J Hum Genet (2007) 52:473–475
DOI 10.1007/s10038-007-0128-3

SHORT COMMUNICATION

The *ACVR*1 617G > A mutation is also recurrent in three Japanese patients with fibrodysplasia ossificans progressiva

Masahiro Nakajima · Nobuhiko Haga · Kazuharu Takikawa · Noriyo Manabe · Gen Nishimura · Shiro Ikegawa

Received: 15 January 2007 / Accepted: 14 February 2007 / Published online: 10 March 2007

Abstract Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant disorder of skeletal malformations and presents progressive extra-skeletal ossification. The 617G>A (R206H) mutation in the activin receptor type IA (*ACVR*1) gene has been identified in all examined individuals with FOP of various ethnic groups, including Caucasian and Chinese descents. Here, we examined three Japanese patients with FOP for *ACVR*1 mutations. We identified the 617G>A mutation in all three patients. Our results suggest that the mutation in the *ACVR*1 gene is common and recurrent in the global population.

Keywords *ACVR*1 · Fibrodysplasia ossificans progressiva · Mutation · Hot spot · Japanese

M. Nakajima · S. Ikegawa (✉)
Laboratory for Bone and Joint Diseases, SNP Research Center, RIKEN, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan
e-mail: sikegawa@ims.u-tokyo.ac.jp

N. Haga · K. Takikawa
Department of Orthopedics, Shizuoka Children's Hospital, Shizuoka, Japan

N. Haga · K. Takikawa · N. Manabe
Department of Orthopedic Surgery, The University of Tokyo, Tokyo, Japan

G. Nishimura
Department of Radiology, Tokyo Metropolitan Kiyose Children's Hospital, Kiyose, Tokyo, Japan

Present Address:
N. Haga
Department of Rehabilitation Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Introduction

Fibrodysplasia ossificans progressiva (FOP; OMIM 135100) is a rare genetic disorder with autosomal dominant transmission (Kaplan et al. 2002). FOP is the most severe disorder of heterotopic ossification and results in the postnatal formation of an ectopic skeleton (Cohen et al. 1993; Kaplan et al. 1993, 2004). Heterotopic ossification in FOP begins in childhood and can be induced most often by trauma. The ossification is episodic and progressive, leading to extra-articular ankylosis of all major joints of the axial and appendicular skeleton (Cohen et al. 1993; Kaplan et al. 1993, 2004), rendering movement impossible. Congenital malformation of the great toes is common.

Recently, Shore et al. (2006) mapped FOP to chromosome 2q23-24 by linkage analysis and identified a heterozygous mutation (617G>A; R206H) in the glycine-serine (GS) activation domain of *ACVR*1, encoding a BMP type I receptor. They found the mutation in 39 families examined, including African–American, European–American, European (UK), Korean, and Native Brazilian descents. Furthermore, a Taiwanese patient with a de novo *ACVR*1 617G>A mutation has been reported (Lin et al. 2006). Only the 617G>A mutation has been found in FOP so far. To investigate whether *ACVR*1 617G>A mutation is common and recurrent, we examined the *ACVR*1 gene in Japanese FOP patients. We found the 617G>A mutation in all patients examined.

Materials and methods

The diagnosis of FOP was based on clinical and radiographic findings. The phenotypes of the three patients are summarized in Table 1. All patients were sporadic.

Table 1 Clinical summary of the patients with fibrodysplasia ossificans progressiva (FOP)

ID	Age (years)	Sex	Age of onset of ossification	Family history	Great toe abnormality[a]	Short thumb	Other abnormality
FOP1	17	M	2 years	–	+	+	–
FOP2	39	M	10 years	–	+	–	Scalp baldness
FOP3	30	F	3 months	–	+	+	Short broad femoral neck

[a] Halux valgus, hypoplasia of metatarsal/phalanges

Peripheral blood or fingernails were obtained with informed consent from the patients. Genomic DNA was extracted using standard procedures. We amplified exon 4 by polymerase chain reaction (PCR) using primer sequences 5′-CCAGTCCTTCTTCCTTCTTCC-3′ and 5′-AGCAGATTTTCCAAGTTCCATC-3′ (Shore et al. 2006). PCR products were sequenced directly using an ABI Prism 3700 automated sequencer (Applied Biosystems, Foster City, CA).

Results and discussion

Direct sequence analysis of genomic DNA demonstrated the presence of a single heterozygous 617G>A mutation in all three patients with FOP (Fig. 1). No other mutation was identified. Thus, we found that Japanese patients with FOP also had the same *ACVR*1 617G>A mutation. These results suggest that the mutation is common and recurrent in FOP, regardless of ethnic background. The presence of the mutation hot spot facilitates molecular diagnosis in clinical practice. Early diagnosis is very critical for FOP patients to avoid ossification-causing stimuli, including medical intervention.

Accumulation of mutation in a particular single nucleotide is most famous in achondroplasia, the most common skeletal dysplasia (OMIM 100800). Mutations in the transmembrane domain of fibroblast growth factor receptor 3 (*FGFR*3) are identified in achondroplasia, and more than 99% of the *FGFR*3 mutation occurs in a particular single nucleotide, 1138G (1138G>A/C (G380R) mutation). To date, this represents the most mutable single nucleotide reported in the human genome. In both achondroplasia and FOP, the mutations are CpG dinucleotide changes, and paternal age effects in sporadic cases have been reported (Penrose 1955; Tuente et al. 1967). In achondroplasia, the initial and subsequent studies (Shiang et al. 1994; Rousseau et al. 1994; Bellus et al. 1995) found only G380R mutation in more than 200 subjects, which led some researchers to conclude that achondroplasia is defined by recurrent G380R mutation (Bellus et al. 1995). However, the different mutation in *FGFR*3 has been found later in slightly atypical cases (Ikegawa et al. 1995; Superti-Furga et al. 1995). The mutation G375C is also in the transmembrane domain. The phenotypic difference between the common and uncommon mutation are subtle (Nishimura et al. 1995).

