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Abstract

Camurati-Engelmann disease or progressive diaphyseal dysplasia is a rare autosomal dominant sclerosing bone dysplasia. Mainly the skull and the diaphyses of the long tubular bones are affected. Clinically, the patients suffer from bone pain, easy fatigability and decreased muscle mass and weakness in the proximal parts of the lower limbs resulting in gait disturbances. The disease causing mutations are located within the *TGFβ-1* gene and expected to are thought to disrupt the binding between TGFβ1 and its latency associated peptide resulting in an increased signalling of the pathway and subsequently accelerated bone turnover. In preclinical studies it was shown that targeting the type I receptor ameliorates the high bone turnover. In patients, treatment options are currently mostly limited to corticosteroids that may relieve the pain, improve the muscle weakness and fatigue. In this review the clinical and radiological characteristics as well as the molecular genetics of this condition are discussed.

Introduction

Camurati-Engelmann disease (CED) (MIM#131300) is characterized by an increased bone mass and therefore belongs to the group of sclerosing bone dysplasias. The latter is a clinically and genetically heterogeneous group, all with a low prevalence in the population [1, 2]. In the latest update of the Nosology and classification of genetic skeletal disorders in 2015 [3] the sclerosing bone dysplasias are subclassified in three subgroups: the neonatal osteosclerotic dysplasias, the osteopetroses and related disorders and finally the other sclerosing bone disorders. The underlying pathogenic mechanisms can be different but obviously share a disturbance of the balance between bone formation and bone resorption [4]. In some conditions including osteopetrosis and pycnodysostosis, the primary defect is an impaired osteoclastic bone resorption while in others (sclerosteosis, Van Buchem disease, high bone mass phenotype,…) the increased bone mass is caused by augmented osteoblastic bone formation.

Finally, in some conditions the underlying pathogenic mechanism involves a factor coupling the processes of bone resorption and formation. As described below, CED belongs to the latter category with involvement of transforming growth factor β-1 (TGFB1).

Radiological and clinical manifestations

CED is a rare, autosomal dominant sclerosing bone dysplasia that mainly affects the skull and the diaphyses of the long tubular bones (Figure 1, 2). It is also known and often referred to as "progressive diaphyseal dysplasia". It was first reported in three independent case reports in the nineteen-twenties [5-7]. Up to date more than 300 cases have been described [8] but the exact prevalence is unknown. Mild cases of diaphyseal dysplasia with late manifestation and some asymmetry of the lesions have been published under the name "Ribbing disease II" ("Ribbing disease I" refers to multiple epiphyseal dysplasia) but it is now accepted that CED and Ribbing disease II represent phenotypic variations of the same disorder caused by mutations in TGFB1 [8, 9].

Affected individuals usually present with pain in the legs, muscle weakness and easy fatigability. Onset of symptoms can be variable and range from early childhood to late adulthood [10]. Clinical evaluation often reveals decreased muscle mass and weakness in the proximal parts of the lower limbs resulting in difficulties when rising from a sitting position and in gait disturbances. Bone pain is frequently present and may range from mild to severe, requiring narcotic analgesics [8, 11]. The pain is described as aching, often intermittent and worse with activity, stress and cold weather. Bone tenderness upon palpation, usually in the lower limbs, is frequently reported [10]. Some affected individuals have a rather slender (so-called Marfanoid) habitus with reduction of muscle mass and subcutaneous fat. Joint contractures can be observed (Figure 2). Other, less frequent orthopedic problems include radial

head dislocation, kyphosis, scoliosis, coxa valga, genu valga and flat feet [11]. Significant endosteal involvement that narrows the medullary cavity in the long bones, may cause hematological complications such as anemia. Delayed puberty and hypogonadism have been reported in some patients [11-13].

Involvement of the skull base may cause cranial nerve palsies due to sclerosis and narrowing of the foramina. This is rarely seen in childhood but more in an advanced stage of the disorder later on in adulthood. The most common cranial nerve deficits are hearing loss, vision problems and facial paresis. The hearing deficit can be conductive and/or sensorineural [14]. Recurrent cranial hyperostosis after surgical decompression has been reported [15]. Hyperostosis of the cranial vault can result in frontal bossing. Headaches are frequent complaints in affected individuals and may be triggered by increased intracranial pressure.

The diagnosis is usually made by radiographic evaluation of the skeleton. Most frequently, the long tubular bones in the lower limbs (femur and tibia) are affected (Figures 1 and 2). These bones show uneven cortical thickening of the diaphyses with hyperostosis extending to both the periosteal and endosteal sides. The hyperostosis is usually present in both limbs but may be asymmetric. The spine is by definition not affected. Sclerosis of the skull base is more often observed than hyperostosis of the cranial vault [16]. Bone mineral density measured in the hip and femoral necks is usually increased. Healing of fractures may be delayed [10] but there is no evidence for an increased susceptibility to fracture. Bone scintigraphy can be normal despite the radiographic presence of bone lesions [17, 18]. Bone scintigraphy can be helpful in monitoring the activity of the disease but has limited value in the specific diagnosis of the disorder.

