Journal of Human Genetics (2018) 63:1277–1281
https://doi.org/10.1038/s10038-018-0513-0

BRIEF COMMUNICATION

A novel truncating mutation in *MYH3* causes spondylocarpotarsal synostosis syndrome with basilar invagination

Masaki Takagi[1,2] · Satoshi Shimomura[3] · Ryuji Fukuzawa[4] · Satoshi Narumi[1,5] · Gen Nishimura[6] · Tomonobu Hasegawa[1]

Received: 24 March 2018 / Revised: 14 August 2018 / Accepted: 20 August 2018 / Published online: 18 September 2018

Abstract

Spondylocarpotarsal synostosis syndrome (SCT) is a rare group of skeletal dysplasias, characterized by disproportionate short stature with a short trunk, abnormal segmentation of the spine with vertebral fusion, scoliosis and lordosis, carpal and tarsal synostosis, and mild facial dysmorphisms. While the majority of the cases show autosomal recessive inheritance, only a few cases of vertical transmissions, with *MYH3* mutations, have been reported. Here we report a case with typical SCT, carrying a novel heterozygous mutation in *MYH3*. This observation supports the hypothesis of a pathogenic link between autosomal dominant SCT and heterozygous mutations in *MYH3*. Of note, our case showed basilar invagination on brain magnetic resonance imaging at the age of 10 years. Basilar invagination could be a rare complication of both autosomal recessive and dominant SCT, indicating that prompt investigation are warranted for SCT patients.

Introduction

Spondylocarpotarsal synostosis syndrome (SCT: MIM #272460) is a rare group of skeletal dysplasias, characterized by disproportionate short stature with a short trunk, abnormal segmentation of the spine with vertebral fusion, scoliosis and lordosis, carpal and tarsal synostosis, and mild facial dysmorphisms. The majority of the cases show autosomal recessive inheritance with mutations in *FLNB* gene, encoding the cytoskeleton protein filamin B. [1] The genetic basis of the rarer cases of vertical transmissions remained unknown until recently. [2] However, two groups have identified heterozygous *MYH3* gene mutations, in several families transmitted with complete co-segregation. [3, 4] To date, only four *MYH3* mutations associated with autosomal dominant SCT (AD-SCT) have been reported. Here we report on another case with typical SCT, carrying a novel heterozygous mutation in *MYH3*.

Case report

The patient, now a 14-year-old Japanese girl, is the first child of non-consanguineous healthy parents. Her father's and mother's heights were 178 cm (1.2 SD) and 152 cm (−1.2 SD), respectively. She was vaginally delivered at 39 weeks of gestation. Her birth weight was 2.5 kg (−1.3 SD), length was 43.6 cm (−2.3 SD), and occipital frontal circumference was 32.0 cm (−0.6 SD). She had a short stature (−3.5 SD) at the age of 6 years and 5 months. A growth hormone deficiency was excluded by several provocation tests. Her intellectual development was apparently normal, and her karyotype was 46, XX. She was referred to us at the age of 8 years and 1 month. Her height was 105.3 cm (−3.7 SD), body weight was 15.6 kg (−2.1 SD).

Electronic supplementary material The online version of this article (https://doi.org/10.1038/s10038-018-0513-0) contains supplementary material, which is available to authorized users.

