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Case Report

Rubinstein-Taybi Syndrome: Musculoskeletal Abnormality and Its Treatment, A Report of Two Sisters

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Rubinstein-Taybi syndrome (RTS) is an autosomal dominant disorder with multiple congenital anomalies that is characterized by distinctive facial appearance, growth, and mental retardation, and musculoskeletal (MSK) abnormalities. Here, we report two sisters with RTS with serial MSK problems.

The older sister, a 27-year-old female with a history of RTS diagnosed at the age of 10 years, was found to have left elbow instability with habitual dislocation and left patellar subluxation. The younger sister, a18-year-old female with a history of RTS diagnosed at 8 months old, was found to have several MSK problems: bilateral patellar subluxation, left elbow subluxation, right ankle subluxation, and right lateral cuneiform a vascular necrosis with calcaneonavicular osteophyte. Both sisters had functional deterioration due to joint pain. They underwent serial surgeries and rehabilitation and experienced improved physical function after treatment. (Rehabil Pract Sci 2023; 2023(1): 39 - 47)

Key Words: Rubinstein-Taybi syndrome, musculoskeletal abnormality

INTRODUCTION

Rubinstein-Taybi syndrome (RTS) is an autosomal dominant disorder with multiple congenital anomalies[1] caused by a micro deletion or mutation of cyclic adenosine monophosphate response element-binding protein (CREBBP), which is located at chromosome 16p 13.3, or E1A-binding protein (EP300), which is located at chromosome 22q 13.2.[2] CREBBP mutations (50%-60% in RTS cases) are more common than EP300 mutations (5% of RTS cases).[3]

The birth prevalence of RTS is approximately 1/100,000-1/125,000[4]. It is characterized by distinctive facial appearance,[5] short stature,[6] and mental retardation with an average intelligence quotient (IQ) of between 35 and 50.[7,8] Table 1 presents the percentage of RTS symptoms according to a case report by Cardona in 2008.[9] Additionally, patients with RTS experience some common problems, including recurrent urinary tract infection[10] and sleep apnea.[11] Growth hormone deficiency and pituitary hypoplasia were reported by Marzuillo in 2013[8]. Furthermore, autism spectrum disorder was found in some RTS cases.[12] Specific social behavior patterns were noted

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in children with RTS, such as short attention span, motor stereotypes, and poor coordination.[13] 72% of the RTS cases were reported to have abnormal electroencephalography results, and 25% of them had a history of seizures.[14] Moreover, ocular pathology was found in patients with RTS, including lacrimal duct obstruction, corneal abnormalities, congenital glaucoma, congenital cataract, and colobomata; additionally, up to 78% of the patients had retinal dysfunction.[15]

Most literature mentions exterior musculoskeletal (MSK) problems. Rubinstein[1] reported several major MSK problems of RTS, including skeletal maturation retardation, high-arched palate, beaked nose, and broad thumbs and toes. Other minor MSK problems of RTS include double rows of teeth, microcephaly, large foramen magnum, maxillary hypoplasia, malformation, or spine abnormalities, including intraspinal neurilemmoma, simian sternum, pectus excavatum, rib fusion and laxative muscles and joints.[16-18]

As previously mentioned, four-limb deformity and abnormal function in patients with RTS were rarely explored. In this report, we explored cases of two sisters with RTS, who suffered from serial MSK problems, and the management of pain as well as motor and physical function impairments.

CASE REPORT

Brief summary of cases

Both sisters had the same detectable mutation (6122-6125delCCAT) in the CREBBP gene, which was inherited from their father. The older sister was diagnosed with RTS at the age of 10 years and did not receive early intervention, whereas the younger sister was diagnosed with RTS at 8 months old and received physical, occupational, speech, and psychosocial therapies as early intervention. The younger sister (case 2) had a higher ability to perform activities of daily living (ADLs) (total Barthel index score = 95, Table 2) than the older sister (case 1) (total Barthel index score = 70, Table 3).

Case 1

The first case was the older sister, a 27-year-old female with a history of RTS diagnosed at the age of 10 years, who had multiple organ dysfunction, including diabetes insipidus and urinary incontinence, non-insulin-dependent diabetes mellitus, severe mental retardation, chorioretinitis, epilepsy, and thalassemia. She had poor speech ability due to mental retardation. She has certification of severe mental retardation and was graduated from special vocational high school.

