as having metatropic dysplasia [Dai et al., 2010].

DISCUSSION

Following the distinction of the pseudo-Morquio syndromes and the biochemical and genetic elucidation of the true Morquio A and B (MPS IVA and MPS IVB) (Fig. 3), the condition known as pseudo-Morquio type 2 has been renamed as SED, Maroteaux type [Doman et al., 1990]. The SEDM-PM2 entity has gained access to the Nosology and Classification of Genetic Skeletal Disorders [Hall, 2002; Superti-Furga and Unger, 2007], and more patients have been diagnosed. In an earlier publication on SEDM-PM2, we also emphasized the radiographic differential diagnosis of SEDM-PM2 in comparison to spondylo-peripheral dysplasia (a type 2 collagen disorder), and the relationship of SEDM-PM2 and SMDK or metatropic dysplasia had escaped our notice [Nishimura et al., 2003]. Similarly, in other patient reports on SEDM-PM2 [Doman et al., 1990; Megarbane et al., 2004], attention is given to the distinction of SEDM-PM2 from true Morquio syndrome, and both SMDK and MD are given little consideration in the differential diagnosis. We now report that SEDM-PM2 is caused by mutations in the gene for calcium channel TRPV4 and is thus allelic to brachyolmia, SMD Kozlowski, and MD. The interesting evolution of the nosology of the Morquio syndrome is shown in Figure 3.

In retrospect, the similarity in radiographic changes among SEDM-PM2, SMDK, and classic, non-lethal MD are marked. In SMDK, brachydactyly is usually absent or very mild; in MD, kyphosis, and/or scoliosis develop in childhood, a feature that was not seen in patients with SEDM-PM2. Otherwise, the disorders share many radiographic features, particularly platyspondyly with broad and elongated vertebral bodies that overshadow the vertebral pedicles in anteroposterior radiographs. It must be noted that there is significant variability even within these categories; thus, patient 4 and his affected relatives in the present series have a milder form than do patients 5 and 6. Since the mutation present in patient 4 has not been found in other patients so far, it is possible that that particular mutation may result in a milder phenotype. Variability in metatropic dysplasia is well recognized.

Parastremmatic dysplasia was delineated as a severe dysplasia with deformed limbs [Langer et al., 1970]. Although MD was mentioned in the differential diagnosis of parastremmatic dysplasia, the condition seemed distinct based on the severe involvement of the lower limbs and on the peculiar flaky appearance of metaphyses determined by enchondromatous changes. The condition is very rare and has not been included in the nosology; indeed, the similarity of the spine changes to those seen in metatropic dysplasia prompted us to question whether the condition might be a metatropic dysplasia variant. Our results confirm this hypothesis; it is interesting that the patient with parastremmatic dysplasia had a

TABLE I. Summary of TRPV4 mutations

Patient no.	Previously reported in	Diagnosis	*TRPV4* mutation
Patient 1	Nishimura et al. [2003], patient 1	SEDM-PM2	c.2396_2412del17, p.Pro799Leufs63X
Patient 2	Nishimura et al. [2003], patient 3	SEDM-PM2	c.547G>A, p.Glu183Lys
Patient 3	Megarbane et al. [2004]	SEDM-PM2	C.2396c>*T*, p.Pro799Leu
Patient 4	Unreported	SEDM-PM2	c.1805A>G, p.Tyr602Cys
Patient 5	Unreported	SEDM-PM2	C.2396c>*T*, p.Pro799Leu
Patient 6	Unreported	SEDM-PM2	c.2389G>A, p.Glu797Lys
Patient 7	Unreported	Parastremmatic dysplasia	c.1781G>A, p.Arg594His