✉ Tomonobu Hasegawa
thaseg@a6.keio.jp

[1] Department of Pediatrics, Keio University School of Medicine, Tokyo, Japan

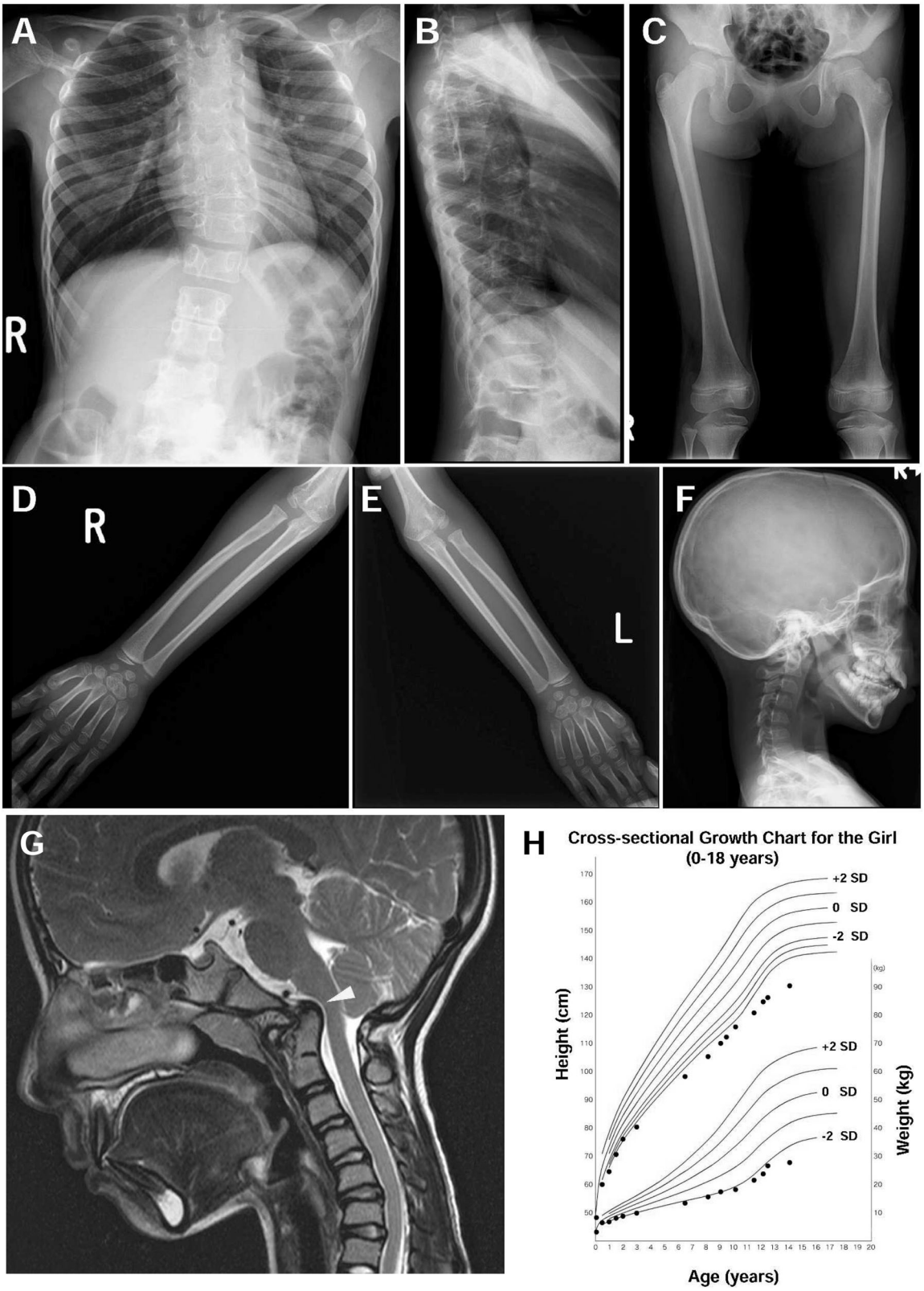
[2] Kojiya Child Clinic, Tokyo, Japan

[3] Department of Orthopedics, Tokyo Metropolitan Children's Medical Center, Tokyo, Japan

[4] Department of Pathology, School of Medicine, International University of Health and Welfare, Chiba, Japan

[5] Department of Molecular Endocrinology, National Research Institute for Child Health and Development, Tokyo, Japan

[6] Center for Intractable Diseases, Saitama Medical University Hospital, Saitama, Japan



Her facial characteristics include deep-sunken eyes, increased philtrum length, and a small mouth. She had a short neck, a disproportionately short trunk, and an arm span of 108 cm. Upon radiological examination, the patient was suspected to have block vertebrae with a right-sided laminar bar from Th8 to Th11 because of narrowing of the

◀ **Fig. 1** Characteristics of the patient. **a**–**f** Radiological examination Block vertebrae with a right-sided laminar bar from Th8 to Th11 was suspected by disk space narrowing and close proximity of the pedicles. Block vertebrae between L1 and L2 were also observed. A thoracolumbar malsegmentation caused a mild scoliosis convex to the right. Capitate-hamate coalition was noted bilaterally. Other bones appeared normal. **g** Brain magnetic resonance imaging at age of 10 years. An upward protrusion of the odontoid process caused a compression of the lower part of the medulla oblongata, without intrinsic signal alterations (arrow head). Furthermore, degenerated disks at C5/6 and C6/7 caused mild canal stenosis. **f** Longitudinal growth record of the patient. No growth spurt during puberty was apparent