She was noted to have functional decline by her mother in 2007 when she was 13 years old. She was brought to our hospital for further evaluation and treatment. Left elbow computed tomography (CT) was performed on December 4, 2007 which revealed left elbow habitual dislocation (Figure 1). Following the suggestion of the orthopedic surgeon, she underwent left ulnar collateral ligament reconstruction with allograft on February 13, 2008. However, left elbow pain recurred 1 year after the surgery. Easy locking and subluxation of the left elbow were noted with an unstable joint with approximately 30° valgus angle during outpatient follow-up. Consequently, open reduction internal fixation and corrective osteotomy of the humerus were performed on January 6, 2010. After the surgery, left elbow pain markedly improved. However, easy locking as a sequela was noted when the elbow was flexed >90°. Left elbow pain did not recur to date. Due to pain relief and improvement in the range of motion (ROM) degree, she can now perform feeding and dressing without assistance. The third surgery for left patellar lateral release due to patellar subluxation was performed in April 21, 2010. The Barthel index scores before and after surgery are presented in Table 2. After operation, she got improvement in feeding, dressing, and stairs.

Case 2

The other case was the younger sister, an 18-year-old female who was diagnosed with RTS at 8 months old due to poor rolling ability, history of psychomotor retardation, status epilepticus on post-antiepileptic drug treatment, and Cushing's syndrome. She had received early intervention since the RTS diagnosis. She has certification of moderate mental retardation and was just graduated from special vocational high school.

Slower walking pace was noted by her mother in 2015 when she was 11 years old. She was subsequently brought to our hospital for consultation. Knee standing and merchant view X-ray were performed on November 4,

2015, and revealed bilateral patellar subluxation (Figure 2). Bilateral arthroscopic synovectomy and patellar retinacular lateral release were performed on February 2, 2016. Bilateral knee pain decreased and walking cadence improved after the surgery.

Limping gait with right ankle swelling recurrence was observed by her mother in 2016. Right ankle magnetic resonance imaging (MRI) was performed on May 20, 2016, and revealed an osteochondral fragment over the calcaneonavicular junction, with adjacent bone sclerosis and edema (Figure3). She underwent interpositional arthroplasty and ostectomy on May 31, 2016. Right ankle pain temporarily improved following the surgery. The left elbow pain with ROM limitation was noted for several years. Surgery for medial instability with valgus deformity and posterior subluxation with anterior laxity of the left elbow was performed on August 17, 2018.However, recurrent and progressive foot pain and swelling while resting and walking were noted 1 year after the ankle surgery. Right ankle MRI was performed on November 21, 2018, revealing right lateral cuneiform avascular necrosis with calcaneonavicular osteophyte (Figure4). Surgery for bone graft and vascularized rotation flap was performed on November 21, 2018. After the surgery, she was referred to the rehabilitation outpatient department. Foot orthoses were applied for arch support. Physiotherapy and occupational therapy were arranged for pain relief and ADL/motor function reconstruction. Right ankle pain and tenderness were improved without recurrence to date. At present, she is a basketball player in a special high school. The Barthel index scores before and after the surgery are presented in Table 3. Under current rehabilitation training and after operation, she got great improvement in toilet use, bathing, dressing, mobility, and stairs.

Table 1. RTS symptoms in previous studies [8–14]

Region or symptoms	**Symptoms**	**Percentage (%)**
Special appearance of RTS		
Head and face	Hypoplastic maxilla with narrow palate	100
	Prominent beaked nose	90
	Antimongoloid palpebral fissures	88
	Lowset/malformed ears	84
	Strabismus	69
	Large anterior fontanelle	41
	Microcephaly	35
	Small mouth	31
Limbs	Broad hallux	100
	Broad thumbs with radial angulation	87
	Broad fingers	87
	Duplicated longitudinal bracketed	49
	Ulnar deviation of the thumb	49
	Fourth cuneiform bones	4.87
	Patellar dislocation, patellofemoral instability	4.87
Trunk	Vertebral and sternal abnormalities (including scoliosis and kyphosis)	4.87
Mentality	Mental retardation (average IQ between 35 and 50)	NA*
Speech function	Speech difficulties	90
Systemic disease	Hypotonia	67
	Hirsutism (female)	75
	Cryptorchidism (male)	78
Eyes	Congenital or juvenile glaucoma	49
	Ptosis	49
	Retinal dysfunction	78
Growth retardation	Growth retardation	49
	Retarded osseous maturation	49