Intra- and interfamilial clinical variability is a feature of CED [8, 11, 19, 20]. There is reduced penetrance as there have been reports of normal radiographs in individuals who are heterozygous for a pathogenic variant in TGFB1 but exact figures are not known [10].

Several years after its delineation in 1922, the progressive character of the disorder was recognized [21] and the condition was therefore also named "progressive diaphyseal dysplasia". In a large Israeli family, sequential skeletal radiographs over a period of up to 32 years, clearly demonstrated worsening of the disease but only in about half of the affected individuals [22]. Furthermore, there are also reports of patients whose symptoms seem to resolve with age [9, 18, 20].

Differential diagnosis

In the differential diagnosis, mainly sclerosing bone dysplasias with abnormal bone shape due to diaphyseal modelling defects should be considered [29]. The distinction with osteopetrosis is usually easy since in the different forms of osteopetrosis, the diaphyses of long tubular bones are by definition normal in shape [16]. The defective modelling in osteopetrosis is more reflected by widening of the (sub)metaphyseal regions ("Erlenmeyer-flask) of the tubular bones. Hyperostosis of the diaphysis of long bones with new periosteal bone formation can be seen in melorheostosis. However, in this disorder there is usually asymmetric and unilateral involvement affecting one or several bones in one limb [30]. The periosteal bone formation is also more pronounced in melorheostosis, resembling the appearance of wax flowing down the side of a candle [31]. In addition, ectopic bone formation is a feature of melorheostosis and not of CED. Cortical hyperostosis of long bones with excessive periosteal bone is observed in infantile cortical hyperostosis (Caffey disease). In this condition however, onset is earlier (usually in infancy) and the hyperostosis is not restricted to the long bones but also involves the mandible, clavicles, scapulae and ribs [32]. The skull base and vault are not affected. Clinical

signs of fever and irritability further distinguish Caffey disease from CED. Ghosal hematodiaphyseal dysplasia can also resemble CED but in general the hyperostosis is less pronounced and the hematological complications with severe anemia are only observed in the former disorder [33]. Diaphyseal expansing of long tubular bones and cranial sclerosis are features of juvenile Paget disease but in this disorder the long bones show more bowing, irregular trabeculation and generalized demineralization [34]. Diaphyseal (mainly endosteal) and skull sclerosis are major features of van Buchem endosteal hyperostosis and sclerosteosis. Involvement of the mandible, widening of the short tubular bones in hands and feet, and presence of syndactyly are the most important characteristics distinguishing these conditions from CED [1, 2]. In craniodiaphyseal dysplasia, sclerosis of the skull and facial bones (including the mandible) is more pronounced and in addition, there is widening of ribs, clavicles and short tubular bones in hands, which are not features of CED [35].

Molecular genetics

The molecular defects underlying CED have been identified by positional cloning as mutations in the gene encoding transforming growth factor beta 1 (*TGFβ-1*) located on chromosome 19q13.2 [36, 37]. The mutations are found in heterozygous state in line with the autosomal dominant segregation of the disease. At present, 13 different mutations have been reported [8, 38, 39]. Eight of these cluster in a small region of the protein between amino acids 218 and 225 (encoded by exon 4) and are identified in more than 80% of the patients (Figure 3). The mutations R218C, R218H and C225R are recurrent mutations and the fact that all these have been described in families of different ethnic background suggests that they are the result of independent mutational events. Especially the arginine at position 218 turns out to be a hotspot for mutations as it is substituted in about 60% of the patients [8]. For the cysteine residue at position 223, 3 different mutations have been reported. In addition to the missense mutations in

exon 4, two different duplications at the same location in the signal peptide of the protein have been reported [36, 39] as well as three missense mutations (Y81H, R156C and E169K) in the more proximal part of the protein (Figure 3) [8, 38].

