研究協力への同意撤回書

東京大学医学部附属病院　病院長　殿

私は、以下の研究について研究協力に同意しておりましたが、この度同意を撤回したいと存じますので何卒宜しくお願い申し上げます。

研究課題名：Kenny-Caffey 症候群類縁疾患の原因遺伝子の同定
研究者　所属・氏名：東京大学医学部附属病院小児科・磯島豪

これまでの同意の状況：本研究協力へ同意された内容について１、２に○を付けて下さい。

１．提供する生体試料等が，本遺伝子解析研究に使用されること

２．提供する生体試料等が，本研究終了後も保存され，将来、新たに計画・実施される Kenny-Caffey 症候群に関連する遺伝子の分析を含む医学研究に使用されること

同意撤回の内容

１．提供した生体試料が，本遺伝子解析研究に使用されることへの同意を撤回しますので試料の破棄をお願いします。

署名＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

２．提供する生体試料等が，本研究に使用されることには同意しますが、本研究終了後も保存され，将来新たに計画・実施される、Kenny-Caffey 症候群に関連する遺伝子の分析を含む医学研究に使用されることの同意は撤回します。

署名＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

平成　　年　　月　　日

氏名（試料提供者本人または代諾者）＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿
（代諾者の場合は、本人との関係）　＿＿＿＿＿＿

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【資料６】

ホームページ　http://kenny-caffey3.webnode.jp/

メインページ　サイトマップ　RSS　印刷

Kenny-Caffey症候群

メニュー

- メインページ
- KCSの分類と症状
- KCSの原因遺伝子
- KCSの治療

サイト内検索

はじめに

Kenny-Caffey症候群(KCS)は、均整のとれた低身長、長管骨の骨膜肥厚と髄質の狭小化、眼の異常、一過性の低カルシウム血症などを呈する非常にまれな疾患です。

本サイトでは、KCSに関する情報を提供し、よりたくさんの方にKCSについて詳しく知っていただくことを目的としています。

お問い合わせ先

東京大学医学部医学系研究科
小児医学講座内分泌チーム

Kenny-Caffey症候群

メニュー

- メインページ
- KCSの分類と症状
- KCSの原因遺伝子
- KCSの治療

サイト内検索

検索

お問い合わせ先

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小児医学講座内分泌チーム

メインページ > KCSの分類と症状

KCSの分類と症状

1. 低身長について

低身長は、ほぼ全員に認められる症状です。四肢短縮を伴う軟骨無形成症などと違いKCSでは均整の取れた低身長を示すことが特徴であり、成人身長は121-152cmと報告されています。成長障害は、子宮内発育遅延として胎内から生じる場合もあれば、出生時の身長、体重は正常範囲内で、その後徐々に成長障害が進行して、1歳過ぎから著名な成長障害を認める場合もあります。KCS1型のほうが成長障害の程度が強いとされています。

- 低カルシウム血症について

新生児期から低カルシウム血症による痙攣を起こすことが多くみられます。低カルシウムの原因は副甲状腺機能低下症であると考えられています。また、KCS症例の剖検例では、副甲状腺が同定されなかったことから、KCSの副甲状腺機能低下症は副甲状腺の形成障害によるものと想定されています。画像所見として、頭部CTで、副甲状腺機能低下症に伴う大脳基底核の石灰化を認めることもあります。しかしながら、副甲状腺機能低下症や低カルシウム血症が指摘されたことのない症例も存在しており、機序の詳細についてはわかっていません。

- 画像所見

II. 研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Isojima T, Doi K, Mitsui J, Oda Y, Tokuhiro E, Yasoda A, Yorifuji T, Horikawa R, Yoshimura J, Ishiura H, Morishita S, Tsuji S, Kitanaka S.	A recurrent *de novo* *FAM111A* mutation causes Kenny-Caffey syndrome type 2.	J Bone Miner Res	29	992-8	2014
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Isojima T, Harita Y, Furuyama M, Sugawara N, Ishizuka K, Horita S, Kajiho Y, Miura K, Igarashi T, Hattori M, Kitanaka S	*LMX1B* Mutation with Residual Transcriptional Activity as a Cause of Isolated Glomerulopathy.	Nephrol Dial Transplant	29	81-8	2014
Tsuyoshi Isojima, Michiyasu Ishizawa, Kazuko Yoshimura, Mayuko Tamura, Shinichi Hirose, Makoto Makishima, Sachiko Kitanaka	Hereditary 1,25-dihydroxyvitamin D-resistant rickets (HVDRR) caused by a VDR mutation: A novel mechanism of dominant inheritance.	Bone Reports	2	68-73	2015

Tamura M, Isojima T, Kawashima M, Yoshida H, Yamamoto K, Kitaoka T, Namba N, Oka A, Ozono K, Tokunaga K, Kitanaka S	Detection of hereditary 1,25-hydroxyvitamin D-resistant rickets caused by uniparental disomy of chromosome 12 using genome-wide single nucleotide polymorphism array.	PLoS One	10	e0131157	2015
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北中幸子	ビタミンD欠乏性くる病	小児疾患診療のための病態生理　改訂5版　小児内科	46増	791－795	2014
北中幸子	小児におけるビタミンD代謝と骨	腎と骨代謝	28	209-215	2015
北中幸子	ビタミンD欠乏症の発症に関する遺伝子多型	ビタミン	89	72-74	2015

III. 研究成果の刊行物・別刷

ORIGINAL ARTICLE

JBMR®

A Recurrent De Novo *FAM111A* Mutation Causes Kenny–Caffey Syndrome Type 2

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ABSTRACT

Kenny–Caffey syndrome (KCS) is a rare dysmorphologic syndrome characterized by proportionate short stature, cortical thickening and medullary stenosis of tubular bones, delayed closure of anterior fontanelle, eye abnormalities, and hypoparathyroidism. The autosomal dominant form of KCS (KCS type 2 [KCS2]) is distinguished from the autosomal recessive form of KCS (KCS type 1 [KCS1]), which is caused by mutations of the tubulin-folding cofactor E (*TBCE*) gene, by the absence of mental retardation. In this study, we recruited four unrelated Japanese patients with typical sporadic KCS2, and performed exome sequencing in three patients and their parents to elucidate the molecular basis of KCS2. The possible candidate genes were explored by a de novo mutation detection method. A single gene, *FAM111A* (NM_001142519.1), was shared among three families. An identical missense mutation, R569H, was heterozygously detected in all three patients but not in the unaffected family members. This mutation was also found in an additional unrelated patient. These findings are in accordance with those of a recent independent report by a Swiss group that KCS2 is caused by a de novo mutation of *FAM111A*, and R569H is a hot spot mutation for KCS2. Although the function of FAM111A is not known, this study would provide evidence that FAM111A is a key molecule for normal bone development, height gain, and parathyroid hormone development and/or regulation. © 2014 American Society for Bone and Mineral Research.