Heart	Cardiac anomalies	32.6
	Electrocardiography abnormalities	30
Genitourinary	Recurrent urinary tract infection	28
Respiratory	Sleep apnea	NA*
Endocrine	Growth hormone deficiency	NA*
	Pituitary hypoplasia	NA*
Behavior	Autistic behaviors, short attention span, Motor stereotypies, and poor coordination	NA*
Neurology	Abnormal electroencephalography	72
	Seizure	25

*NA: This symptom has been reported in previous reports, but the ratio of it in RTS was not calculated yet in current studies.

Table 2. Barthel index of case 1

	Left elbow surgery (February, 2008)		2nd left elbow surgery (January, 2010) And knee surgery (April, 2010)	
	Before	After	Before	After (now)
Feeding	0	5*	0	10*
Grooming	0	0	0	0
Toilet use	5	5	5	5
Bathing	0	0	0	0
Dressing	0	0	0	5*
Bowels	10	10	10	10
Bladder	5	5	5	5
Mobility	15	15	15	15
Stairs	5	5	5	10*
Transfer	10	10	10	10
Total	50	55	50	70

* Functional improvement after surgery.

Table 3. Barthel index of case 2

	Bilateral knee surgery (February, 2016)		1st right ankle surgery (May, 2016)		Left elbow surgery (August 2018) and 2nd right ankle surgery (November 2018)	
	Before	After	Before	After	Before	After(now)
Feeding	10	10	10	10	10	10
Grooming	5	5	5	5	5	5
Toilet use	0	5*	5	5	5	10*
Bathing	5	5	0	5*	5	5
Dressing	10	10	5	10*	10	10
Bowels	10	10	10	10	10	10
Bladder	10	10	10	10	10	10
Mobility	10	15*	5	15*	5	15*
Stairs	5	10*	5	10*	5	10*
Transfer	10	10	10	10	10	10
Total	75	90	65	90	75	95

* Functional improvement after surgery.