TGFβ−1 belongs to the TGF-beta superfamily, consisting of more than 40 members, including the bone morphogenetic proteins, inhibins, and activins. Like almost all other members, it is initially encoded as a precursor, containing a signal peptide, the latency associated peptide (LAP) and finally the mature TGF-β1 at the carboxyterminal part of the protein [40]. This precursor is processed in different steps. First, the precursor molecule dimerizes by means of cysteine bridges and subsequently undergoes proteolytic cleavage by furin at the dibasic protease site to yield the three sub-domains. The signal peptide is cleaved off during passage through the endoplasmic reticulum and also the LAP is cleaved from the mature peptide. This homodimer with the mature peptide being non-covalently linked to the LAP is secreted and stored in the extracellular matrix as a latent complex [40]. This can happen either alone as the small latent complex or in conjunction with a latent TGF-β-binding protein as a large latent complex [41, 42]. In this latent state, TGF-β1 cannot bind to its receptor and will therefore not be able to activate the signalling pathway. However, once activated, TGF-β1 can bind to the type II receptor (TRII) which is constitutively active [40]. Subsequently the type I receptor (TRI) is recruited resulting in a heteromeric complex [43]. TRI becomes phosphorylated and activated and in turn phosphorylates intracellularly R-Smads 2 or 3. These activated R-Smads form heteromeric complexes with Smad4 which are translocated to the nucleus, where they can bind either directly to DNA or they interact with other transcription factors regulating gene transcription [44].

Probably due to the limited number of patients and the presence of inter- and intrafamilial variability, no robust genotype-phenotype correlations have yet been made between patients with one of the exon 4 mutations and patients with other variants in the *TGF-β1* gene. This

makes the prognosis of the disease unpredictable. The clinical variability, even among patients with the same mutation, could be due to genetic modifiers either within the *TGF-β1* gene or in other genes. The former has been tested in some families both for some promotor polymorphisms as well as for some coding variants but no evidence for an association with disease severity was obtained [10, 45]. More recently, two members of a CED family were described both having a *TGF-β1* mutation but in addition a rare variant in the *TNFSF11* gene encoding the RANKL protein. This variant was identified in homozygous state in the son while heterozygous in the mother. The authors suggested this as a putative explanation for the milder phenotype in mother compared to her son [39] but additional studies are needed to confirm this hypothesis.

In one extended CED family, the observation of anticipation was reported implicating both a decreasing age of onset and increasing severity over generations [20, 46]. However, this could not be confirmed in other families and the nature of CED mutations are not indicative for this phenomenon. Anticipation is usually seen in disorders caused by dynamic mutations such as expansions of a triplet repeat.

In 2001, a family diagnosed with CED was reported without a mutation in the *TGF-β1* gene suggesting locus heterogeneity for the disease [8]. However, since this is the only mutation-negative family reported so far, further evidence to support this conclusion is awaited since the presence of a missed or atypical *TGF-β1* mutation or another diagnosis cannot be excluded. Along the same line, Nishimura et al. [47] described two Japanese CED patients without a *TGF-β1* mutation but the presence of striations in the bones of these patients are atypical for classical CED suggesting that they may suffer from another disease.

Pathogenesis

TGF-β1 plays a role in a lot of biological processes. It regulates cell proliferation, differentiation, migration, and apoptosis. Furthermore, it influences embryogenesis, angiogenesis, immune suppression, wound healing, and many other processes [48]. TGF-β1 is one of the most abundant cytokines in the bone matrix [49]. When osteoclasts resorb bone, TGF-β1 is released from the matrix. Due to the low pH at the ruffled border, the binding between LAP and the mature peptide is broken and the growth factor becomes active. Active TGF-β1 will act on osteoblasts stimulating the chemotaxis, proliferation and differentiation of osteoblast precursors [50]. Furthermore, it will indirectly inhibit further osteoclast differentiation and activation. Therefore it is considered an important regulator in the coupling of the processes of bone formation and bone resorption making CED a bone remodelling disease [51]. A transgenic mouse model for the H222D mutation resulted in diaphyseal thickening of the long bones and increased fracturing supporting defective bone remodelling [51]. Furthermore, administration of a bone-targeted TGF-β type 1 receptor inhibitor rescues uncoupled bone remodelling in CED [52]. Some of the clinical observations such as the reduction in fat and muscle mass seem to be unrelated to the skeletal abnormalities. But they can be explained by the fact that TGF-β1 is an inhibitor of myogenesis as well as adipogenesis [53, 54].

The cluster of exon 4 mutations in CED patients is located in the LAP region which is essential for the dimerization of the protein. These mutations involve or are next to the cysteine residues at position 223 and 225 which form cysteine bridges to stabilize the dimer. Based on that, it was suggested that the result of the mutations is a reduced ability of the LAP to bind the mature TGF-β1 resulting in an increased activity. This was confirmed *in vitro* for several of these mutations [55]. Functional evaluation of the Y81H mutation and the 9-basepair duplication in the signal peptide indicated a decreased secretion of the protein but the resulting intracellular

accumulation leads also to increased signalling, although the underlying mechanism of this is still unclear [55].