KEY WORDS: KENNY–CAFFEY SYNDROME; *FAM111A*; PARATHYROID-RELATED DISORDERS; HYPOMAGNESEMIA

Introduction

Kenny–Caffey syndrome (KCS) (OMIM #244460, %127000) is a rare dysmorphologic syndrome characterized by severe proportionate short stature with adult heights of 121 to 149 cm, cortical thickening and medullary stenosis of tubular bones, delayed closure of the anterior fontanelle, eye abnormalities, and hypocalcemia owing to hypoparathyroidism.[1–4] KCS is classified into two types according to its clinical features and inheritance pattern. Classical cases have normal intelligence and are transmitted as an autosomal dominant trait or sporadically and are called KCS type 2 (KCS2) (OMIM %127000).[5] Cases having mental and prenatal growth retardation and transmitted as an autosomal recessive trait are called KCS type 1 (KCS1) (OMIM #244460).[4,6,7]

In 2002, a study of 65 individuals from 34 pedigrees of Middle Eastern origin resulted in the identification of mutations of the tubulin-folding cofactor E (*TBCE*) gene as the cause of KCS1. *TBCE* encodes a molecular chaperone required for heterodimerization of α-tubulin with β-tubulin.[8] KCS2 is extremely rare, with only 5 sporadic cases reported in Japan.[9–12] Because of this rarity, the cause of KCS2 has been unknown until it was recently reported to involve the "family with sequence similarity 111, member A" (*FAM111A*) gene (NM_001142519.1) by a Swiss group in 2013.[13]

In this study, we recruited 4 Japanese patients with typical sporadic KCS2 having normal intelligence and performed whole exome sequencing in 3 unrelated trios to elucidate the molecular basis of KCS2. We hypothesized that KCS2 is caused by de novo mutations and built a de novo mutation detection pipeline to

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Additional Supporting Information may be found in the online version of this article.

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process the raw data from exome sequencing. Using this method, we found an identical de novo mutation in *FAM111A* in all 4 patients. This and the reported independent studies provide evidence that *FAM111A* is the cause of KCS2, and R569H is a hot spot mutation for KCS2.

Materials and Methods

Subjects

Case 1

This 10-year-old girl (Fig. 1, I-1)[9] was born at 40 weeks of gestation to nonconsanguineous, healthy Japanese parents. Polysyndactyly was noticed at birth. At 3 months of age, she was referred to a pediatric endocrinologist because of growth retardation. Her body length, body weight, and head circumferences were 55 cm (−2.5 SD), 5092 g (−1.8 SD), and 37.3 cm (0.2 SD), respectively. She was found to have liver dysfunction with a serum aspartate aminotransferase (AST) level of 227 U/L (reference range 21 to 75) and serum alanine aminotransferase (ALT) level of 227 U/l (reference range 11 to 69). Basal serum insulin-like growth factor (IGF-I), calcium (Ca), and phosphorus (P) levels were within normal limits. At the age of 1 year, hypocalcemia was revealed. Her serum Ca, P, and intact parathyroid hormone (PTH) levels were 1.6 mmol/L (reference range 2.1 to 2.4), 2.6 mmol/L (reference range 0.88 to 1.4), and 11 ng/L (reference range 15 to 50), respectively, with a normal magnesium (Mg) level of 0.86 mmol/L (reference range 0.74 to 0.90). Her serum $1,25(OH)_2D$ level, serum alkaline phosphatase level, and urine Ca/creatinine ratio were within normal ranges. Brain computed tomography (CT) revealed calcification in the basal ganglia (Fig. 2*A*). She was diagnosed with primary hypoparathyroidism and was treated with alfacalcidol [$1\alpha(OH)D_3$]. At 2 years of age, she was diagnosed with KCS2 based on clinical manifestations of proportionate short stature, cortical thickening and medullary stenosis confirmed by radioscopic study (Fig. 2*B*), macrocephaly with delayed closure of the anterior fontanelle, eye abnormalities (hypermetropia and pseudopapilledema), and normal intelligence. Magnesium oxide was administered because of a low serum Mg level (below 0.62 mmol/L) at 3 years of age.

Case 2

This 16-year-old boy (Fig. 1, II-4)[10] was born at 41 weeks of gestation to nonconsanguineous, healthy Japanese parents. When he was 23 days old, he had a generalized convulsion because of hypocalcemia. At this time, his serum Ca, P, Mg, and intact PTH levels were 1.5 mmol/L, 3.1 mmol/L, 0.74 mmol/L, and undetectable, respectively. T-cell subset was normal. He was treated with alfacalcidol on the basis of a diagnosis of primary hypoparathyroidism. Magnesium sulfate was added because of his low serum Mg level at the age of 1 year. He suffered repeated bouts of acute otitis media until the age of two years. His serum IgG level was within the normal range. At 3 years and 1 month, his height, weight, and head circumference were 77.9 cm (−4.4 SD), 9.9 kg (−2.7 SD), and 47.4 cm (−1.5 SD), respectively. He had normal intelligence for his age. He was diagnosed with KCS2 based on clinical findings of proportionate short stature, medullary stenosis revealed by radiography, a widely open anterior fontanelle (Fig. 2*C*, skull radiograph at 9 years), and hypermetropia. He also suffered severe atopic dermatitis after normalization of his serum Ca levels. His growth chart is shown in Fig. 2*D*.

Case 3

This 22-year-old woman (Fig. 1, III-9)[11] was born at 40 weeks of gestation to nonconsanguineous, healthy Japanese parents following an uneventful pregnancy. At 1 month, she had an episode of generalized convulsions because of hypocalcemia. At this episode, her serum Ca, P, Mg, and intact PTH levels were 1.3 mmol/L, 2.9 mmol/L, 0.49 mmol/L, and undetectable, respectively. Oral alfacalcidol administration was started on the basis of a diagnosis of primary hypoparathyroidism. At the age of 5 years 1 month, she was referred to another hospital. Her height was 84.2 cm (−5.3 SD), and her weight was 12.2 kg (−2.2 SD). She had normal intelligence. Brain CT revealed fine calcification in the basal ganglia. Based on clinical manifestations of proportionate short stature, medullary stenosis of the long bones typical of KCS, a 1 × 1-cm opening of her anterior fontanelle, normal intelligence, and hypermetropia, she was diagnosed with KCS2. The patient was started with a combination therapy of vitamin D and magnesium sulphate. Fig. 2*E* shows her radiograph at 14 years of age.