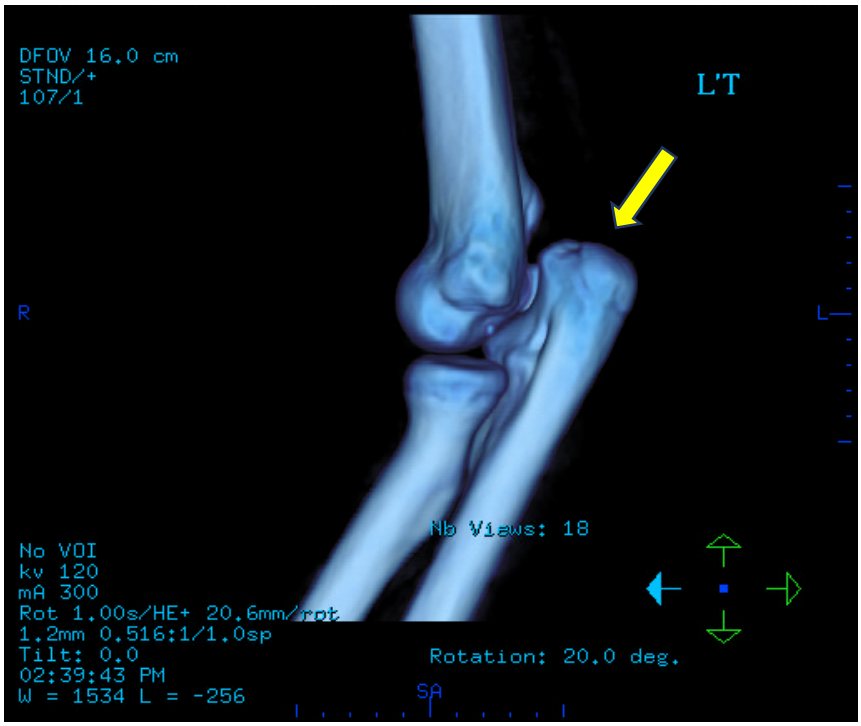

Figure 1. December 4, 2007 left elbow CT: left elbow with habitual dislocation

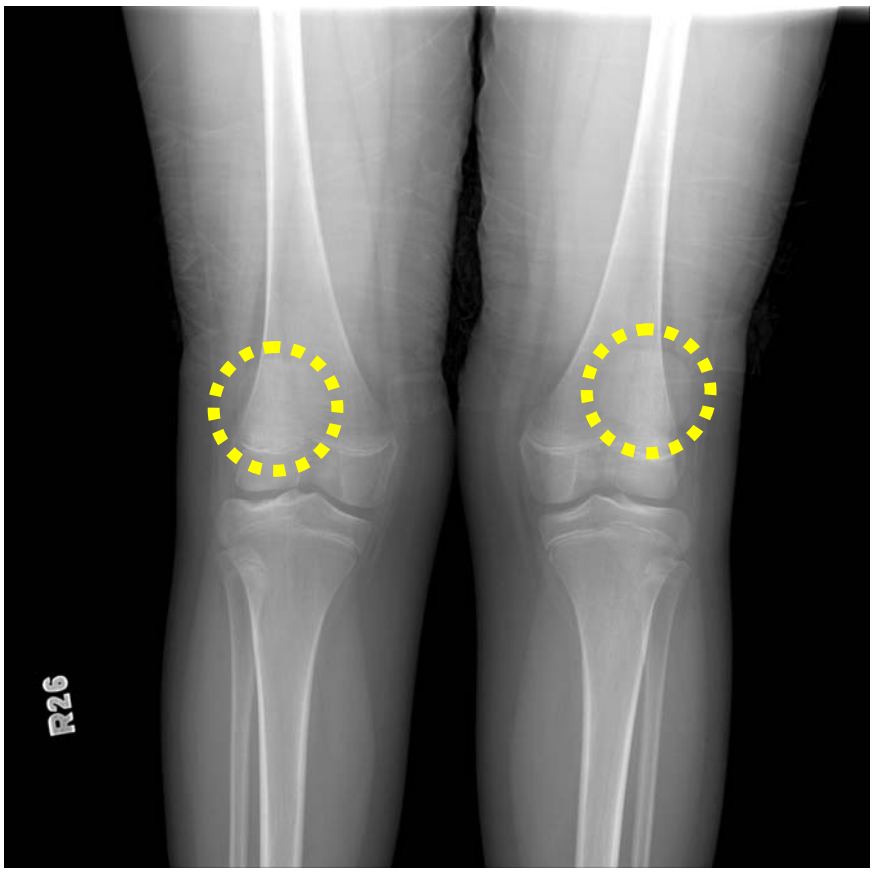

Figure 2. November 5. 2015 knee X-ray standing: bilateral patellar subluxation

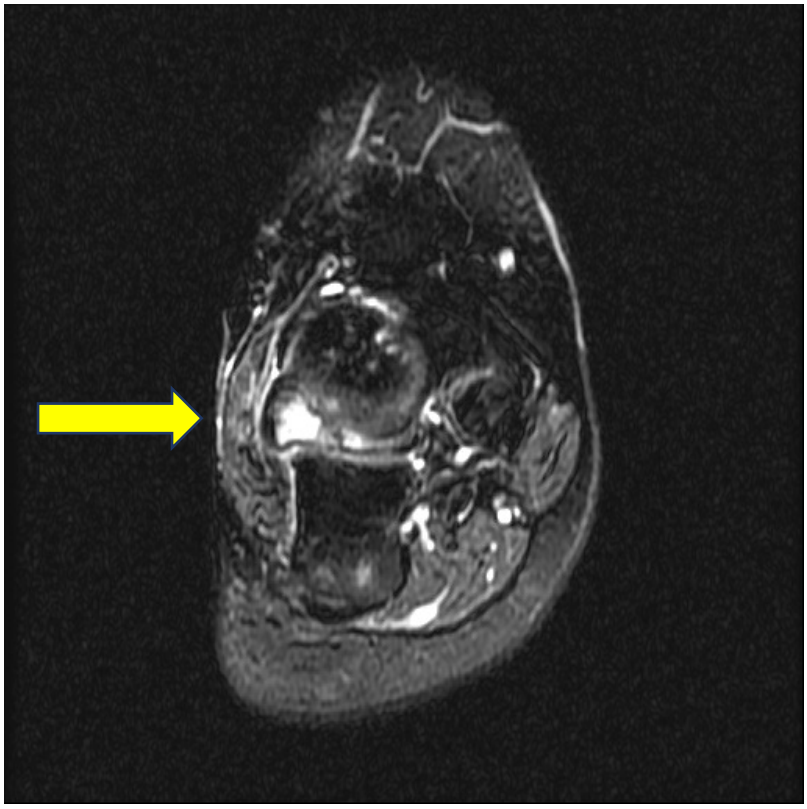

Figure 3. May 20, 2016 right ankle MRI: osteochondral fragment over the calcaneonavicular junction. Adjacent bone sclerosis and edema

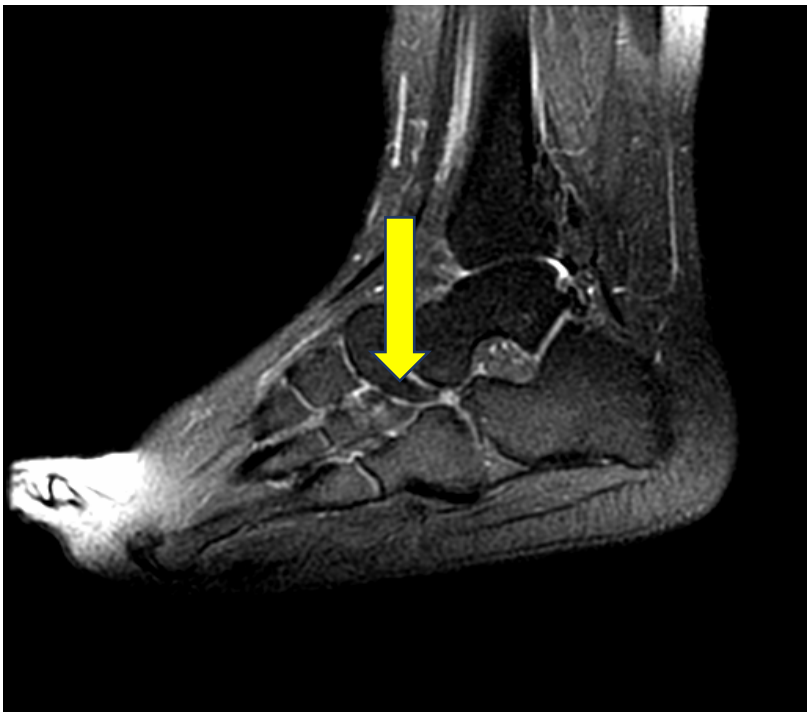

Figure 4. November 21, 2018 right ankle MRI: right lateral cuneiform avascular necrosis with calcaneonavicular osteophyte

DISCUSSION

RTS is a rare autosomal dominant genetic condition, and most patients with RTS were caused by de novo mutation. Familial RTS with siblings carrying the same gene mutation but with unaffected parents is rare. Only a few case reports are available.[19] In the current evidence, unaffected parents may carry genetic mutation by genetic mosaicism.[20,21] A low level of genetic mosaicism of RTS-related mutations can be observed in the peripheral blood (3.64%) and buccal mucosa (1.94%) of unaffected parents in a previous case report.[19]

Similar to Down syndrome[22] and Prader-Willi syndrome,[23]and having joint instability, hypotonia, and lax ligaments, patients with RTS had a higher risk of experiencing joint pain or deformity and may even require surgical intervention at a young age for pain relief and bone alignment correction, resulting in early degeneration and faster deterioration than normal group.

Elbow dislocation was rarely explored in previous studies. RTS medical guidelines have reported that the incidence of radial head dislocation was 2%;[18] however, the ulnar type of elbow dislocation has not been reported to date. In our report, the two siblings both had ulnar dislocation of the elbow, which should be also alerted if there were limitations of elbow ROM[18] or declining ADL function, including feeding or dressing.