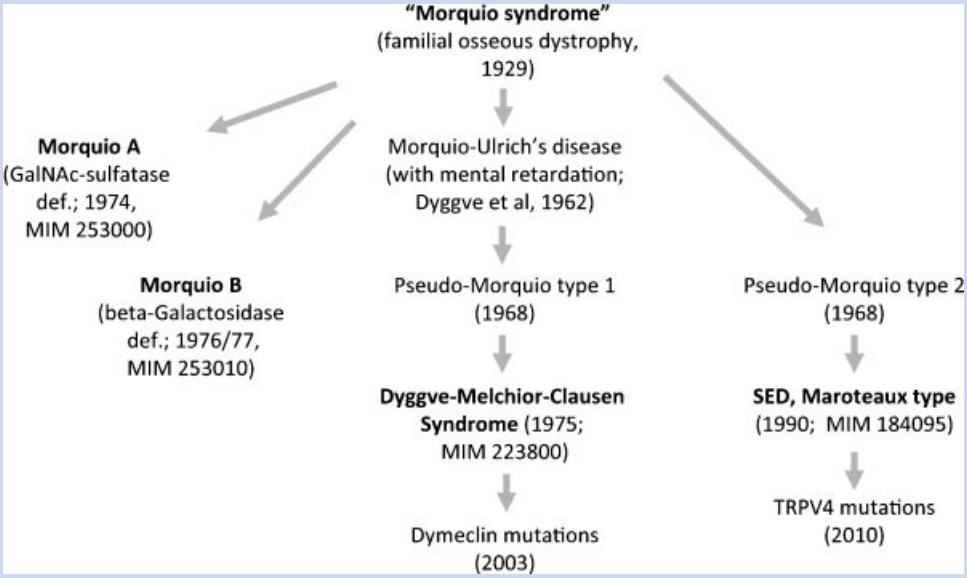

FIG. 3. Evolution of the nosology of Morquio disease.

mutation that has been associated with the milder condition, SMDK, rather than with MD (see below).

Some of the *TRPV4* mutations identified in the patients with SEDM-PM2 reported here are novel, while others have been identified previously in individuals who have been diagnosed as SMDK or MD [Krakow et al., 2009; Dai et al., 2010]. This reinforces the close relationship among SMDK, SEDM-PM2, and MD and the fact that they constitute variations on a common theme. It seems that genotype–phenotype correlations are not robust, and that in presence of a *TRPV4* mutation, some allowance must be made for modulation of the clinical phenotype by other genes and/or by non-genetic factors.

The clustering of mutations in exon 15 at amino acid residues 797 and 799 within the MAP7 (microtubule-associated protein 7) binding region is intriguing. Clustering of mutations in the MAP7 region is not specific for SEDM-PM2, as we have seen similar clustering in our cohort of patients with metatropic dysplasia [Dai et al., 2010]. The girl with parastremmatic dysplasia was found to have mutation R594H in exon 11; this is another recurrent TRPV4 mutation that has been associated with SMDK in more than 10 unrelated individuals [Krakow et al., 2009; Dai et al., 2010] again underscoring the relatively loose genotype–phenotype association.

The precise pathogenetic mechanism leading from *TRPV4* mutations to chondrodysplasia is not well understood. A gain-of-function mechanism has been postulated [Rock et al., 2008], but the observation of a large number of different mutations at the heterozygous state in individuals with either SMDK or MD, including in-frame deletions [Dai et al., 2010] (and unpublished results), makes it unlikely that all of them result in a gain-of-function, and a different dominant negative mechanism may be operational.

Two *TRPV4* mutations in the present series are of special interest. The substitution p.Glu797Lys (seen in patient 6) has been previously engineered in vitro and found to result in constitutionally activated TRPV4 [Watanabe et al., 2003]. The p.Pro799Leufs63X mutation seen in patient 1 predicts abolition of 77 amino acids c-terminal from Pro799 and substitution by a stretch of 63 missense amino acids. A C-terminal stretch of amino acids in TRPV4, particularly beyond residue 828, is required for oligomerization of TRPV4 and transport to the membrane [Becker et al., 2008]. Assuming that the mutation does not cause nonsense-mediated decay (that seems unlikely because the novel stop codon shortens the protein by 14 amino acids only), it seems likely that TRPV4 with mutated C-terminus may not be correctly assembled and transported to the membrane, and thus it is difficult to hypothesize a simple gain of function. Aberrant signaling might occur nevertheless; a similar phenomenon is known to occur with several FGFR3 mutations [Lievens et al., 2006, 2008]. The fact that TRPV4 assembles into homotetramers (and possibly heterotetramers with other TRPVs) and interacts with PACSIN3, MAP7, and other proteins, offers manifold possibilities for dominant mechanisms other than simple gain-of-function [Everaerts et al., 2009]. In summary, the cellular pathogenesis of TRPV4 chondrodysplasias is intriguing and remains to be explored before therapeutic strategies aimed at modulating TRPV4 activity can be designed.