Treatment

No consensus management guidelines have been developed to date. Treatment with corticosteroids may relieve the pain, improve the muscle weakness and fatigue, and even correct the anemia [10, 23]. Individuals with severe symptoms can be treated with a bolus of prednisolone 1.0-2.0 mg/kg/day followed by rapid tapering to the lowest alternate-day dose tolerated. Less symptomatic individuals can be started on 0.5-1.0 mg/kg every other day. Some individuals may be able to discontinue steroid therapy during quiescent periods [24]. It is not yet clear if steroid therapy can delay or prevent hyperostosis in the appendicular skeleton and skull [23, 25, 26]. Histologic studies following steroid therapy have shown increased bone resorption and secondary remodeling with increased osteoblast activity and decreased lamellar bone deposition. However, several studies reported no regression of sclerosis on radiographs or scintigrams after steroid treatment [23, 25].

There are some conflicting reports on the effect of losartan treatment in individuals with CED [11, 27, 28]. Losartan is an angiotensin II type 1 receptor antagonist that has been shown to downregulate TGFβ1 signaling [56]. In some patients reduced bone pain and increased muscle strength was reported whilst in others no effect was observed. There is no evidence that treatment with bisphosphonates is successful in individuals with CED. Surgery is rarely needed. Recently, good results have been reported by performing radical craniectomy with titanium mesh cranioplasties for the treatment of recurrent cranial hyperostosis with resultant increased intracranial pressure [15]. In case of hearing loss, surgical decompression of the internal auditory canal can improve hearing, however since the skull hyperostosis is progressive,

compression of the auditory nerve may recur. Preclinical studies show that targeting the type I receptor can ameliorate the high bone turnover (48) but no data from clinical trials are available.

Legends to figures

Fig 1: Radiographs of individual VDBI at the age of 15 years with the p.Y81H mutation in the TGFβ-1 gene. (a) Lateral view of the skull shows distinct sclerosis of the skull base and mild hyperostosis of the calvarium, especially in the frontal bones. (b) Anteroposterior view of the left femur reveals a fusiform enlargement of the mid-diaphysis of the femur with both endosteal and periosteal hyperostosis, mostly pronounced on the medial side. (c) Anteroposterior view of the right lower limb. Sclerosis is present on the lateral side of the tibia with relative sparing of the fibula. (d) Anteroposterior view of the right humerus also shows widening of the diaphysis due to endosteal and (to a milder degree) periosteal hyperostosis.

Fig 2: Clinical photographs (a-b) and radiographs (c-f) of individual VR at the age of 17 years p.Y81H mutation in the TGFβ-1 gene. The clinical pictures show contractures in the knees and relatively long and slender limbs. (c) Lateral view of the skull showing mild sclerosis of the skull base and frontal bones of the vault. (d) Anteroposterior view of the left femur reveals fusiform widening of the mid-diaphysis with both endosteal and periosteal hyperostosis. Cortical sclerosis results in obliteration of the medullary space. Note also cortical hyperostosis

in the proximal part of the tibia and fibula. (e) The pelvis shows coxa valga but no signs of

sclerosis in the pelvic bones. Bilateral cortical hyperostosis of the femoral diaphyses is visible.

(f) Anteroposterior views of the left lower limb show hyperostosis in the diaphysis of both tibia

and fibula with narrowing of the medullary cavity.

Fig 3. CED causing mutations in the *TGFβ-1* gene at cDNA and protein level.