In previous studies, ligamentous laxity was reported in 70%–80% of patients with RTS; however, the incidence rate of patellar dislocation was approximately 4%.[24-26] Delayed attainment of motor skills was reported by families of children with RTS with patellar dislocation and improved after receiving surgical stabilization of the patella.[24] Pain relief, increased knee ROM, and improved gait pattern were also noted after surgical treatment.[27] Nonsurgical treatment, including quadriceps strengthening exercise, orthosis, and medication, was also required for those children.[25] In our case, the two siblings had partial improvement in toilet use, mobility, and stairs after receiving the surgical intervention.

Ankle pain or deformity in patients with RTS was rarely reported in current evidence. In our case, the young sister, soft tissue laxity, and bony deformity distorted the alignment of the foot and ankle, which resulted in calcaneonavicular coalition and lateral cuneiform bone necrosis. The pain affected her gait pattern and ability to perform ADLs, which subsequently improved after the surgery.

As both of our cases had elbow and knee problems, it is reasonable to doubt that the prevalence of MKS problems seemed to be underestimated in previous studies. According Rubinstein-Taybi syndrome medical guidelines in 2003[18], patients with RTS should have their joints or spine periodically exanimated due to high risk of MSK abnormality. However, children with RTS hardly express their discomfort or pain from MSK problems due to mental retardation and limited verbal ability.[7] This makes the detection of MSK problems in children with RTS more difficult. Regular daily function monitoring by family or caregiver is important. In our cases, the mother carefully and sensitively monitored her daughters' daily living and observed joint abnormalities that facilitated timely treatment. The Barthel index scores of the sisters were restored since the symptoms improved after surgery. Therefore, we suggest that physician or therapist should score the Barthel index of the children with RTS if parents found their kids with RTS had a decline in activity level. A decrease in the Barthel index score warrants further evaluation of joint pain or deformation. Otherwise, a delay in the treatment or rehabilitation of MSK problems will result in poor prognosis.

According to the report on congenital diseases from the Ministry of Health and Welfare in Taiwan, a total of 45 RTS cases was diagnosed until March 2022.[29] In the future, researchers may gather enough cases for case control studies to analyze the advantages of early intervention by rehabilitation and surgery.

CONCLUSION

RTS is a multiple organ disease, and functional decline may result not only from the disease itself but also from MSK problems. MSK problems, which are relatively common in patients with RTS, may influence their daily physical activities and life quality, which may be a major cause of the functional decline. Learning from these two cases, regular surveillance, early detection, and aggressive treatment for pain or abnormality are necessary. Surgery for MSK or other organ defects, medicine

for systemic disease or infection, and rehabilitation programs, such as physiotherapy, occupational, speech, and psychosocial therapies, for their functional reconstruction, is the current treatment strategy for RTS.[28] Furthermore, prevention strategies, such as muscle strengthening of the limbs, work style change, correction of lower limb alignment and gait pattern, shoe modification, and lifelong follow-up and treatment, are needed to maintain or achieve better life quality for patients with RTS.