disk space and close proximity of the pedicles. Block vertebrae between L1 and L2 were also observed. A thoracolumbar malsegmentation caused a mild scoliosis convex to the right. Capitate-hamate coalition was noted to be bilaterally. Other bones appeared normal (Figs. 1a–f). Overall, the patient was diagnosed with SCT. Brain and spinal magnetic resonance imaging at the age of 10 years revealed basilar invagination and cervical spinal canal stenosis. An upward protrusion of the odontoid process caused a compression of the lower part of the medulla oblongata without intrinsic signal alterations. Furthermore, degenerated disks at C5/6 and C6/7 caused a mild canal stenosis (Fig. 1g). At her last examination at the age of 14 years and 1 month, she was 130.4 cm (−4.8 SD) tall and weighed 27.7 kg (−2.7 SD). She showed spontaneous pubertal development (breast, Tanner stage 3; pubic hair, stages 2–3), however, no growth spurt during puberty was apparent on growth chart (Fig. 1h).

The study was approved by the Institutional Review Board of the Tokyo Metropolitan Children's Medical Center (H25-118) and informed consent was obtained from the parents. We checked all coding exons and flanking introns of *FLNB* by PCR-direct sequencing; however, no pathological mutations were identified. We then performed whole exome sequencing (WES) and identified a novel heterozygous frameshift mutation, c.5198_5205dupCAGACCTC, p.Met1736fs*10 in *MYH3*, which has not been previously reported in any databases (Fig. 2). The details of WES methods have been described previously. [5] The patient's healthy mother, who did not have a short stature, also carried this mutation. To determine the presence of somatic mosaicism in the mother, we subcloned PCR products of DNA from the peripheral blood of the proband, the peripheral blood and nail from the mother, took 50 colonies of each, screened for the mutation, and calculated the ratio of mutant to wild-type alleles. The ratio of mutant to wild-type alleles was 26/24 in the peripheral blood of the proband, 16/34 in the peripheral blood and 19/31 in the nail of the mother (Fig. 2). Lower intensity in peripheral blood and nail of the mother compared to the proband was considered to be a consequence of somatic mosaicism. Neither the patient nor her mother had a cleft palate or overt hearing loss. The mother refused radiological examinations. Trio de novo approach using the DNAs from parents was refused.

Discussion

The *MYH3* gene encodes the skeletal muscle myosin MYH3, which is composed of a myosin head-like domain, a neck domain, and a long coiled-coil rod domain. The majority of the rod region comprises of the myosin tail domain. [6] To date, about 30 heterozygous *MYH3* mutations in patients with several skeletal dysplasia, including distal arthrogryposis type 1 (MIM #108120), type 2 A (MIM #193700), type 2B (MIM #601680), type 8 (MIM #178110), and SCT, have been described. [3, 4, 6–11] Only four mutations, p.Ser243del, p.Thr333Arg, and p.Phe645-Cys in the head-like domain, and p.Leu900fs*9 in the coiled-coil rod domain of MYH3 have been reported to be associated with AD-SCT. [3, 4] Here, we report on another case with a typical SCT phenotype caused by a novel heterozygous mutation in the tail domain of MYH3. This observation supports the hypothesis of a pathogenic link between AD-SCT and heterozygous mutations in *MYH3*. Here, we summarize the clinical phenotypes for patients with MYH3-related SCT (Supplemental table 1).

To date, most *MYH3* mutations reported so far have been missense or in-frame mutations (Supplemental Fig. 1); Only one truncating mutation, p.Leu900fs*9, has been identified in an AD-SCT case. [4] Therefore, the p.Met1736fs*10 is the second case of a truncating mutation in *MYH3*. It has remained unclear whether *MYH3* related skeletal dysplasia is caused by haploinsufficiency or a dominant negative mechanism. In decipher database (https://decipher.sanger.ac.uk/), a carrier of heterozygous entire *MYH3* gene deletion (2.45 Mb deletion including 28 genes, inherited from normal parent) has been reported to have no phenotype of bone dysplasia, indicating that heterozygous *MYH3* mutations are assumed to cause a human disease via dominant negative effect. The p.Met1736fs*10 is a distal truncating variant in the tail domain of MYH3, which is supposed to be associated with some residual protein function, could be the cause of MYH3-related skeletal dysplasia.

To date only single case with SCT due to homozygous mutation in *FLNB* has been reported to have basilar invagination, platybasia, and stenosis of the foramen magnum. [12] Basilar invagination could be a rare complication of both autosomal recessive and dominant SCT, indicating that prompt investigation for cervicomedullary abnormalities are warranted for SCT patients.

