Hayashi S, Imoto I, Aizu Y, Okamoto N, Mizuno S, Kurosawa K, Okamoto N, Honda S, Araki S, Mizutani S, Numabe H, Saitoh S, Kosho T, Fukushima Y, Mitsubuchi H, Endo F, Chinen Y, Kosaki R, Okuyama T, Ohki H, Yoshihashi H, Ono M, Takada F, Ono H, Yagi M, Matsumoto H, Makita Y, Hata A, Inazawa J	Clinical application of array-based comparative genomic hybridization by two-stage screening for 536 patients with mental retardation and multiple congenital anomalies.	J Hum Genet	56(2)	110-24	2011
Naiki M, Mizuno S, Yamada K, Yamada Y, Kimura R, Oshiro M, Okamoto N, Makita Y, Seishima M, Wakamatsu N	MBTPS2 mutation causes BRESEK/BRESHECK syndrome.	Am J Med Genet A			In press
Niihori T, Aoki Y, Okamoto N, Kurosawa K, Ohashi H, Mizuno S, Kawame H, Inazawa J, Ohura T, Arai H, Nabatame S, Kikuchi K, Kuroki Y, Miura M, Tanaka T, Ohtake A, Omori I, Ihara K, Mabe H, Watanabe K, Niijima S, Okano E, Numabe H, Matsubara Y. Matsubara Y. Inazawa J, Ohura T, Arai H, Nabatame S, Kikuchi K, Kuroki Y, Miura M, Tanaka T, Ohtake A, Omori I, Ihara K, Mabe H, Watanabe K, Niijima S, Okano E, Numabe H, Matsubara Y	HRAS mutants identified in Costello syndrome patients can induce cellular senescence: possible implications for the pathogenesis of Costello syndrome.	J Hum Genet	56(10)	707-15	2011

Seiji Mizuno, Daisuke Fukushi, Reiko Kimura, Kenichiro Yamada, Yasukazu Yamada, Toshiyuki Kumagai, Nobuaki Wakamatsu	Clinical and genomic characterization of siblings with a distal duplication of chromosome 9q (9q34.1-qter)	Am J Med Genet A	155 (9)	2274-80	2011
Liang JS, Shimojima K, Takayama R, Natsume J, Shichiji M, Hirasawa K, Imai K, Okanishi T, Mizuno S, Okumura A, Sugawara M, Ito T, Ikeda H, Takahashi Y, Oguni H, Imai K, Osawa M, Yamamoto T	CDKL5 alterations lead to early epileptic encephalopathy in both genders.	Epilepsia	52(10)	1835-42	2011
Miyajima Y, Kitase Y, Mizuno S, Sakai H, Matsumoto N, Ogawa A	Acute lymphoblastic leukemia in a pediatric patient with Marfan's syndrome	Rinsho Ketsueki	52(1)	28-31	2011
Waga C, Okamoto N, Ondo Y, Fukumura-Kato R, Goto YI, Kohsaka S, Uchino S	Novel variants of the SHANK3 gene in Japanese autistic patients with severe delayed speech development.	Psychiatr Genet	21	208-11	2011
Sasaki K, Okamoto N, Kosaki K, Yorifuji T, Shimokawa O, Mishima H, Yoshiura KI, Harada N	Maternal uniparental isodisomy and heterodisomy on chromosome 6 encompassing a CUL7 gene mutation causing 3M syndrome.	Clin Genet	80(5)	478-83	2011
Hiraki Y, Nishimura A, Hayashidani M, Terada Y, Nishimura G, Okamoto N, Nishina S, Tsurusaki Y, Doi H, Saitsu H, Miyake N, Matsumot	A de novo deletion of 20q11.2-q12 in a boy presenting with abnormal hands and feet, retinal dysplasia, and intractable feeding difficulty.	Am J Med Genet A	155	409-14	2011
Okamoto N, Hatsukawa Y, Shimojima K, Yamamoto T	Submicroscopic deletion in 7q31 encompassing CADPS2 and TSPAN12 in a child with autism spectrum disorder and PHPV.	Am J Med Genet A	155	1568-73	2011