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REFERENCES

1. Rubinstein JH, Taybi H. Broad thumbs and toes and facial abnormalities: a possible mental retardation syndrome. Am J Dis Child 1963;105:588-608.
2. Hennekam R. Rubinstein-Taybi syndrome. Eur J Hum Genet 2006;14:981-5.
3. Roelfsema JH, White SJ, Ariyürek Y, et al. Genetic heterogeneity in Rubinstein-Taybi syndrome: mutations in both the CBP and EP300 genes cause disease. Am J Hum Genet 2005;76:572-80.
4. Hennekam RC, Stevens CA, Van de Kamp J. Etiology and recurrence risk in Rubinstein-Taybi syndrome. Am J Med Genet 1990;37:56-64.
5. Hennekam RC, Van Doorne JM. Oral aspects of Rubinstein-Taybi syndrome. Am J Med Genet 1990;37: 42-7.
6. Stevens CA, Hennekam RC, Blackburn BL. Growth in the Rubinstein-Taybi syndrome.Am J Med Genet 1990;37:51-5.
7. Hennekam RC, Baselier AC, Beyaert E, et al. Psychological and speech studies in Rubinstein-Taybi syndrome.Am J Ment Retard 1992.
8. Marzuillo P, Grandone A, Coppola R, et al. Novel cAMP binding protein-BP (CREBBP) mutation in a girl with Rubinstein-Taybi syndrome, GH deficiency, Arnold Chiari malformation and pituitary hypoplasia. BMC Med Genet 2013;14:1-6.
9. Cardona T, Al Kline D. Rubinstein-Taybi syndrome: a case report. The Foot & Ankle Journal 2008;1:3.
10. Stevens CA, Carey JC, Blackburn BL. Rubinstein-Taybi syndrome: A natural history study. Am J Med Genet 1990;37:30-7.
11. Zucconi M, Ferini-Strambi L, Erminio C, et al. Obstructive sleep apnea in the Rubinstein-Taybi syndrome. Respiration 1993;60:127-32.
12. Waite J, Moss J, Beck SR, et al. Repetitive behavior in Rubinstein-Taybi syndrome: Parallels with autism spectrum phenomenology. J Autism Dev Disord 2015; 45:1238-53.
13. Galéra C, Taupiac E, Fraisse S, et al. Socio-behavioral characteristics of children with Rubinstein-Taybi syndrome. J Autism Dev Disord 2009;39:1252-60.
14. Giacobbe A, Ajmone PF, Milani D, et al. Electroclinical phenotype in Rubinstein-Taybi syndrome. Brain Dev 2016;38:563-70.
15. van Genderen MM, Kinds GF, Riemslag FC, et al. Ocular features in Rubinstein-Taybi syndrome: investigation of 24 patients and review of the literature. Br J Ophthalmol 2000;84:1177-84.
16. COFFIN GS. Brachydactyly, peculiar facies and mental retardation. Am J Dis Child 1964;108:351-9.
17. Robson M, Brown L, Sharrard W. Cervical spondylolisthesis and other skeletal abnormalities in Rubinstein-Taybi syndrome. J Bone Joint Surg Br. 1980; 62:297-9.
18. Wiley S, Swayne S, Rubinstein JH, et al. Rubinstein-Taybi syndrome medical guidelines. Am J Med Genet A 2003;119:101-10.
19. Lin S, He Z, Huang L, et al. Case report: low-level maternal mosaicism of a novel CREBBP variant causes recurrent Rubinstein-Taybi syndrome in two siblings of a chinese family. Front Genet 2021;12:286.
20. Aarabi M, Sniezek O, Jiang H, et al. Importance of complete phenotyping in prenatal whole exome sequencing. Hum Genet 2018;137:175-81.
21. Smith TA, Yau SC, Bobrow M, et al. Identification and quantification of somatic mosaicism for a point mutation in a Duchenne muscular dystrophy family. J Med Genet 1999;36:313-5.

22. Rako K, Ranade S, Allen A. Orthopaedic Management in Down Syndrome: Current Concept Review. JPOSNA® 2021;3.
23. Shim JS, Lee SH, Seo SW, et al. The musculoskeletal manifestations of Prader-Willi syndrome. J Pediatr Orthop 2010;30:390-395.
24. Stevens CA. Patellar dislocation in Rubinstein-Taybi syndrome. Am J Med Genet 1997;72:188-90.
25. Lázaro JS, Herráez SS, Gállego LD, et al. Spontaneous patella dislocation in Rubinstein Taybi Syndrome. Knee 2007;14:68-70.
26. Ceynowa M, Mazurek T. Congenital patella dislocation in a child with Rubinstein-Taybi syndrome. J Pediatr Orthop B 2009;18:47-50.
27. Tyrakowski M, Pietrzak S, Przybysz W, et al. Dislocation of the patella in a patient with Rubinstein-Taybi syndrome-a case study.Ortop Traumatol Rehabil 2011;13:511-20.
28. Milani D, Manzoni FMP, Pezzani L, et al. Rubinstein-Taybi syndrome: clinical features, genetic basis, diagnosis, and management.Ital J Pediatr 2015;41:1-9.
29. 衛生福利部國民健康署罕見疾病通報個案統計表 https://www.hpa.gov.tw/Pages/List.aspx?nodeid=1558