The apparently healthy mother of the patient also had the *MYH3* mutation, in somatic mosaicism state, and the amount of mutated DNA is about 30 % of total DNA in the mother. The relatively high rate of mosaicism enabled us to

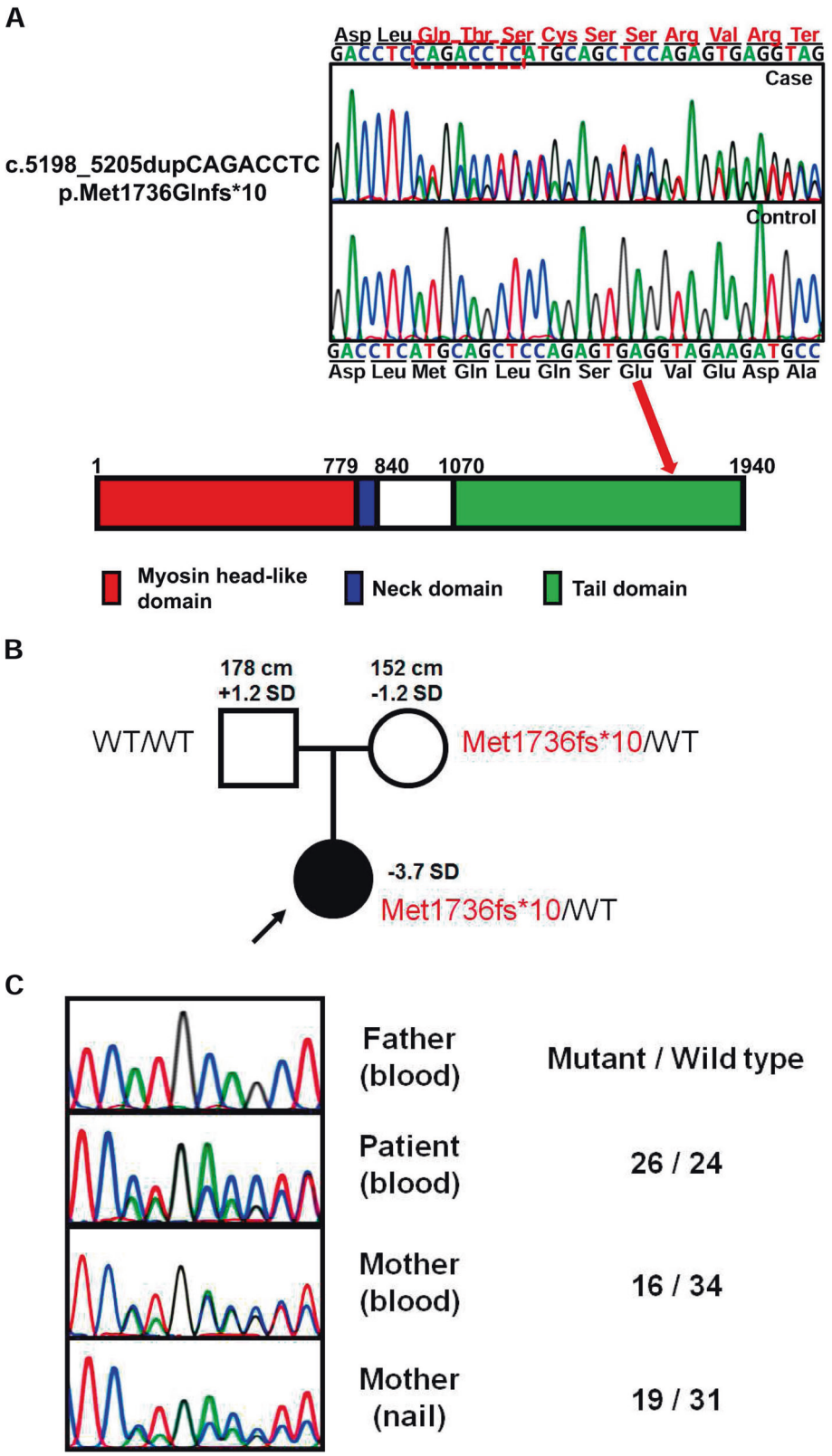


Fig. 2 Identification of the sequence variation of *MYH3*. Partial sequence of a PCR product and schematic diagrams of the MYH3 protein

show that the mother also had the mutation by PCR-direct sequence methods. Previously, a single case of Freeman–Sheldon syndrome, carrying p.Arg672His *MYH3* mutation, where the phenotypically normal mother is a molecularly confirmed somatic mosaicism (about 25% on white blood cell analysis), has been reported. [13] These results

emphasize the importance of parental genetic testing, when a clinically apparent de novo diagnosis is suspected in affected child. Deep sequencing with next generation sequencing may improve the detection rate of mosaicism.