Shimizu K, Okamoto N, Miyake N, Taira K, Sato Y, Matsuda K, Akimaru N, Ohashi H, Wakui K, Fukushima Y, Matsumoto N, Kosho T	Delineation of dermatan 4-O-sulfotransferase 1 deficient Ehlers-Danlos syndrome: Observation of two additional patients and comprehensive review of 20 reported patients.	Am J Med Genet A	155A	1949-58	2011
Hayashi S, Okamoto N, Chinen Y, Takanashi JI, Makita Y, Hata A, Imoto I, Inazawa J	Novel intragenic duplications and mutations of CASK in patients with mental retardation and microcephaly with pontine and cerebellar hypoplasia (MICPCH).	Hum Genet	131(1)	99-110	2012
Yukiko Kawazu, Noboru Inamura, Futoshi Kayatani, Nobuhiko Okamoto, Hiroko Morisaki	Prenatal complex congenital heart disease with Loeys-Dietz syndrome.	Cardiology in the Young			In press
Tsurusaki Y, Okamoto N, Suzuki Y, Doi H, Saitsu H, Miyake N, Matsumoto N	Exome sequencing of two patients in a family with atypical X-linked leukodystrophy.	Clin Genet	80	161-6	2011
Misako Naiki,,Seiji Mizuno,Kenichiro Yamada, Yasukazu Yamada, Reiko Kimura, Makoto Oshiro, Nobuhiko Okamoto, Yoshio Makita, Mariko Seishima, and Nobuaki Wakamats	MBTPS2 mutation causes BRESEK/BRESHECK syndrome	Am J Med Genet			In press
Okamoto N, Tamura D, Nishimura G, Shimojima K, Yamamoto T	Submicroscopic deletion of 12q13 including HOXC gene cluster with skeletal anomalies and global developmental delay.	Am J Med Genet A	155	2997-3001	2011
Soneda A, Teruya H, Furuya N, Yoshihashi H, Enomoto K, Ishikawa A, Matsui K, Kurosawa K	Proportion of malformations and genetic disorders among cases encountered at a high-care unit in a childre n's hospital.	Eur J Pediatr	171	301-5	2012

Kurosawa K, Masuno M, Kuroki Y	Trens of occurrence of twin births in Japan.	Am J Med Genet Part A	158A	75-77	2012
Yagihashi T, Kosaki K ,Okamoto N ,Mizuno S, Kurosawa K,Takahashi T, Sato Y, Kosaki R	Age-dependent change in behavioral phenotype in Rubinstein-Taybisyndrome.	Congenit Anomalies			In press
Kosaki R, Fujita H, Takada H, Okada M, Torii C, Kosaki K	Monozygotic twins of Rubinstein-Taybi syndrome discordant for glaucoma.	Am J Med Genet A	155A(5)	1189-91	2011
Kosaki R, Kikuchi S, Koinuma G, Higuchi M, Torii C, Kawasaki K, Kosaki K	Two patients with Rubinstein-Taybi syndrome and severe pulmonary interstitial involvement.	American Journal of Medical Genetics	152	1844-6	2010