References

1. Boudin E, Van Hul W (2018) Sclerosing bone dysplasias. Best practice & research. Clinical endocrinology & metabolism 32:707-723
2. De Ridder R, Boudin E, Mortier G, Van Hul W (2018) Human Genetics of Sclerosing Bone Disorders. Current osteoporosis reports 16:256-268
3. Bonafe L, Cormier-Daire V, Hall C, Lachman R, Mortier G, Mundlos S, Nishimura G, Sangiorgi L, Savarirayan R, Sillence D, Spranger J, Superti-Furga A, Warman M, Unger S (2015) Nosology and classification of genetic skeletal disorders: 2015 revision. American journal of medical genetics. Part A 167A:2869-2892
4. Boudin E, Fijalkowski I, Hendrickx G, Van Hul W (2016) Genetic control of bone mass. Molecular and cellular endocrinology 432:3-13
5. Cockayne EA (1920) Case for Diagnosis. Proc R Soc Med 13:132-136
6. Camurati M (1922) Di un raro caso di osteite simmetrica ereditaria degli arti inferiori. Chirurgia degli Organi di Movimento 6:662-665
7. Engelmann G (1929) Ein fall von ostheopathia hyperostotica (sclerotisans) multiplex infantilis. Forschritte auf dem Gebiete der Röntgenstrahlen und der Nuklearmedizin 39:1101–1106
8. Janssens K, Vanhoenacker F, Bonduelle M, Verbruggen L, Van Maldergem L, Ralston S, Guanabens N, Migone N, Wientroub S, Divizia MT, Bergmann C, Bennett C, Simsek S, Melancon S, Cundy T, Van Hul W (2006) Camurati-Engelmann disease: review of the clinical, radiological, and molecular data of 24 families and implications for diagnosis and treatment. Journal of medical genetics 43:1-11
9. Makita Y, Nishimura G, Ikegawa S, Ishii T, Ito Y, Okuno A (2000) Intrafamilial phenotypic variability in Engelmann disease (ED): are ED and Ribbing disease the same entity? American journal of medical genetics 91:153-156
10. Wallace SE, Lachman RS, Mekikian PB, Bui KK, Wilcox WR (2004) Marked phenotypic variability in progressive diaphyseal dysplasia (Camurati-Engelmann disease): report of a four-generation pedigree, identification of a mutation in TGFB1, and review. American journal of medical genetics. Part A 129A:235-247
11. Yuldashev AJ, Shin CH, Kim YS, Jang WY, Park MS, Chae JH, Yoo WJ, Choi IH, Kim OH, Cho TJ (2017) Orthopedic Manifestations of Type I Camurati-Engelmann Disease. Clin Orthop Surg 9:109-115
12. Gupta S, Cheikh IE (2005) Camurati-Engelmann disease in conjunction with hypogonadism. Endocr Pract 11:399-407
13. Meczekalski B, Czyzyk A, Podfigurna-Stopa A, Rydzewski B, Sroczynski J, Lipinska M, Sokalski J, Krawczynski M, Jamsheer A, Katulski K, Genazzani A (2013) Hypothalamic amenorrhea in a Camurati-Engelmann disease--a case report. Gynecol Endocrinol 29:511-514
14. Carlson ML, Beatty CW, Neff BA, Link MJ, Driscoll CL (2010) Skull base manifestations of Camurati-Engelmann disease. Arch Otolaryngol Head Neck Surg 136:566-575
15. Wong T, Herschman Y, Patel NV, Patel T, Hanft S (2017) Repeat Intracranial Expansion After Skull Regrowth in Hyperostotic Disease: Technical Note. World Neurosurg 102:555-560
16. Spranger J, Brill P, Hall C, Nishimura G, Superti-Furga A, Unger S (2018) Bone Dysplasias: An Atlas of Genetic Disorders of Skeletal Development (4 ed.). Oxford University Press, United State of America, New York

17. Clybouw C, Desmyttere S, Bonduelle M, Piepsz A (1994) Camurati-Engelmann disease: contribution of bone scintigraphy to genetic counseling. Genet Couns 5:195-198

18. Kumar B, Murphy WA, Whyte MP (1981) Progressive diaphyseal dysplasia (Engelmann disease): scintigraphic-radiographic-clinical correlations. Radiology 140:87-92

19. Sparkes RS, Graham CB (1972) Camurati-Engelmann disease. Genetics and clinical manifestations with a review of the literature. Journal of medical genetics 9:73-85

20. Saraiva JM (1997) Progressive diaphyseal dysplasia: a three-generation family with markedly variable expressivity. American journal of medical genetics 71:348-352

21. Neuhauser EB, Shwachman H, et al. (1948) Progressive diaphyseal dysplasia. Radiology 51:11-22

22. Kaftori JK, Kleinhaus U, Naveh Y (1987) Progressive diaphyseal dysplasia (Camurati-Engelmann): radiographic follow-up and CT findings. Radiology 164:777-782

23. Bas F, Darendeliler F, Petorak I, Sadikoglu B, Bilir A, Bundak R, Saka N, Gunoz H (1999) Deflazacort treatment in progressive diaphyseal dysplasia (Camurati-Engelmann disease). J Paediatr Child Health 35:401-405

24. Wallace SE, Wilcox WR (1993) Camurati-Engelmann Disease. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Stephens K, Amemiya A (eds) GeneReviews((R)). Seattle (WA)

25. Verbruggen LA, Bossuyt A, Schreuer R, Somers G (1985) Clinical and scintigraphic evaluation of corticosteroid treatment in a case of progressive diaphyseal dysplasia. J Rheumatol 12:809-813

26. Lindstrom JA (1974) Diaphyseal dysplasia (Engelmann) treated with corticosteroids. Birth Defects Orig Artic Ser 10:504-507

27. Ayyavoo A, Derraik JG, Cutfield WS, Hofman PL (2014) Elimination of pain and improvement of exercise capacity in Camurati-Engelmann disease with losartan. The Journal of clinical endocrinology and metabolism 99:3978-3982

28. Simsek-Kiper PO, Dikoglu E, Campos-Xavier B, Utine GE, Bonafe L, Unger S, Boduroglu K, Superti-Furga A (2014) Positive effects of an angiotensin II type 1 receptor antagonist in Camurati-Engelmann disease: a single case observation. American journal of medical genetics. Part A 164A:2667-2671