Case 4

This 38-year-old man (Fig. 1, IV-13)[12] was born at 40 weeks of gestation to nonconsanguineous, healthy Japanese parents following an uneventful pregnancy. At 8 days of age, he had a generalized convulsion, and hypocalcemia (0.75 mmol/L) and hypomagnesemia (0.18 mmol/L) were detected. The convulsion was controlled by intravenous administration of Ca gluconate and magnesium sulfate until he was 15 days old. At 4 years of age, he again had an episode of generalized convulsion because of hypocalcemia. At this episode, his serum Ca, P, and intact PTH levels were 1.2 mmol/L, 2.6 mmol/L, and undetectable, respectively. He was diagnosed with primary hypoparathyroidism, and oral alfacalcidol and Ca lactate administration were started. He suffered repeated acute otitis media during infancy and was affected with empyema and bacterial meningitis at 4 years of age. Hypogammaglobulinemia was found, and he was administered gamma globulin intermittently. At 12 years of age, he was referred to another hospital for further investigation. His height was 99 cm (−6.3 SD), and his weight was 16.2 kg (−3.3 SD). He had normal intelligence with an intelligence quotient score of 105. Brain CT revealed fine calcification in the basal ganglia. Based on clinical manifestations of proportionate short stature, medullary stenosis of the long bones, a 4.2 × 1.8-cm opening of his anterior fontanelle, and eye abnormalities (hypermetropia, amblyopia, and pseudopapilledema), he was diagnosed with KCS2. Mg loading and Ca restriction tests revealed that his hypoparathyroidism was secondary to hypomagnesemia. The patient was then changed from vitamin D and Ca lactate to magnesium sulfate treatment, which successfully corrected his serum Ca levels.

We recruited these 4 Japanese patients with clinically diagnosed typical sporadic KCS2 (Fig. 1). Supplemental Table S1{TBL S1} summarizes the clinical characteristics of the 4 patients. We obtained peripheral blood samples from all 4 patients, together with those of 9 unaffected parents or siblings, with informed consent for DNA analysis (Fig. 1). The study was performed with the approval of the Ethics Committee of The University of Tokyo and of each institution where the samples

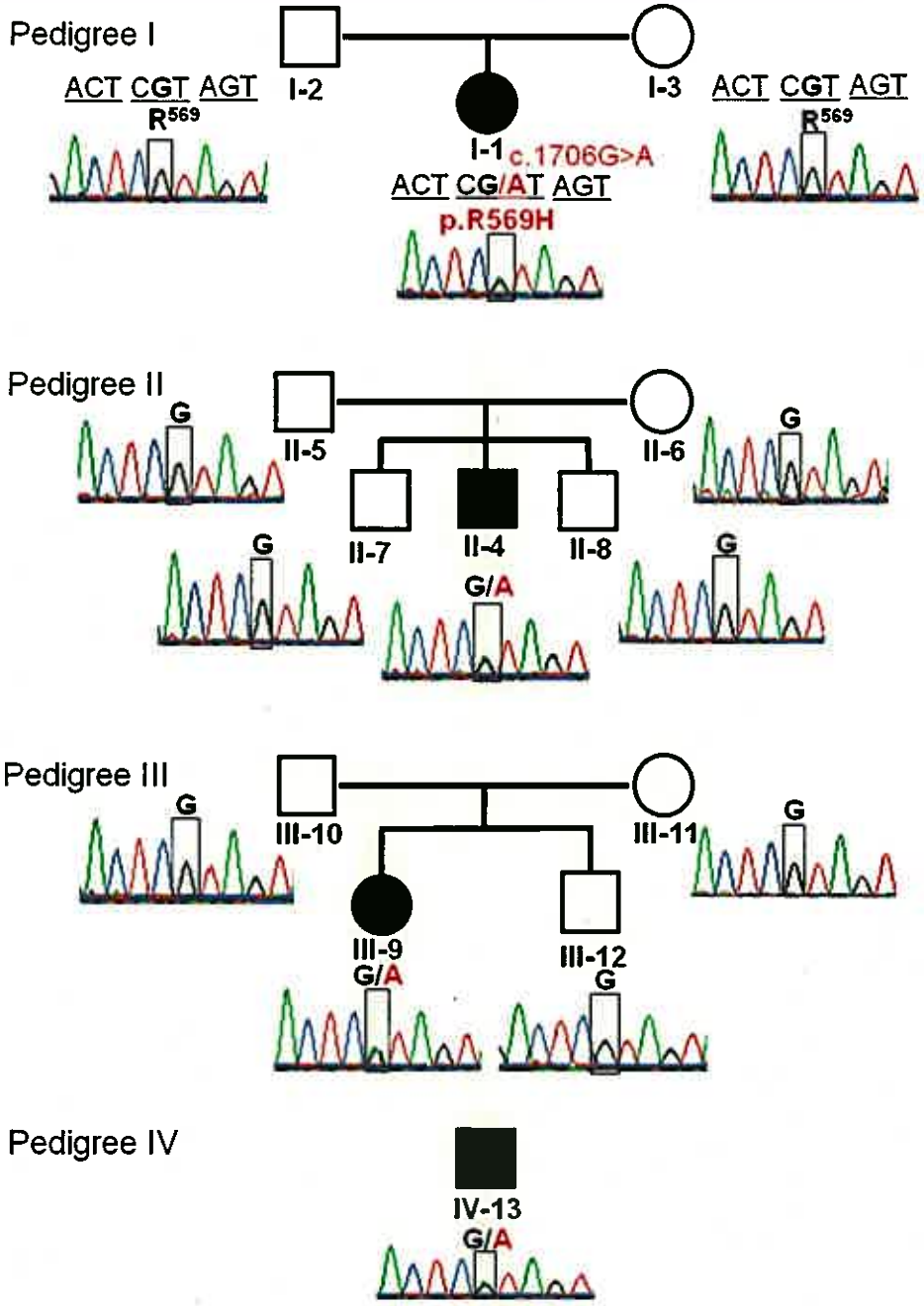

Fig. 1. Four pedigrees analyzed in this study, showing the chromatograms of Sanger sequencing reactions of the *FAM111A* mutation in patients and family members. Data were obtained by Sanger sequencing during the confirmation process. All mutations were checked by bidirectional sequencing. In each pedigree, a black symbol represents the proband, a square indicates a male, and a circle shows a female. In the chromatogram, black letters indicate the wild-type nucleotide sequence. Nucleotides in red indicate mutations. R569H was identified in all probands but not in any of the unaffected family members.

were collected, and conducted in accordance with the Declaration of Helsinki. Genomic DNA was extracted from peripheral white blood cells of the patients and family members using a QIAamp DNA Blood Midi Kit (Qiagen, Hilden, Germany). Healthy Japanese volunteers were recruited, and DNA was extracted with informed consent.