〔V〕

資　　料

2011.7.23　こすもす(ルビンシュタイン・テイビ症候群児・者 親の会)　交流会に参加

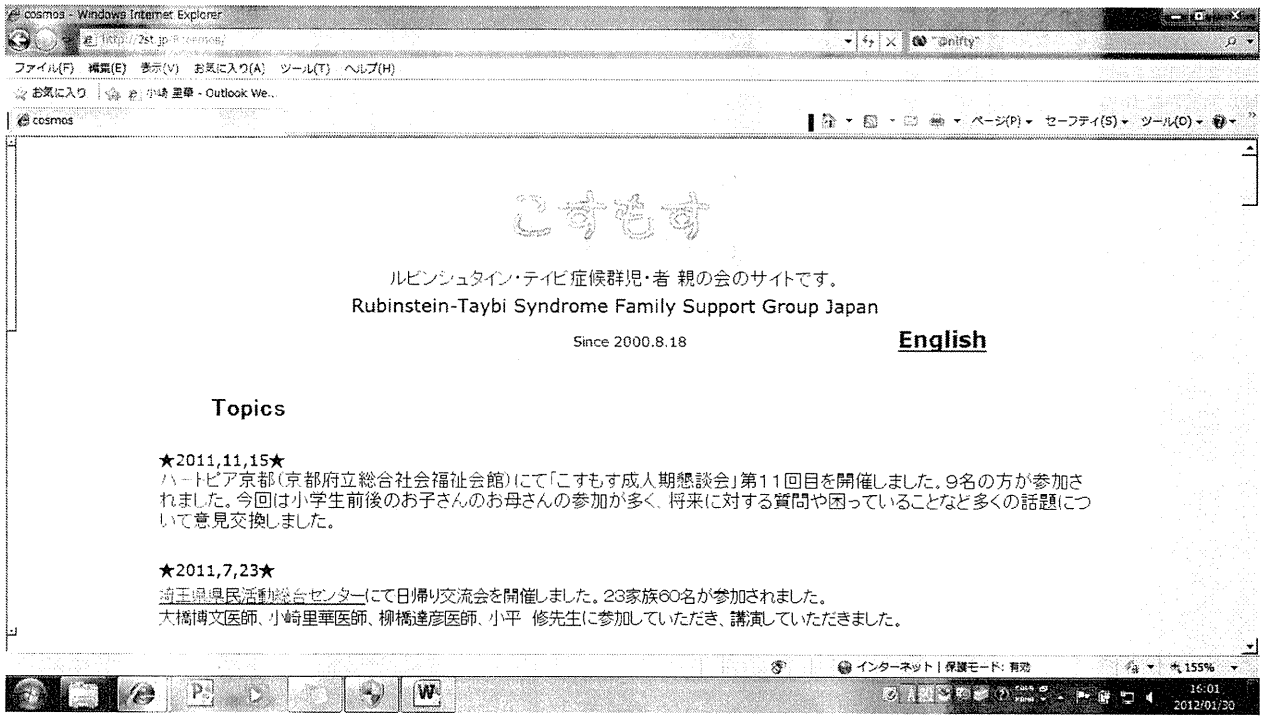
講演

小崎里華　国立成育医療研究センター 遺伝診療科（主任研究者）

「平成 21～23 年度 厚生労働省科学研究費補助金 難治性疾患克服研究事業「Rubinstein-Taybi 症候群の臨床診断基準の策定と新基準にもとづく有病率の調査研究」班について」

柳橋達彦　慶應義塾大学医学部 小児科（分担研究者）

「ルビンスタイン・テイビ症候群の行動とこころの問題～アンケート調査から～」



RESEARCH LETTER

AMERICAN JOURNAL OF medical genetics PART A

Monozygotic Twins of Rubinstein–Taybi Syndrome Discordant for Glaucoma

Rika Kosaki,[1]* Hideki Fujita,[1] Hazuki Takada,[1] Michiyo Okada,[1] Chiharu Torii,[2] and Kenjiro Kosaki[2]

[1]Division of Medical Genetics, National Center for Child Health and Development, Tokyo, Japan

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

Received 15 December 2010; Accepted 3 February 2011

How to Cite this Article:
Kosaki R, Fujita H, Takada H, Okada M, Torii C, Kosaki K. 2011. Monozygotic twins of Rubinstein–Taybi syndrome discordant for glaucoma.
Am J Med Genet Part A 155:1189–1191.