29. Vanhoenacker FM, De Beuckeleer LH, Van Hul W, Balemans W, Tan GJ, Hill SC, De Schepper AM (2000) Sclerosing bone dysplasias: genetic and radioclinical features. European radiology 10:1423-1433

30. Freyschmidt J, Freyschmidt-Paul P (2001) SKIBO diseases: a concept to avoid bloody diagnostic procedures in ambiguous skeletal lesions. European radiology 11:1729-1742

31. Leri A, Joanny J (1922) Une affection non décrite des os hyperostose "en coulée" sur toute la longeur d'un member ou "melorhéostose.". Bull Mem Soc Med Hosp Paris 46:1141–1145

32. Nistala S (2014) "Whirl" in the abdomen: beware. Indian J Gastroenterol 33:492

33. Arora R, Aggarwal S, Deme S (2015) Ghosal hematodiaphyseal dysplasia-a concise review including an illustrative patient. Skeletal radiology 44:447-450

34. Whyte MP, Tau C, McAlister WH, Zhang X, Novack DV, Preliasco V, Santini-Araujo E, Mumm S (2014) Juvenile Paget's disease with heterozygous duplication within TNFRSF11A encoding RANK. Bone 68:153-161

35. Brueton LA, Winter RM (1990) Craniodiaphyseal dysplasia. Journal of medical genetics 27:701-706

36. Janssens K, Gershoni-Baruch R, Guanabens N, Migone N, Ralston S, Bonduelle M, Lissens W, Van Maldergem L, Vanhoenacker F, Verbruggen L, Van Hul W (2000) Mutations in the gene encoding the latency-associated peptide of TGF-beta 1 cause Camurati-Engelmann disease. Nature genetics 26:273-275

37. Kinoshita A, Saito T, Tomita H, Makita Y, Yoshida K, Ghadami M, Yamada K, Kondo S, Ikegawa S, Nishimura G, Fukushima Y, Nakagomi T, Saito H, Sugimoto T, Kamegaya M, Hisa K, Murray JC, Taniguchi N, Niikawa N, Yoshiura K (2000) Domain-specific mutations in TGFB1 result in Camurati-Engelmann disease. Nature genetics 26:19-20

38. Chen Y, Xie W, Hu F, Chen J, Zheng H, Zhou H, Ni B, Li W, Zhou J (2017) Clinical diagnosis and mutation analysis of a Chinese family with Camurati-Engelmann disease. Molecular medicine reports 15:235-239

39. Whyte MP, Totty WG, Novack DV, Zhang X, Wenkert D, Mumm S (2011) Camurati-Engelmann disease: unique variant featuring a novel mutation in TGFbeta1 encoding transforming growth factor beta 1 and a missense change in TNFSF11 encoding RANK ligand. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 26:920-933

40. Shi M, Zhu J, Wang R, Chen X, Mi L, Walz T, Springer TA (2011) Latent TGF-beta structure and activation. Nature 474:343-349

41. Miyazono K, Hellman U, Wernstedt C, Heldin CH (1988) Latent high molecular weight complex of transforming growth factor beta 1. Purification from human platelets and structural characterization. The Journal of biological chemistry 263:6407-6415

42. Wakefield LM, Thompson NL, Flanders KC, O'Connor-McCourt MD, Sporn MB (1988) Transforming growth factor-beta: multifunctional regulator of cell growth and phenotype. Annals of the New York Academy of Sciences 551:290-297; discussion 297-298

43. Wrana JL, Attisano L, Wieser R, Ventura F, Massague J (1994) Mechanism of activation of the TGF-beta receptor. Nature 370:341-347

44. ten Dijke P, Miyazono K, Heldin CH (2000) Signaling inputs converge on nuclear effectors in TGF-beta signaling. Trends Biochem Sci 25:64-70

45. Campos-Xavier B, Saraiva JM, Savarirayan R, Verloes A, Feingold J, Faivre L, Munnich A, Le Merrer M, Cormier-Daire V (2001) Phenotypic variability at the TGF-beta1 locus in Camurati-Engelmann disease. Human genetics 109:653-658

46. Saraiva JM (2000) Anticipation in progressive diaphyseal dysplasia. Journal of medical genetics 37:394-395

47. Nishimura G, Nishimura H, Tanaka Y, Makita Y, Ikegawa S, Ghadami M, Kinoshita A, Niikawa N (2002) Camurati-Engelmann disease type II: progressive diaphyseal dysplasia with striations of the bones. American journal of medical genetics 107:5-11