Exome sequencing

Exome sequences were enriched using a TruSeq Exome Enrichment Kit (Illumina, San Diego, CA, USA) from 1 μg of genomic DNA, according to the manufacturer's instructions. The captured DNA samples were subjected to massively parallel

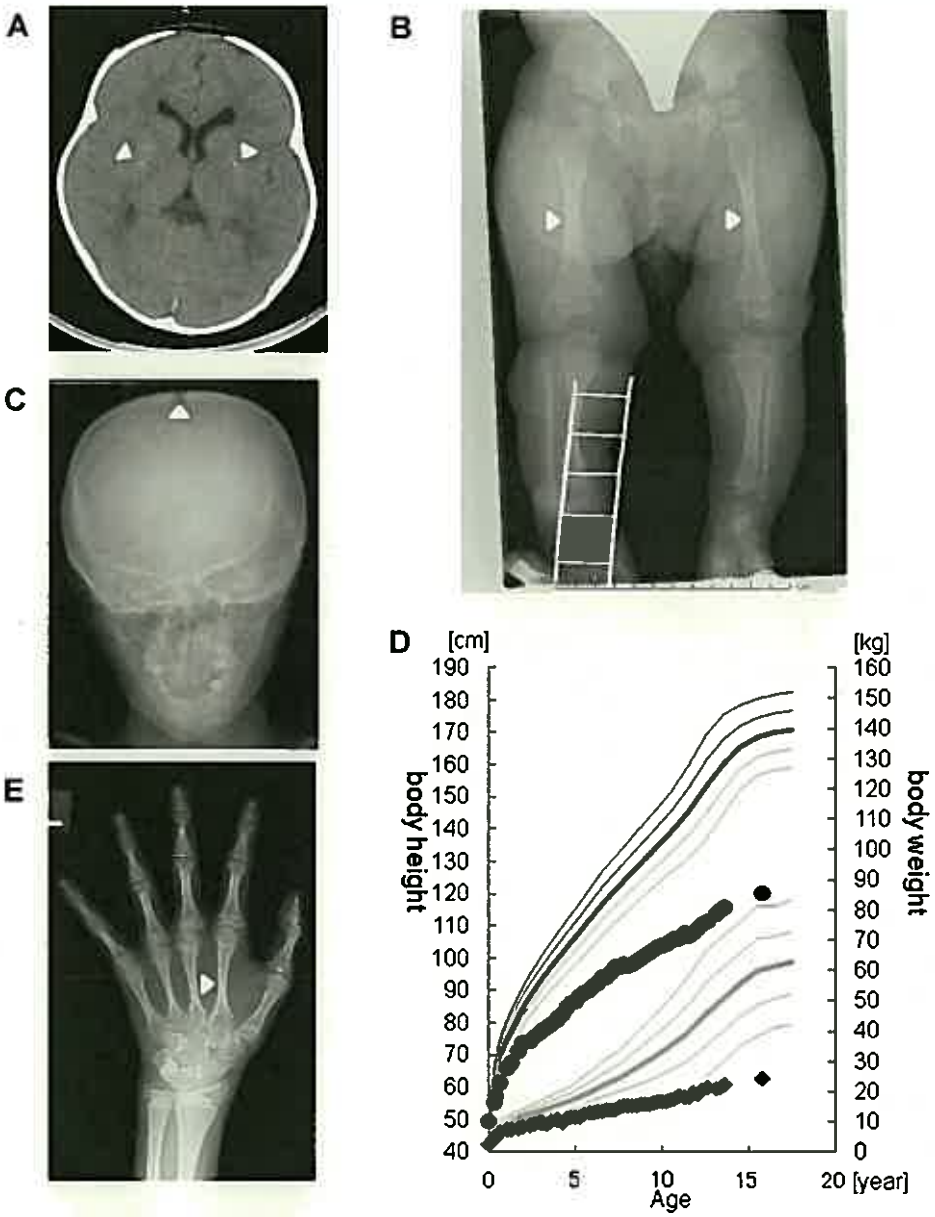

Fig. 2. Radiographic studies and growth charts of probands. (*A*) Brain computed tomography of patient I-1. The arrowheads indicate calcification in the basal ganglia. (*B*) Radiograph of patient I-1 at diagnosis. Cortical thickening and medullary stenosis are evident. The object shown in the right leg is used for fixing a peripheral catheter. (*C*) Radiograph of patient II-4 at age 9 years. It is of note that the anterior fontanelle is open. (*D*) Growth chart of patient II-4 superimposed on the standard growth chart for a Japanese boy. Black circles indicate the patient's height, and black squares indicate his weight. (*E*) Radiograph of patient III-9. Cortical thickening and medullary stenosis can be observed.

sequencing (100-bp paired-end reads) on an Illumina HiSeq2000 sequencing system (Illumina). An average of 95 million reads of the sequence data was obtained for each individual. On an average, 98.50% of the total bases were mapped to the reference genome with a mean coverage of 140.5 ×, which encompassed 91.94% of the targeted regions with coverage >10× (Supplemental Table S2).{TBL S2} The Burrows-Wheeler Aligner (BWA) package[14] and SAMtools[15] were used as default settings for alignment of raw reads and detection of single-nucleotide variants (SNVs) and indels. Subsequently, SNVs and indels were filtered with three trio samples (ie, pedigrees I, II, and III) (Supplemental Fig. S1). We extracted both homo/heterozygous nonsynonymous coding variants, which were called in the proband, and filtered these candidates using the following three steps:

Step 1: Using candidate de novo mutations that are homozygous references in both parents and are supported by 10 or more high-quality reads at the mutated sites for every trio member.

Step 2: Using reliable homozygous references in each parent such that the likelihood of heterozygosis, ${}_nC_i\,(1/2)^i\,(1/2)^{n-i}$, is less than that of homozygosis, ${}_nC_i\,(999/1000)^i(1/1000)^{n-i}$, where the average error rate is assumed to be 1/1000, n represents the number of total reads, and i is the number of reads consistent with the reference. One may have an impression that this condition does not often hold true; however, we often observed cases that violated this condition, especially when the reference base was mutated into one of the other three bases with an almost equal probability.

Step 3: Using reliable de novo mutations of the proband such that the number of alternative allele reads was at least 30% among the total reads, which is the condition proposed in a recent report.[16]

Sanger sequencing

Sanger sequencing was performed to detect *TBCE* (KCS1) and validate the presence of each variant detected by exome sequencing in patients with KCS2 and the absence of each in the genomes of the parents and siblings. The entire coding region and exon–intron boundaries of *TBCE* and *FAM111A* were amplified from genomic DNA by polymerase chain reaction (PCR) using the designed PCR primers (Supplemental Table S3). {TBL S3} Subsequently, PCR products were sequenced using an ABI Prism BigDye Terminator Cycle Sequencing Ready Reaction Kit (PE Applied Biosystems, Foster City, CA, USA) and the forward and reverse primers used for PCR amplification. Direct sequencing in both directions was performed on an autosequencer (PE Applied Biosystems 3130 × 1, Genetic Analyzer).

FAM111A mRNA expression analysis

Total RNA was prepared using ISOGEN reagent (Nippon Gene, Osaka, Japan), according to the manufacturer's instructions, from peripheral white blood cells of the patients and family members. Total RNA (4 μg) was used to synthesize cDNA with the SuperScript Preamplification System for first-strand cDNA synthesis (Life Technologies, Rockville, MD, USA). mRNA levels were measured using an ECO real-time PCR system (Illumina) and KAPA SYBR Fast qPCR Kit (Kapa Biosystems, Woburn, MA, USA) using the following primer pairs: FAM111Ae5-2F and FAM111Ae5-2R; FAM111Ae5-3F and 5′-CCTCATCACTCATCATTTCTACATCC-3′; GAPDH, 5′-GAAGGTGAAGGTCGGAGTC-3′ (F) and 5′-GAAGATGGTGATGGGATTTC-3′ (R). The relative mRNA level was calculated using an arithmetic formula based on the difference between the threshold cycle of a given target cDNA and that of an endogenous reference cDNA. Direct sequencing of the RT-PCR products was performed by Sanger sequencing as for DNA samples.