TO THE EDITOR:

Rubinstein–Taybi syndrome (RTS) is characterized by broad thumbs and toes, downward slanted palpebral fissures, a prominent nose with the nasal septum extending below the alae nasi, a hypoplastic maxilla with a narrow plate, thick eyebrows, long eyelashes, a short stature, and moderate intellectual disability [Hennekam, 2006]; its incidence is estimated to be 1 in 100,000. Most cases are sporadic, and about half of all cases have a heterozygous mutation in the *CREBBP* gene; rare cases have a heterozygous *EP300* mutation. Both genes encode histone acetyltransferases (HAT), which are transcriptional co-activators that play critical roles in epigenetic regulation through histone acetylation [Roelfsema and Peters, 2007]. Among the more than 600 cases of RTS reported to date, at least 11 sets of monozygotic twins [Pfeifer, 1968; Gorlin et al., 1976; Schinzel et al., 1979; Kajii et al., 1981; Baraitser and Preece, 1983; Widd, 1983; Ghanem and Dawod, 1990; Hennekam et al., 1990; Robinson et al., 1993; Preis and Majewski, 1995] have been documented.

Here, we present monozygotic twins concordant for the RTS phenotype. The monozygosity and RTS diagnosis were both confirmed using molecular methods. Interestingly, the twins were concordant for facial and limb features but were discordant for body size and the presence of congenital glaucoma. The discordance in the former characteristic (i.e., the body size) was ascribed to a twin-to-twin transfusion between the twins, whereas the discordance in the latter characteristic (i.e., the glaucoma) could not be explained.

The male twins were born to a 24-year-old Japanese G1P1-2 woman with no previous medical problems. Consanguinity or a family history of mental retardation was not present. The placentation was diamniotic and monochorionic. The pregnancy was remarkable for the disproportionate growth of the twins. An ultrasonographic diagnosis of twin-to-twin transfusion syndrome was made, and the vascular connection on the placenta between the twins was successfully disconnected using laser ablation.

The twins were delivered at 30 weeks of gestation. At birth, the weight of Twin A was 1,174 g and his length was 36 cm whereas the birth weight of Twin B was 960 g and his length was 34.5 cm. The postnatal courses of the twins were similar. Developmental delays were apparent: the twins were able to hold their heads up at 10 months, to sit alone at around 18 months, to walk alone at 3–1/2 years, and to speak meaningful words at 7 years.

At the age of 16 months, the twins were referred to our genetic department because of developmental delays. Dysmorphic features (Fig. 1), which were all concordant between the twins, included broad thumbs and toe, downward slanting pleural fissures, a hypoplastic maxilla, a prominent nose with the nasal septum extending below the alae nasi, heavy eyebrows and long eyelashes, salmon patches, undescended testes, patent ductus arterious and a hearing impairment. However, only Twin A had bilateral congenital glaucoma and lens dislocations. A genotyping analysis using nine microsatellite markers (ALAS2, DXS1236, D7S527, D7S630, D9S1779, D9S15, D10S595, D10S2454, and D17S1705) confirmed the monozygosity of the twins. Chromosome analyses revealed normal karyotypes. Molecular screening of the *CREBBP* gene using denaturing high-performance liquid chromatography (DHPLC) was negative [Udaka et al., 2005].

Array comparative genomic hybridization using the Agilent 180K format CGH array designed by the International Standards for Cytogenomic Arrays Consortium (backbone resolution of 35 or 25 kb and 500 targeted regions including telomeres, centromeres, microdeletion/duplication regions, and X-linked mental retarda-

Grant sponsor: The Ministry of Health, Labour, and Welfare of Japan.
*Correspondence to:
Rika Kosaki, M.D., Division of Medical Genetics, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo 157-8535, Japan. E-mail: kosaki-r@ncchd.go.jp
Published online 7 April 2011 in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/ajmg.a.33967

FIG. 1. Facial features of monozygotic twins with Rubinstein–Taybi syndrome (left: Twin A and right: Twin B).

tion genes) revealed a loss in the copy number for the 16p13.3 region (Fig. 2). The size of the deletion was 210 kb, extending from 3,810,524 to 4,0233,361 on 16p13.3 (hg18; NCBI Build 36.1). Genes within the deleted region included the 5′ half of the *CREBBP* locus and its adjacent *ADCV9* locus. We further compared the genomic DNA of Twin A and Twin B using the array, but no copy number differences were detected.