The identification of *TRPV4* mutations is useful for establishing recurrence risks for families affected with SEDM-PM2, as molecular confirmation as well as the possibility of prenatal recognition of this dominant disorder may be appropriate for reproductive decisions. In fact, we are aware of individuals with either SMDK or SEDM-PM2 who had been given recurrence risks for a recessive condition based on the superficial similarity of the phenotype with Morquio

syndrome, and who were surprised by unexpected recurrence in their offspring.

ACKNOWLEDGMENTS

This project was supported by grants from the German Ministry for Education and Research (BMBF contract grant SKELNET; www.skelnet.de, www.skeldys.org) and by the European Union (FP6, Contract grant EuroGrow), by grants-in-aids from the Ministry of Education, Culture, Sports, and Science of Japan (Contract grant No. 20390408), from Research on Child Health and Development (Contract grant No. 20-S-3), and from the Korea Healthcare technology R&D Project, Ministry for Health, Welfare and Family Affairs, Republic of Korea (No. A080588). This project was also supported by the European Skeletal Dysplasia Network (ESDN; www.esdn.org), through which patient 5 was co-ascertained, as well as the Japanese Skeletal Dysplasia Consortium (JSDC; http://www.riken.jp/lab-www/OA-team/JSDC/), and by the University of Freiburg. E.L. and B.Z. are supported by individual grants from Deutsche Forschungsgemeinschaft (La 1381/1-3).

REFERENCES

Becker D, Muller M, Leuner K, Jendrach M. 2008. The C-terminal domain of TRPV4 is essential for plasma membrane localization. Mol Membr Biol 25:139–151.

Cohn DH, Ehtesham N, Krakow D, Unger S, Shanske A, Reinker K, Powell BR, Rimoin DL. 2003. Mental retardation and abnormal skeletal development (Dyggve-Melchior-Clausen dysplasia) due to mutations in a novel, evolutionarily conserved gene. Am J Hum Genet 72:419–428.

Dai J, Kim OH, Cho TJ, Schmidt-Rimpler M, Tonoki H, Takikawa K, Haga N, Miyoshi K, Kitoh H, Yoo WJ, Choi IH, Song HR, Jin DK, Kim HT, Kamasaki H, Bianchi PG, Grigelioniene G, Nampoothiri S, Minagawa M, Miyagawa SI, Fukao T, Marcelis C, Jansweijer MCE, Hennekam RCM, Bedeschi MF, Mustonen A, Jiang Q, Ohashi H, Furuichi T, Unger S, Zabel B, Lausch E, Superti-Furga A, Nishimura G, Ikegawa S. 2010. Novel and recurrent TRPV4 mutations and their association with distinct phenotypes within the TRPV4 dysplasia family. J Med Genet (in press).

Doman AN, Maroteaux P, Lyne ED. 1990. Spondyloepiphyseal dysplasia of Maroteaux. J Bone Joint Surg Am 72:1364–1369.

Dyggve H, Melchior J, Clausen J. 1962. Morquio-Ullrich's disease: an inborn error of metabolism? Arch Dis Child 37:525–534.

El Ghouzzi V, Dagoneau N, Kinning E, Thauvin-Robinet C, Chemaitilly W, Prost-Squarcioni C, Al-Gazali LI, Verloes A, Le Merrer M, Munnich A, Trembath RC, Cormier-Daire V. 2003. Mutations in a novel gene dymeclin (FLJ20071) are responsible for Dyggve-Melchior-Clausen syndrome. Hum Mol Genet 12:357–364.