Results

We first confirmed by Sanger sequencing that none of the 4 patients had *TBCE* mutations. This finding, together with the fact that all the patients were of normal intelligence, distinguishes these patients from patients with KCS1.

We hypothesized that these sporadic cases may be caused by de novo mutations in novel nonsynonymous coding variants. Whole exome sequencing was performed for 3 patients (I-1, II-4, and III-9; Fig. 1) and their parents (I-2, I-3, II-5, II-6, III-10, and III-11; Fig. 1). Statistical data of exome sequencing experiments are shown in Supplemental Table S2. The candidate variants were selected according to the processes described in Materials and Methods based on the de novo mutation detection pipeline designed in the present study (Supplemental Fig. S1). Supplemental Table S4{TBL S4} summarizes the results of filtering to detect candidate genes for KCS2. To select variants as candidate mutations for KCS2, variations that caused amino acid substitution were extracted, which resulted in 11,024 (pedigree I), 10,828 (pedigree II), and 11,020 (pedigree III) SNVs and indels. After three filtering steps, 5 (pedigree I), 5 (pedigree II), and 6 (pedigree III) SNVs were identified. Among the candidate genes filtered using the three aforementioned filtering steps, only one single gene, *FAM111A* (NM_001142519.1), was shared among all 3 families. Sanger sequence analysis of all exons of *FAM111A* confirmed an identical c.1706G > A heterozygous mutation in exon 5 in all 3 patients (Fig. 1). This mutation is predicted to result in substitution of arginine to histidine in codon 569 (R569H). None of the unaffected family members had this mutation, indicating that R569H was a de novo mutation. This mutation was also found in an additional unrelated patient (IV-13).

R569H is not present in 373 Japanese healthy control subjects of an in-house exome database, and not in another 100 alleles from 50 unrelated healthy Japanese individuals by Sanger sequencing. It was also not found in the Japanese SNP control database established by the National Bioscience Data Base Center that has 1 million genome-wide SNPs of 700 samples (http://gwas.biosciencedbc.jp/snpdb/snp_top.php), nor among 6500 samples listed on the exome variant server (http://evs.gs.washington.edu/EVS/), implying that the minor allele frequency is less than 0.01% in these data. However, one SNP was found in the 1000 Genomes database at R569 (rs184251651), which results in substitution to "cysteine" (minor allele frequency 0.1%).

We assessed the functionality of the R569H mutation using the Sorting Intolerant From Tolerant (SIFT) (http://sift.jcvi.org) and Polymorphism Phenotyping 2 (PolyPhen2) (http://genetics.bwh.harvard.edu/pph2) tools, by homology modeling and threading. These in silico studies predicted R569H as "tolerated" and "benign," respectively.

We analyzed the expression levels of *FAM111A* mRNA in peripheral white blood cells by real-time PCR. *FAM111A* expression levels in the patients were comparable with those in unaffected family members and normal controls (data not shown). We also found that mutant and wild-type *FAM111A* were equivalently expressed in the patients, which were identified by sequencing the reverse-transcribed PCR products.

Discussion

In the present study, we identified *FAM111A* as the gene responsible for KCS2 by applying an exome sequencing strategy, and we identified a heterozygous identical de novo *FAM111A* mutation, R569H, in 4 Japanese patients with KCS2. While preparing this article, another independent research group from Switzerland reported similar findings following whole exome sequencing of the patients.[13] They reported that all 5 clinically diagnosed KCS2 patients had de novo *FAM111A* mutations. Most interestingly, 4 of the 5 patients from different countries had the same R569H mutation as detected in our patients. Our 4 pedigrees are unrelated to each other and live in different areas in Japan. Moreover, the parents of the 3 patients did not have the mutation, suggesting that this recurrent mutation was caused by sporadic mutation. Taken together, these two independent

studies confirm that *FAM111A* is the causative gene for KCS2, and R569H is the hot spot mutation of KCS2.

FAM111A encodes a previously uncharacterized protein consisting of 611 amino acids. The carboxy-terminal half of the protein has homology to trypsin-like peptidases, and the catalytic triad specific to such peptidases is conserved.[17] Transcriptional expression of *FAM111A* is ubiquitous according to the human protein atlas (http://www.proteinatlas.org/ENSG00000166801/normal). It is expressed in the parathyroid gland and bone, but the expression levels are similar to those in other tissues. FAM111A has 35% amino acid homology to FAM111B, a paralog located on 11q12.1 at a distance of only 16 kb from FAM111A. The functions of FAM111A and FAM111B are largely unknown. A recent report showed that FAM111A functions as a host range restriction factor and is required for viral replication and gene expression by specifically interacting with Simian Virus 40 large T antigen (LT).[17] In addition, *FAM111A* mRNA and protein levels have been shown to be regulated in a cell cycle-dependent manner with the lowest expression during the G0 or quiescent phase and peak expression during the G2/M phase.[17] Another recent report revealed that variants in the region including *FAM111A* and *FAM111B* were associated with prostate cancer.[18] However, the clinical course of disease in our 4 patients revealed neither increased viral infections nor carcinogenesis up to early adulthood.

In silico analyses suggested that the de novo mutation (R569H) would not significantly affect the function of FAM111A. We also found that the mutant *FAM111A* mRNA was expressed similarly to the wild type in peripheral blood cells. This raises the question of how this mutation causes KCS2. One hypothesis is that this mutation does not cause loss of function of the protein but rather modulates its peptidase activity for a particular target peptide in a mutant-specific way. Another possibility is that FAM111A functions with some physiological partner(s) and the disease occurs as a result of specific modulation of this putative network. This may fit the observation that FAM111A is regulated in a cell-dependent manner and interacts with the LT C-terminal region.[17] We speculate that one of the candidate partner proteins is TBCE because KCS1 and KCS2 share distinctive phenotypic features: skeletal dysmorphic features and primary hypoparathyroidism.

Some diseases are caused by specific mutations of a single gene. Some mutations may cause a gain-of-function effect, as in achondroplasia or McCune–Albright syndrome,[19,20] whereas others have an unknown function, as in Caffey syndrome caused by mutations in *COL1A1*[21] or in several diseases related to *FGFR3*. In this study, we found that a specific mutation (R569H) of *FAM111A* would lead to KCS2. Intriguingly, one SNP was found in the 1000 Genomes database at R569 (rs184251651), which results in substitution to "cysteine." This SNP has been reported to have minor allele frequency of 0.1% (only one allele) and is not validated. Moreover, the absence of the SNP in 6500 samples in the exome variant server suggests a possibility of sequencing error in the database. Nevertheless, it might be speculated that a specific change to "histidine" may lead to an unidentified function of this protein resulting in KCS2, which is not caused by other amino acids. This hypothesis will be supported by the fact that this amino acid is not well conserved among various species (Fig. 3).