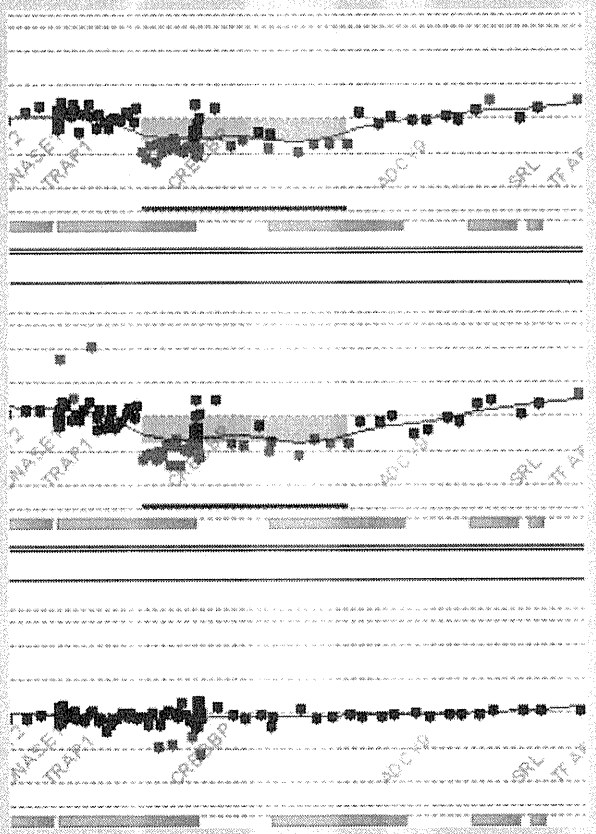


FIG. 2. Result of CGH array analysis (top: Twin A vs. control; middle: Twin B vs. control; bottom: Twin A vs. Twin B). The CGH array analysis revealed a 210 kb interstitial deletion of 16p13.3 involving *CREBBP* gene (top: gray area; middle: blue area).

Here, we document a case of monozygotic twins concordant for the RTS phenotype. To our knowledge, this twin pair represents the first twins whose monozygosity and RTS diagnosis have been confirmed using molecular methods. The monozygosity and diagnosis of several twin pairs with genetically determined multiple congenital anomaly syndromes have been reported including those with Smith–Magenis syndrome [Kosaki et al., 2007], Crouzon syndrome, Alagille syndrome, Sotos syndrome, and 22q11.2 deletion syndrome. RTS can now be added to this list.

The twins had concordant facial and limb features but were discordant for the presence of congenital glaucoma. Three potential mechanisms are capable of explaining this discordance: first, the glaucoma phenotype may not be causally related to the deletion of the RTS locus and may have appeared by chance as a polygenetic trait [Libby et al., 2005]. However, the occasional documentation of glaucoma in other RTS cases [Hennekam, 2006] suggests that the glaucoma phenotype is likely to be associated with the RTS deletion. Second, only Twin A might have experienced a "second hit" in a genomic region(s) other than chromosome 16p. Indeed, array CGH genomic studies of monozygotic twin genomes have revealed occasional differences in copy numbers [Bruder et al., 2008]. However, we did not detect such differences in the presently reported twins (data not shown). Thirdly, the discordance in the severities of the twin pairs could be ascribed to chance-like variations in the pathogenetic actions of the mutated gene. Intriguingly, epigenetic regulation plays a critical role in the stochastic nature of embryonic development, and *CREBBP*, the causative gene in the presently reported twins, represents an epigenetic regulator of embryogenesis [Robinson et al., 1993]. Indeed, a previously reported difference in the neurodevelopment of twins with RTS may support such a notion [Pfeifer, 1968; Buchinger and Stroder, 1973; Preis and Majewski, 1995].