In contrast to homogeneity of the achondroplasia phenotype, the clinical manifestation of FOP is considerably diverse, which argues against the homogeneity of the FOP mutation. In a family reported by Shore et al. (2006) who showed ambiguous FOP feature, the *ACVR*1 617G>A mutation was not identified. More extensive search for the FOP/*ACVR*1 mutation that includes patients with atypical FOP phenotypes is necessary to conclude that the single mutation determines the FOP phenotype.

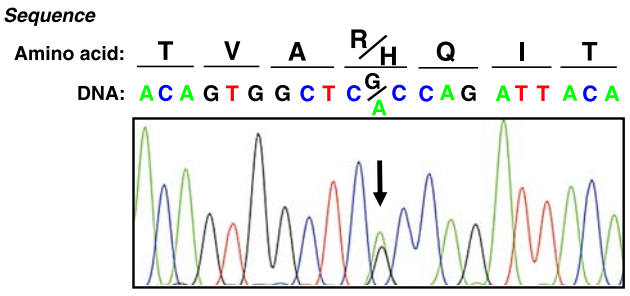

Fig. 1 A direct sequence of genomic DNA from a Japanese patient with fibrodysplasia ossificans progressiva (FOP), showing the common *ACVR*1 mutation 617G>A (R206H) (*arrow*)

Acknowledgments We thank the patients and their relatives who co-operated in this study, and Ms. Tomoko Kusadokoro for her technical assistance.

References

Bellus GA, Hefferon TW, Ortiz de Luna RI, Hecht JT, Horton WA, Machado M, Kaitila I, McIntosh I, Francomano CA (1995) Achondroplasia is defined by recurrent G380R mutations of FGFR3. Am J Hum Genet 56(2):368–373

Cohen RB, Hahn GV, Tabas JA, Peeper J, Levitz CL, Sando A, Sando N, Zasloff M, Kaplan FS (1993) The natural history of heterotopic ossification in patients who have fibrodysplasia ossificans progressiva. A study of forty-four patients. J Bone Joint Surg Am 75(2):215–219

Ikegawa S, Fukushima Y, Isomura M, Takada F, Nakamura Y (1995) Mutations of the fibroblast growth factor receptor-3 gene in one familial and six sporadic cases of achondroplasia in Japanese patients. Hum Genet 96(3):309–311

Kaplan FS, McCluskey W, Hahn G, Tabas JA, Muenke M, Zasloff MA (1993) Genetic transmission of fibrodysplasia ossificans progressiva. Report of a family. J Bone Joint Surg Am 75(8):1214–1220

Kaplan FS, Shore EM, Connor JM (2002) Fibrodysplasia ossificans progressiva (FOP). In: Royce PM, Steinmann B (eds) Connective tissue and its heritable disorders: molecular, genetic, and medical aspects, 2nd edn. Wiley-Liss, New York, pp 827–840

Kaplan FS, Glaser DL, Hebela N, Shore EM (2004) Heterotopic ossification. J Am Acad Orthop Surg 12(2):116–125

Lin GT, Chang HW, Liu CS, Huang PJ, Wang HC, Cheng YM (2006) De novo 617G-A nucleotide mutation in the ACVR1 gene in a Taiwanese patient with fibrodysplasia ossificans progressiva. J Hum Genet 51(12):1083–1086

Nishimura G, Fukushima Y, Ohashi H, Ikegawa S (1995) Atypical radiological findings in achondroplasia with uncommon mutation of the fibroblast growth factor receptor-3 (FGFR-3) gene (Gly to Cys transition at codon 375). Am J Med Genet 59(3):393–395

Penrose LS (1955) Parental age and mutation. Lancet 269(6885):312–313

Rousseau F, Bonaventure J, Legeai-Mallet L, Pelet A, Rozet JM, Maroteaux P, Le Merrer M, Munnich A (1994) Mutations in the gene encoding fibroblast growth factor receptor-3 in achondroplasia. Nature 371(6494):252–254

Shiang R, Thompson LM, Zhu YZ, Church DM, Fielder TJ, Bocian M, Winokur ST, Wasmuth JJ (1994) Mutations in the transmembrane domain of FGFR3 cause the most common genetic form of dwarfism, achondroplasia. Cell 78(2):335–342

Shore EM, Xu M, Feldman GJ, Fenstermacher DA, Brown MA, Kaplan FS (2006) A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva. Nat Genet 38(5):525–527

Superti-Furga A, Eich G, Bucher HU, Wisser J, Giedion A, Gitzelmann R, Steinmann B (1995) A glycine 375-to-cysteine substitution in the transmembrane domain of the fibroblast growth factor receptor-3 in a newborn with achondroplasia. Eur J Pediatr 154(3):215–219

Tuente W, Becker PE, Von Knorre GV (1967) Zur Genetik der Myositis ossificans progressiva. Humangenetik 4(4):320–351