It is reported that 95% and 97% of KCS1 cases had prenatal and postnatal growth retardation, and mental retardation, respectively.[22] In contrast, most of the reported KCS2 patients, including our patients with *FAM111A* mutations, had normal

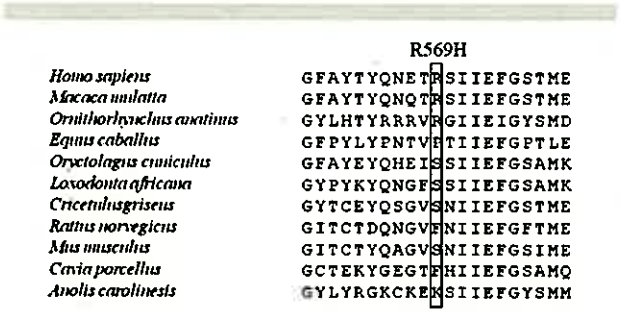

Fig. 3. Homologous comparison of the altered protein. Letters in the rectangular box indicate the human *FAM111A* R569 residue. It is of note that R569 is not well conserved among various species.

birth weight and length and normal intelligence (Supplemental Table S1).[13] These phenotypic differences between KCS1 and KCS2 suggest that the *FAM111A* mutation does not affect bone development and height gain in the fetus but becomes important postnatally. It also suggests that the *FAM111A* mutation does not affect mental development. Now that *FAM111A* has been identified as a causative gene for KCS2, further studies on the physiological function of FAM111A and TBCE should be performed to uncover the phenotypic differences between these two types.

There are several human diseases, as well as mouse models of hypoparathyroidism, caused by aberrations in the cascade of genes indispensable for the development and regulation of the parathyroid gland.[23,24] To date, FAM111A is not known to relate to any of these genes. There have been only a few reports describing the pathophysiology of hypoparathyroidism in KCS. Absence of the parathyroid glands has been reported in some patients with KCS2 and KCS1.[25,26] In contrast, some patients do not have hypoparathyroidism from early infancy, suggesting the presence of some parathyroid gland as in our patient I-1.[4,27] Furthermore, hypoparathyroidism may be secondary to hypomagnesemia as in our patient IV-13. Considering the fact that all of our 4 patients as well as another reported KCS2 case had hypomagnesemia,[4] FAM111A might be involved in magnesium homeostasis. Although further investigation is necessary to reveal the cause of hypoparathyroidism in KCS2, this study shows that a new gene, *FAM111A*, is indispensable for PTH development and/or regulation.

In conclusion, our finding that all 4 Japanese KCS2 patients we tested have the same de novo mutation (R569H) of *FAM111A* indicates that KCS2 is caused by a heterozygous mutation of *FAM111A*, and R569H is the hot spot mutation in patients with KCS2. Although the function of FAM111A is largely unknown, this study provides evidence that FAM111A is a key molecule for normal bone development, height gain, and PTH development and/or regulation. Our finding further creates a new research area in the fields associated with shared phenotypic features in KCS and different phenotypes between KCS1 and KCS2.

Disclosures

TI has received research grants and speaker's fees from Novo Nordisk and has received speaker's fees from Eli Lilly. SK has received research grants and speaker's fees from Novo Nordisk,

Pfizer, Eli Lilly, and JCR Pharmaceuticals and has received speaker's fees from Chugai Pharmaceutical. All other authors state that they have no conflicts of interest.

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Kenny−Caffey症候群と類縁疾患

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Kenny-Caffey症候群と類縁疾患

Kenny-Caffey syndrome and its related syndromes

磯島 豪　北中幸子

Abstract

Kenny-Caffey syndrome (KCS) is a very rare dysmorphologic syndrome characterized by proportionate short stature, cortical thickening and medullary stenosis of tubular bones, delayed closure of anterior fontanelle, eye abnormalities, and hypoparathyroidism. Two types of KCS were known: the autosomal recessive form (KCS type 1), which is caused by mutations of the *TBCE* gene, and the autosomal dominant form (KCS type 2), which is caused by mutations of the *FAM111A* gene. *TBCE* mutation also causes hypoparathyroidism-retardation-dysmorphism syndrome, and *FAM111A* mutation also causes gracile bone dysplasia. These two diseases can be called as KCS-related syndromes. In this article, we review the clinical manifestations of KCS and discuss its related syndromes.

Key words: Kenny-Caffey syndrome, TBCE, FAM111A, short stature, hypoparathyroidism

はじめに

Kennyと Linarelliは，一過性の低カルシウム血症によるテタニーを伴い，長管骨の骨膜が肥厚した著明な低身長の母子例(39歳の母は身長121 cm)を報告した[1]．その他の症状として，大泉門の閉鎖遅延，近視，低出生体重が認められたが，精神発達は正常であった．さらに，Caffeyは，その母子例の単純X線像について詳細に報告した[2]．文献上，これらの報告以前にも同様の報告が散見されたこともあり，均整のとれた低身長，長管骨の骨膜肥厚と髄質の狭小化，眼の異常，一過性の低カルシウム血症を伴う症候群が確立した症候群として認知されるようになり，Kenny-Caffey症候群(KCS)と呼ばれるようになった．その後も散発例や母子例の報告が散見されるものの，KCSは非常にまれな症候群であり，日本ではこれまで文献上数例の散発例の報告しか存在しない．

1. KCSの分類と臨床症状

KCSは，常染色体劣性遺伝のKCS1型と常染色体優性遺伝をするKCS2型に分類されている．KennyとLinarelliが最初に報告した母子例は，常染色体優性遺伝形式を示すKCS2型と考えられるが，最初に原因遺伝子が同定されたのが常染色体劣性遺伝形式を示すKCSであったため，こちらがKCS1型と呼ばれるようになった．

KCSは，均整のとれた著明な低身長，様々な程度の低カルシウム血症(多くは，副甲状腺機能低下症)，長管骨の骨膜肥厚と髄質の狭小化，大泉門の開大と閉鎖遅延，眼の異常を伴う症候

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表1　Kenny-Caffey症候群(KCS)の臨床所見のまとめ