In summary, we describe an additional case with typical SCT, harboring a novel heterozygous truncating mutation in *MYH3*. This validates a recent studies that reported an association between autosomal dominant SCT and a heterozygous mutation in *MYH3*. Basilar invagination could be a rare complication of both autosomal recessive and dominant SCT, indicating that prompt investigation are warranted for SCT patients. Overall, we expand our understanding of the phenotypic features and developmental course that is associated with *MYH3* mutations.

Acknowledgements We thank the patient and their families for participation in this study. We also thank Yukihiro Hasegawa for fruitful discussion.

Funding The Japan Society for the Promotion of Science (Number: 16K10007). Grant sponsors: Takeda Science Foundation and Foundation for Growth Science.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Krakow D, Robertson SP, King LM, Morgan T, Sebald ET, Bertolotto C, et al. Mutations in the gene encoding filamin B disrupt vertebral segmentation, joint formation and skeletogenesis. Nat Genet. 2004;36:405–10.
2. Isidor B, Cormier-Daire V, Le Merrer M, Lefrancois T, Hamel A, Le Caignec C, et al. Autosomal dominant spondylocarpotarsal synostosis syndrome: phenotypic homogeneity and genetic heterogeneity. Am J Med Genet A. 2008;146A:1593–1597.
3. Carapito R, Goldenberg A, Paul N, Pichot A, David A, Hamel A, et al. Protein-altering MYH3 variants are associated with a spectrum of phenotypes extending to spondylocarpotarsal synostosis syndrome. Eur J Hum Genet. 2016;24:1746–51.
4. Zieba J, Zhang W, Chong JX, Forlenza KN, Martin JH, Heard K, et al. A postnatal role for embryonic myosin revealed by MYH3 mutations that alter TGFβ signaling and cause autosomal dominant spondylocarpotarsal synostosis. Sci Rep. 2017;7:41803.
5. Takagi M, Dobashi K, Nagahara K, Kato M, Nishimura G, Fukuzawa R, et al. A novel de novo germline mutation Glu40Lys in AKT3 causes megalencephaly with growth hormone deficiency. Am J Med Genet A. 2017;173:1071–6.
6. Chong JX, Burrage LC, Beck AE, Marvin CT, McMillin MJ, Shively KM, et al. Autosomal-dominant multiple pterygium syndrome is caused by mutations in MYH3. Am J Hum Genet. 2015;96:841–9.
7. Toydemir RM, Rutherford A, Whitby FG, Jorde LB, Carey JC, Bamshad MJ. Mutations in embryonic myosin heavy chain (MYH3) cause Freeman-Sheldon syndrome and Sheldon-Hall syndrome. Nat Genet. 2006;38:561–5.
8. Tajsharghi H, Kimber E, Kroksmark AK, Jerre R, Tulinius M, Oldfors A. Embryonic myosin heavy-chain mutations cause distal arthrogryposis and developmental myosin myopathy that persists postnatally. Arch Neurol. 2008;65:1083–90.
9. Alvarado DM, Buchan JG, Gurnett CA, Dobbs MB. Exome sequencing identifies an MYH3 mutation in a family with distal arthrogryposis type 1. J Bone Jt Surg Am. 2011;93:1045–50.
10. Beck AE, McMillin MJ, Gildersleeve HI, Kezele PR, Shively KM, Carey JC, et al. Spectrum of mutations that cause distal arthrogryposis types 1 and 2B. Am J Med Genet A. 2013; 161A:550–5.
11. Beck AE, McMillin MJ, Gildersleeve HI, Shively KM, Tang A, Bamshad MJ. Genotype-phenotype relationships in Freeman-Sheldon syndrome. Am J Med Genet A. 2014;164A:2808–13.
12. Brunetti-Pierri N, Esposito V, De Brasi D, Mattiacci DM, Krakow D, Lee B, et al. Spondylocarpotarsal synostosis: long-term follow-up of a case due to FLNB mutations. Am J Med Genet A. 2008;146A:1230–3.
13. Hague J, Delon I, Brugger K, Martin H, Abbs S, Park SM. Molecularly proven mosaicism in phenotypically normal parent of a girl with Freeman-Sheldon Syndrome caused by a pathogenic MYH3 mutation. Am J Med Genet A. 2016;170A:1608–12.