48. Massague J (1990) The transforming growth factor-beta family. Annu Rev Cell Biol 6:597-641

49. Seyedin SM, Thomas TC, Thompson AY, Rosen DM, Piez KA (1985) Purification and characterization of two cartilage-inducing factors from bovine demineralized bone. Proceedings of the National Academy of Sciences of the United States of America 82:2267-2271

50. Janssens K, ten Dijke P, Janssens S, Van Hul W (2005) Transforming growth factor-beta1 to the bone. Endocrine reviews 26:743-774

51. Tang Y, Wu X, Lei W, Pang L, Wan C, Shi Z, Zhao L, Nagy TR, Peng X, Hu J, Feng X, Van Hul W, Wan M, Cao X (2009) TGF-beta1-induced migration of bone mesenchymal stem cells couples bone resorption with formation. Nature medicine 15:757-765

52. Qin Y, Tang S, Zhen G, Ding Q, Ding S, Cao X (2018) Bone-targeted delivery of TGF-beta type 1 receptor inhibitor rescues uncoupled bone remodeling in Camurati-Engelmann disease. Annals of the New York Academy of Sciences 1433:29-40

53. Massague J, Cheifetz S, Endo T, Nadal-Ginard B (1986) Type beta transforming growth factor is an inhibitor of myogenic differentiation. Proceedings of the National Academy of Sciences of the United States of America 83:8206-8210

54. Ignotz RA, Massague J (1985) Type beta transforming growth factor controls the adipogenic differentiation of 3T3 fibroblasts. Proceedings of the National Academy of Sciences of the United States of America 82:8530-8534

55. Janssens K, ten Dijke P, Ralston SH, Bergmann C, Van Hul W (2003) Transforming growth factor-beta 1 mutations in Camurati-Engelmann disease lead to increased signaling by altering either activation or secretion of the mutant protein. The Journal of biological chemistry 278:7718-7724