	KCS1型	頻度(%)	KCS2型	頻度(%)	総　数	頻度(%)
報告例	27		37		64	
性別(男性/女性)	5/20		17/20		22/40	
遺伝形式	常染色体劣性		常染色体優性			
精神運動発達遅滞	16/19	84%	4/31	13%	20/50	40%
単純X線所見						
骨膜肥厚と髄質の狭小化	22/25	88%	33/37	89%	55/62	89%
頭蓋冠の板間層欠失	17/22	77%	20/25	80%	37/47	79%
大泉門閉鎖遅延	5/25	20%	28/30	93%	33/55	60%
成長障害						
低身長	26/27	96%	35/37	95%	61/64	95%
子宮内発育遅延	23/27	85%	8/28	29%	31/55	56%
骨年齢の遅れ	13/21	62%	12/24	50%	25/45	56%
成長ホルモン分泌不全症					4/17	24%
低カルシウム血症						
低カルシウム血症	25/27	93%	31/35	89%	56/62	90%
症状を伴う低カルシウム血症	24/27	89%	30/35	86%	54/62	87%
副甲状腺機能低下症	18/21	86%	22/28	79%	40/49	82%
特徴的な顔貌						
前額の突出	20/22	91%	21/22	95%	41/44	93%
小眼症	10/14	71%	19/27	70%	29/41	71%
小顎症	19/25	76%	16/22	73%	35/47	74%
歯の異常	11/13	85%	14/17	82%	25/30	83%
相対的大頭	2/16	13%	18/19	95%	20/35	57%
小頭	16/18	89%	14/17	82%	30/35	86%
眼の異常	21/27	78%	32/36	89%	53/63	84%
遠視	7/20	35%	24/30	80%	31/50	62%
斜視	21/27	78%	32/36	89%	53/63	84%
その他						
貧血	5/9	56%	8/19	42%	13/28	46%

(文献[1]に他の報告症例を加えて作成)

群である[1]．新生児期から低カルシウム血症により痙攣を起こし，成長障害を伴うため著明な低身長を呈する．さらにKCS1型は，小頭を呈し精神運動発達遅滞を伴うことが多い．一方で，KCS2型は相対的に大頭を呈し精神運動発達遅滞を伴わないことが多い．これまでに文献上KCSとして報告された症例に認められた主要な臨床症状について表1にまとめた[1]．

KCSの臨床症状の中でも，低身長はほぼ全員に認められる症状である(表1)．四肢短縮を伴う軟骨無形成症などと違いKCSでは均整の取れた低身長を示すことが特徴であり，成人身長は，121-152 cmと報告されている[1]．成長障害は，子宮内発育遅延として胎内から生じる症例もいれば，出生時の身長，体重は正常範囲内で，その後徐々に成長障害が進行して，1歳過ぎから著明な成長障害を認めるものもいる．KCS1型では子宮内発育遅延が85%存在し，出生前から成長障害がみられ，出生後も成長障害が進行するのが特徴の一つであるのに対して，KCS2型では子宮内発育遅延は29%しか存在せず，出生後から成長障害がみられるのが特徴の一つである．さらにKCS1型の方が成長障害の程度が強いとされている．図1にKCS2型の男児例

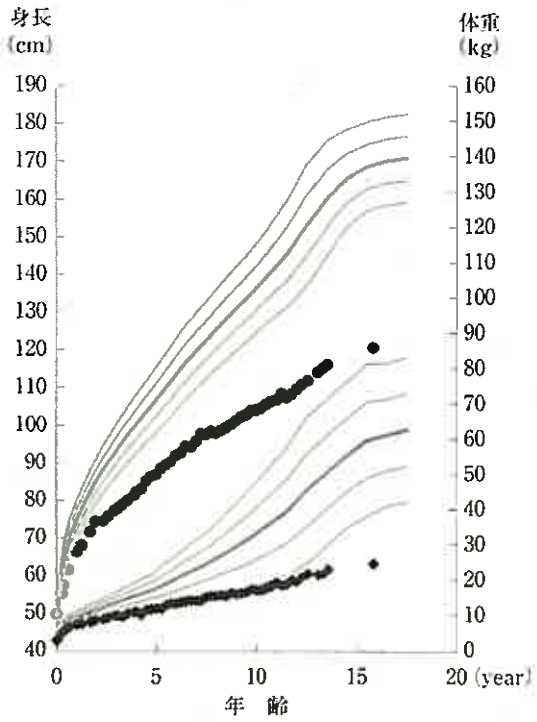

図1　Kenny-Caffey症候群2型男児の成長曲線
1歳過ぎからの著明な成長障害が認められる.

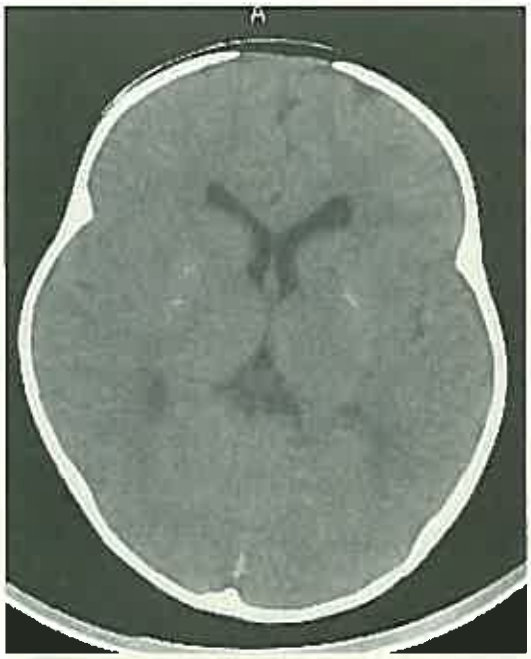

図2　Kenny-Caffey症候群に認められた大脳基底核の石灰化

の成長曲線を示す[1]. 児は, 出生時体重2,882g(−0.4SD), 出生時身長50.0cm(0.5SD)であったが, その後成長障害が進行して16歳で120.6cm(−8.2SD)と著明な成長障害を認めている.

低カルシウム血症については, 新生児期から低カルシウム血症による痙攣を起こすものが多い(87%, **表1**). また, 多くの場合には, 低カルシウム血症, 高リン血症のときに, 副甲状腺ホルモンが低値または同定できないことが多く, 低カルシウムの原因は副甲状腺機能低下症であると考えられている. さらに, KCS症例の剖検例では, 副甲状腺は同定されなかったことから, KCSの副甲状腺機能低下症は副甲状腺の形成障害によると想定されている[63]. 画像所見として, 頭部CTにおいて副甲状腺機能低下症に伴う大脳基底核の石灰化を認めることもある(**図2**). しかしながら, 副甲状腺機能低下症や低カルシウム血症が指摘されたことのない症例も存在する[6]. また, 軽度の低マグネシウム血症を伴うことが多く[55], 二次的な副甲状腺機能低下症も疑われている. 様々な程度の低カルシウム血症は, KCSの大きな特徴であり診断上重要な所見であるが, その詳細な機序については, まだ正確にはわかっていない.

KCSの診断において骨の単純X線写真での所見は重要である. **図3**にKCS症例に認められた骨単純X線像を示す. KCSでは大泉門の閉鎖の遅延を認めるため**図3-a**に示すように, 2歳を超えても大泉門が開大していることが多い. この特徴は相対的な大頭を示すKCS2型では93%とよく認められるが, 小頭を示すKCS1型では20%とKCS2型に比べて少ない. **図3-b**にみられるような頭蓋冠の板間層欠失は, KCS1型にも2型にも特徴的な所見である. さらに, KCSの骨単純X線像上最も特徴的なのは, **図3-c, d**に示すように, 長管骨の骨膜肥厚と髄質の狭小化である. この所見は, 長管骨の中心部において特に顕著に認められるが, 骨端, 骨幹端では普通は認められない. 骨の成熟そのものは問題ないとされ, 骨年齢は遅れるものもいれば, 年齢相応のものも存在する.