Everaerts W, Nilius B, Owsianik G. 2009. The vallinoid transient receptor potential channel Trpv4: From structure to disease. Prog Biophys Mol Biol [Epub ahead of print], available online at www.sciencedirect.com.

Hall CM, International Working Group on Constitutional Diseases of Bone. 2002. International nosology and classification of constitutional disorders of bone, 2001 revision. Am J Med Genet 113:65–77.

Kochs J. 1932. Beitrag zur Chondrodystrophie und Chondromatose. Arch Orthop Unfallchir 31:419–433.

Krakow D, Vriens J, Camacho N, Luong P, Deixler H, Funari TL, Bacino CA, Irons MB, Holm IA, Sadler L, Okenfuss EB, Janssens A, Voets T, Rimoin DL, Lachman RS, Nilius B, Cohn DH. 2009. Mutations in the gene encoding the calcium-permeable ion channel TRPV4 produce spondylometaphyseal dysplasia, Kozlowski type and metatropic dysplasia. Am J Hum Genet 84:307–315.

Langer LO, Petersen D, Spranger J. 1970. An unusual bone dysplasia: Parastremmatic dwarfism. Am J Roentgenol Radium Ther Nucl Med 110:550–560.

Lievens PM, Roncador A, Liboi E. 2006. K644E/M FGFR3 mutants activate Erk1/2 from the endoplasmic reticulum through FRS2 alpha and PLC gamma-independent pathways. J Mol Biol 357:783–792.

Lievens PM, De Servi B, Garofalo S, Lunstrum GP, Horton WA, Liboi E. 2008. Transient dimerization and interaction with ERGIC-53 occur in the fibroblast growth factor receptor 3 early secretory pathway. Int J Biochem Cell Biol 40:2649–2659.

Maroteaux P, Lamy M. 1961. Les Chondrodystrophies Génotypiques. Paris, France: L'expansion Scientifique Française.

Maroteaux P, Wiedemann R, Spranger J, Kozlowski K, Lenzi L. 1968. Essai de classification des dysplasies spondylo-epiphysaires. Lyon, France: SIMEP Editions.

Matteini M, Cotrozzi G, Relli P, Valenza T. 1981. Sindrome pseudo-Morquio tipo II [pseudo-Morquio type II syndrome]. Arch Putti Chir Organi Mov 31:225–235.

Megarbane A, Maroteaux P, Caillaud C, Le Merrer M. 2004. Spondyloepimetaphyseal dysplasia of Maroteaux (pseudo-Morquio type II syndrome): Report of a new patient and review of the literature. Am J Med Genet Part A 125A:61–66.

Morquio L. 1935. Sur une forme de dystrophie osseuse familiale. Arch Med Enfants 38:5–24.

Nishimura G, Kizu R, Kijima Y, Sakai K, Kawaguchi Y, Kimura T, Matsushita I, Shirahama S, Ikeda T, Ikegawa S, Hasegawa T. 2003. Spondyloepiphyseal dysplasia Maroteaux type: Report of three patients from two families and exclusion of type II collagen defects. Am J Med Genet Part A 120A:498–502.

Rock MJ, Prenen J, Funari VA, Funari TL, Merriman B, Nelson SF, Lachman RS, Wilcox WR, Reyno S, Quadrelli R, Vaglio A, Owsianik G, Janssens A, Voets T, Ikegawa S, Nagai T, Rimoin DL, Nilius B, Cohn DH. 2008. Gain-of-function mutations in TRPV4 cause autosomal dominant brachyolmia. Nat Genet 40:999–1003.

Sensenbrenner JA, Dorst JP, Hungerford DS. 1974. Parastremmatic dwarfism. Birth Defects Orig Artic Ser 10:424–429.

Superti-Furga A, Unger S. 2007. Nosology and classification of genetic skeletal disorders: 2006 revision. Am J Med Genet Part A 143A:1–18.

Watanabe H, Vriens J, Janssens A, Wondergem R, Droogmans G, Nilius B. 2003. Modulation of TRPV4 gating by intra- and extracellular Ca2+. Cell Calcium, 33(5–6):489–495.