REFERENCES

Baraitser M, Preece MA. 1983. The Rubinstein–Taybi syndrome: Occurrence in two sets of identical twins. Clin Genet 23:318–320.

Bruder CE, Piotrowski A, Gijsbers AA, Andersson R, Erickson S, Diaz de Stahl T, Menzel U, Sandgren J, von Tell D, Poplawski A, Crowley M, Crasto C, Partridge EC, Tiwari H, Allison DB, Komorowski J, van Ommen GJ, Boomsma DI, Pedersen NL, den Dunnen JT, Wirdefeldt K, Dumanski JP. 2008. Phenotypically concordant and discordant monozygotic twins display different DNA copy-number-variation profiles. Am J Hum Genet 82:763–771.

Buchinger G, Stroder J. 1973. Rubinstein–Taybi syndrome of probably monocygotic twins and 3 other children. Klin Padiatr 185:296–307.

Ghanem Q, Dawod S. 1990. Monozygotic twins concordant for Rubinstein–Taybi syndrome. Clin Genet 37:429–434.

Gorlin RJ, Pindborg JJ, Cohen MM. 1976. Rubinstein–Taybi syndrome. In: Gorlin RJ, Pindborg JJ, Cohen MM, editors. Syndromes of the Head and Neck, 2e. New York: McGraw Hill, Inc. pp 657–660.

Hennekam RC. 2006. Rubinstein–Taybi syndrome. Eur J Hum Genet 14:981–985.

Hennekam RC, Stevens CA, Van de Kamp JJ. 1990. Etiology and recurrence risk in Rubinstein–Taybi syndrome. Am J Med Genet Suppl 6:56–64.

Kajii T, Hagiwara K, Tsukahara M, Nakajima H, Fukuda Y. 1981. Monozygotic twins discordant for Rubinstein–Taybi syndrome. J Med Genet 18:312–314.

Kosaki R, Okuyama T, Tanaka T, Migita O, Kosaki K. 2007. Monozygotic twins of Smith–Magenis syndrome. Am J Med Genet Part A 143A: 768–769.

Libby RT, Gould DB, Anderson MG, John SW. 2005. Complex genetics of glaucoma susceptibility. Annu Rev Genomics Hum Genet 6:15–44.

Pfeifer RA. 1968. Rubinstein–Taybi syndrome in probably monozygotic twins. Humangenetik 6:84–87.

Preis S, Majewski F. 1995. Monozygotic twins concordant for Rubinstein–Taybi syndrome: Changing phenotype during infancy. Clin Genet 48:72–75.

Robinson TW, Stewart DL, Hersh JH. 1993. Monozygotic twins concordant for Rubinstein–Taybi syndrome and implications for genetic counseling. Am J Med Genet 45:671–673.

Roelfsema JH, Peters DJ. 2007. Rubinstein–Taybi syndrome: Clinical and molecular overview. Expert Rev Mol Med 9:1–16.

Schinzel AA, Smith DW, Miller JR. 1979. Monozygotic twinning and structural defects. J Pediatr 95:921–930.

Udaka T, Samejima H, Kosaki R, Kurosawa K, Okamoto N, Mizuno S, Makita Y, Numabe H, Toral JF, Takahashi T, Kosaki K. 2005. Comprehensive screening of CREB-binding protein gene mutations among patients with Rubinstein–Taybi syndrome using denaturing high-performance liquid chromatography. Congenit Anom (Kyoto) 45:125–131.

Widd S. 1983. Rubinstein–Taybi syndrome. Nurse Times 79:61–65.