図3　Kenny－Caffey 症候群に認められた単純X線像

a. KCS 症例 9 歳時の単純X線像であるが，大泉門は閉鎖していない．
b. 頭蓋冠の板間層欠失が認められる．
c，d. 長管骨における骨膜肥厚と髄質狭小化が認められる．

特徴的な顔貌も KCS の特徴の一つである．具体的には，前額の突出，小眼症，小頭症，歯の異常を伴うことが多く，前述のとおり KCS1 型では小頭症を，KCS2 型では相対的大頭症を伴うことが多い．過去の文献で報告された KCS1 型と考えられる症例と KCS2 型と考えられる症例について，それぞれ図4－a[11]，b[11]に示す．

眼の異常については，最初の母子例では近視と報告されたが，その後再検査したところ遠視であったと報告された．KCS では小眼球症による遠視を認めることが多く，偽性乳頭浮腫を認めることもある．そのほかにも，帯状角膜症，両側視神経萎縮，閉塞性緑内障，弱視などが報告されている．

その他の症状としては，貧血，肝機能障害，男性の性腺機能低下症，免疫能の異常などが挙げられる．貧血については表1に示すとおり 46％と比較的よく報告されている．髄質の狭小化と関係あるのかは不明であるが，鉄欠乏性貧血が特徴的とされている[1]．肝機能障害については，原因は不明であるが，症例報告が散見される．性腺機能低下症については，KCS 男児に

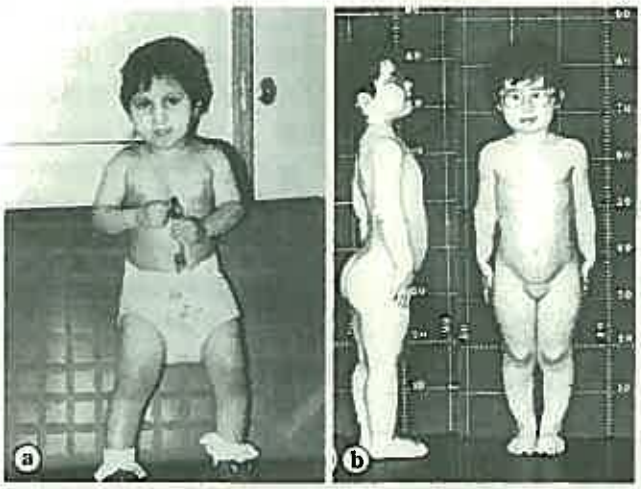

図4　Kenny–Caffey症候群の報告例
a. KCS1型(文献[1]より引用)，b. KCS2型(文献[4]より引用)．
均整のとれた低身長，眼の異常，特徴的な顔貌を認める．

おいて，精巣が小さいことが報告されている[11]．KCSは希少疾患のため確定は難しいが，これまでKCS母子例は報告されているが，父子例は報告されておらず，男性の性腺機能低下症は存在しそうである．一方で，最初に報告された母子例において，母は3回妊娠して，2人の児を産んでおり，現在のところ女性において性腺機能低下症はないと考えられている．免疫能の異常については，KCS1型でよくみられる症状であり，繰り返す細菌感染症が特徴的で液性免疫の異常が想定されるが，細胞性免疫の異常の報告もある．

2. KCSと類縁疾患

KCS1型とhypoparathyroidism–retardation–dysmorphism(HRD)症候群は，1998年にクウェートの近親婚の8家系の連鎖解析から原因遺伝子が常染色体1q42–43にあることが報告され，2002年にtubulin chaperone E(*TBCE*)遺伝子が原因であることが明らかにされた[12]．多くの症例においてエクソン2の12塩基欠失が認められている．TBCEは，αチューブリンを折りたたみ，α–βチューブリンヘテロダイマーを形成するのに必要なシャペロンタンパクであるが，KCS1型およびHRD症候群の発症機序はほとんどわかっていない．

KCS2型は，文献上報告数も少ないこともあり，長年の間原因が不明であった．2013年にスイスのグループと日本のグループがそれぞれ独立した研究により，KCS2型の原因が*FAM111A*遺伝子の*de novo*の変異が原因であると報告した[3,4]．さらに，2つの研究で明らかになった*de novo*変異は，解析された9人中8人が全く同じ変異(R569H)であり，この変異がKCS2型のホットスポットであることも同時に判明した．さらに，*FAM111A*遺伝子は，子宮内発育遅延，著明に細い長管骨，頭蓋骨の骨化不全，顔面形成異常，脾臓の無形成を伴う予後不良の症候群であるgracile bone dysplasia(osteocraniostenosis)の原因であることも報告された[13]．*FAM111A*遺伝子は，全身に発現する611個のアミノ酸からなる遺伝子で，C末端にトリプシン様ペプチダーゼ相同領域をもつことが知られているが，FAM111Aの機能についてはほとんどわかっていない．ホットスポットであるR569は，種族間であまり保存されていない場所であり，さらに興味深いことに同じ場所におけるミスセンス変異(R569C)のSNPが1000ゲノムプロジェクトにおいて報告されていた．*In silico*解析ではR569Hは，FAM111Aの機能

に影響がないという予測であり，さらに，real time PCR法を用いた研究では，患者の白血球におけるFAM111Aの発現はコントロールと比較して差を認めなかった[5]．これらのことから，KCS2型は*FAM111A*の変異により疾患を生じるのは，FAM111Aそのものの機能が直接失われるのではなく，特定の変異により特異的な機能異常が起こるためと推定されている．KCS1型の原因遺伝子が発見されてから10年以上経過したが，その発症機序についてはほとんどわかっていないが，FAM111Aとの関連において研究が進むことが期待されている．

劣性遺伝形式のHRD症候群の中には，*TBCE*遺伝子変異を伴わないものが存在し別の原因遺伝子の存在が示唆されている[11]．一方で，著明な低身長で原因のわからない児を対象としてエクソームシークエンスを行ったところ*FAM111A*遺伝子の変異が同定されKCSと診断がついた報告も存在する[5]．現在のところ，*TBCE*遺伝子，*FAM111A*遺伝子変異が原因のKCS，HRD症候群，gracile bone dysplasiaがKCSおよびKCS類縁疾患と考えられるが，今後KCSの新しい原因遺伝子が同定されれば，さらに類縁疾患が増える可能性がある．また，原因不明の低身長症や原因不明の副甲状腺機能低下症の児の中にも，*TBCE*遺伝子や*FAM111A*遺伝子の変異が見つかる可能性もある．

おわりに

KCSとKCS類縁疾患について概説した．ゲノム解析技術の進歩によって，KCSの原因遺伝子が判明したことにより，今後は原因遺伝子に基づいた症候群の理解が深まっていくものと考えられる．

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