56. Cohn RD, van Erp C, Habashi JP, Soleimani AA, Klein EC, Lisi MT, Gamradt M, ap Rhys CM, Holm TM, Loeys BL, Ramirez F, Judge DP, Ward CW, Dietz HC (2007) Angiotensin II type 1 receptor blockade attenuates TGF-beta-induced failure of muscle regeneration in multiple myopathic states. Nature medicine 13:204-210
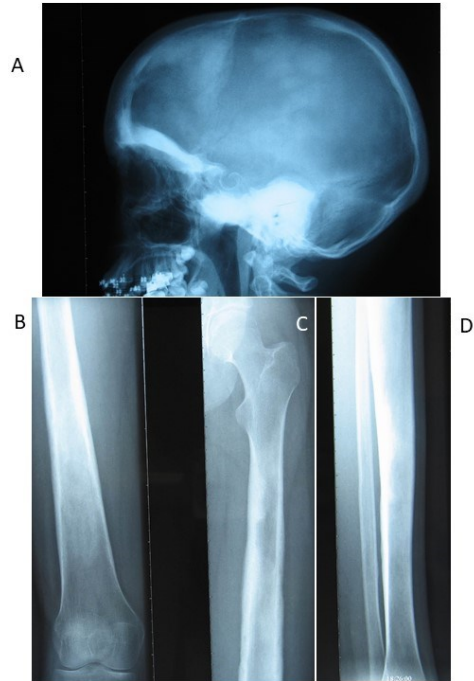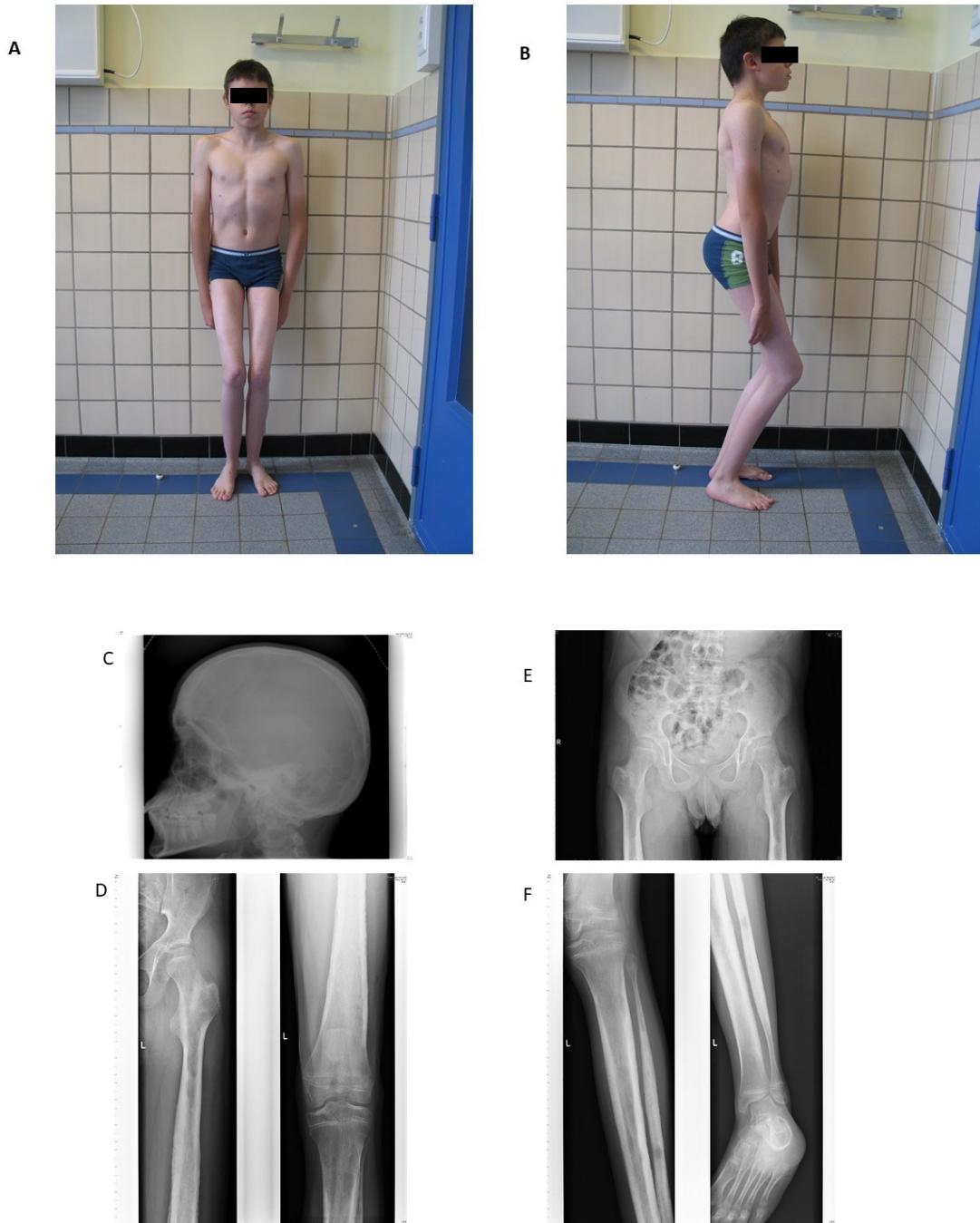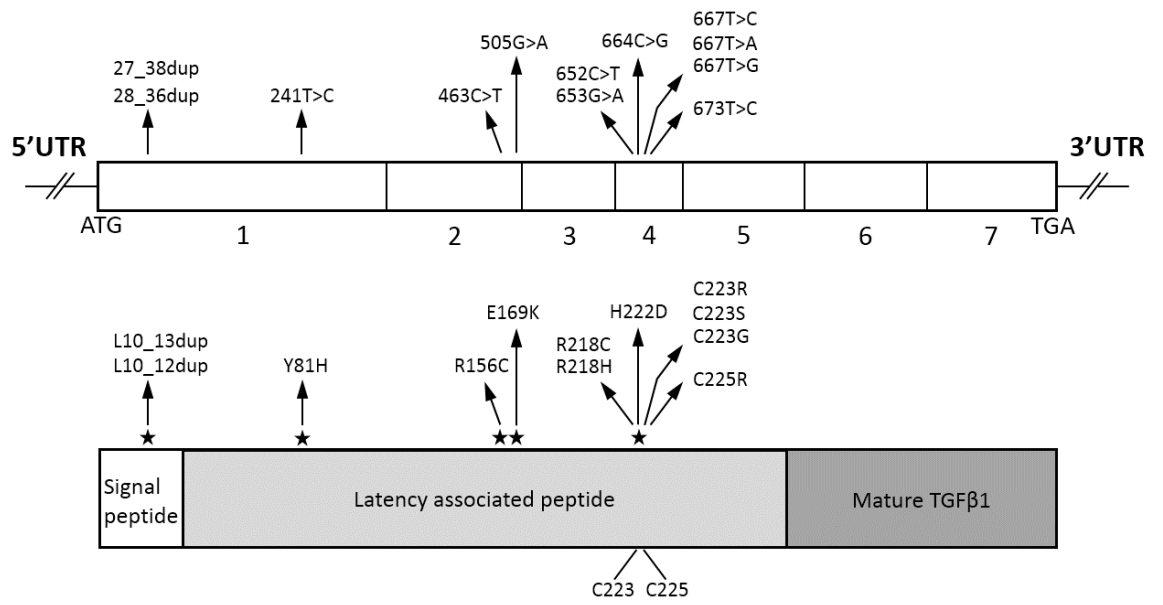
Figure 1

Figure 2

Figure 3