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Rubinstein-Taybi syndrome with ganglioneuroblastoma: a case report and literature review

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Abstract

Background Rubinstein-Taybi syndrome (RSTS) is a rare genetic disorder characterized by severe global developmental delay (GDD) and distinctive facial grimacing. The loss of function of the *CREBBP* and *EP300* genes is recognized as a genetic etiology of RSTS. However, the association between *CREBBP* variants and an increased risk of tumors remains unknown, despite multiple reports of tumor comorbidities related to RSTS. The aim of this study is to elucidate the tumors associated with *CREBBP* variants in the context of RSTS by presenting a case of ganglioneuroblastoma (GNB) in a patient diagnosed with RSTS.

Case presentation We describe a 9-month-old male patient exhibiting distinctive facial features, enorchia, and GDD. Whole exome sequencing (WES) revealed a *de novo* pathogenic variant in NM_004380 (*CREBBP*): c.1068del (p.Gln356Hisfs*33). At one year of age, the patient experienced an unexplained fever lasting for two months, and the definitive diagnosis of GNB was established.

Conclusions We report a case of RSTS co-morbid with GNB and conduct phenotypic and genotypic analyses of 43 individuals with documented *CREBBP* variants and associated tumors in the literature. We observed that frameshift variations are common in malignancies among the individuals studied, while more microdeletions were noted in patients with benign tumors. Currently, there is insufficient evidence to support a correlation between the types of *CREBBP* variants and specific tumor types. Further research is required to clarify the role of *CREBBP* variants in tumorigenesis.

Keywords *CREBBP*, Rubinstein-Taybi syndrome, Ganglioneuroblastoma

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Introduction

Rubinstein-Taybi syndrome (RSTS [OMIM# 180849]) is a rare group of syndromes characterized by intellectual disability, slow growth, short stature, distinctive facial features (such as a grimacing smile), and broad, often angulated thumbs and halluces. The estimated birth prevalence of RSTS in the Netherlands is between 1 in 100,000 and 125,000 [1]. Loss-of-function variants in *CREBBP* (MIM # 600140) and *EP300* (MIM # 602077) have been associated with RSTS. Pathogenic variants in *CREBBP* affect approximately 50–60% of RSTS patients, while *EP300* pathogenic variants affect about 8–10% of individuals [2]. As our understanding of RSTS deepens, individuals of co-morbid tumors have been increasingly documented [3, 4]. Previous researchs have found RSTS co-morbidities tumors are observed in 5–30% of patients, such as neuroblastoma, rhabdomyosarcoma, medulloblastoma, and hematologic malignancies were reported [3–6]. However, reports of co-morbid tumors in RSTS individuals from China have not yet been documented. In this study, we present a case of a 1-year-old male with RSTS co-morbidities and GNB, and we compare this case with 43 other reported individuals with RSTS and co-morbid tumors. This study aims to provide insights for further establishing the association between RSTS patients and tumors.

Clinical information

A 9-month-old male child was admitted to our hospital due to global developmental delay. At 32 weeks of gestation, ultrasound revealed slow growth of the fetal head circumference. The pregnant woman did not receive further prenatal diagnostic counseling. The child was delivered via cesarean section at 38 weeks, with no asphyxia. Following birth, the child experienced difficulties with feeding and recurrent spitting up. The past medical history includes three episodes of pneumonia, bilateral cryptorchidism, and gastroesophageal reflux. His parents are healthy, non-consanguineous, and have previously given birth to two healthy females. Physical examination revealed a head circumference of 41.5 cm (< 3rd percentile), a length of 65 cm (< 3rd percentile), and a weight of 7.9 kg (< 10th percentile). Other physical characteristics included dense hair, hypertelorism, narrow palpebral fissures, downslanting eyes, a wide nasal bridge, anteriorly tilted nostrils, a high arched palate, a thin upper lip with upturned corners of the mouth, a small pointed jaw, broad thumbs, and hypotonia. The child could hold his head up, engage in social vocalization, and maintain eye contact, but could not roll over or sit without support. The Gesell Developmental Diagnosis Scale (GDDS; Chinese version) was utilized to assess various developmental areas of this child, including gross motor skills, fine motor skills, language, and social-emotional responses. The child's performance across all developmental areas yielded a developmental quotient (DQ) below 75. The developmental age of the infant was assessed at 3.2 months, with a Gesell developmental schedule DQ of 34. Based on the Chinese guidelines for diagnosing global developmental delay, this patient was diagnosed with GDD [7]. Magnetic resonance imaging (MRI) showed no abnormalities. Laboratory tests, including blood cell count, biochemical levels, thyroid hormone levels, serum electrolytes, blood glucose, lipid metabolism, blood ammonia, blood gas analysis, homocysteine, and urinary organic acid metabolism, were unremarkable, thereby excluding urea cycle disorders, certain fatty acid oxidation deficiencies, and aminoacidopathies. Given that the patient presents with multisystem malformation and a global developmental delay (GDD) phenotype, whole exome sequencing (WES) was chosen to elucidate the genetic etiology after consultation with medical geneticists and obtaining informed consent from the patient's parents. WES revealed a variant in the NM_004380 (*CREBBP*: c.1068del (GRCh38) (p. Gln356Hisfs*33). Sanger sequencing confirmed the absence of this variant in both parents (Fig. 1). According to the American College of Medical Genetics and Genomics (ACMG) Criteria and Guidelines for the Classification of Genetic Variants, this variant meets the criteria for a "Pathogenic variant " PVS1[Very strong evidence of pathogenicity; frameshift variant in a gene where loss of function (LOF)] + PM6(Assumed *de novo*, but without confirmation of paternity and maternity) + PM2_Supporting(Absent from controls in Exome Sequencing Project, 1000 Genomes or the Exome Aggregation Consortium (ExAC) [8].

This variant has not been documented in the gnomAD, HGMD (The Human Gene Mutation Database), or ClinVar databases (ClinVar (nih.gov)). A diagnosis of RSTS has been confirmed. We have developed a structured follow-up and early intervention program aimed at enhancing the child's quality of life.

At one year of age, the patient was brought to a community health center with a provisional diagnosis of bacterial diarrhea due to excessive sweating, intermittent diarrhea, poor weight gain, and recurring fever lasting two months. Laboratory analysis revealed white blood cell count: 12.3×10^9 (normal range: $5.6–15 \times 10^9$), neutrophil count: 11.8×10^9 (normal range: $3.2–10.7 \times 10^9$), and C-reactive protein (CRP): 44 mg/L (normal range: 0–10 mg/L). Lactate dehydrogenase (LDH): 421 U/L (normal range: 165–395 U/L). Stool samples microscopy and culture results: negative. Polymerase chain reaction (PCR) tests for Influenza A and B, rhinovirus, adenovirus, Epstein–Barr virus, and Mycoplasma were also conducted, all of which returned negative results. Blood biochemistry and erythrocyte sedimentation rate (ESR)

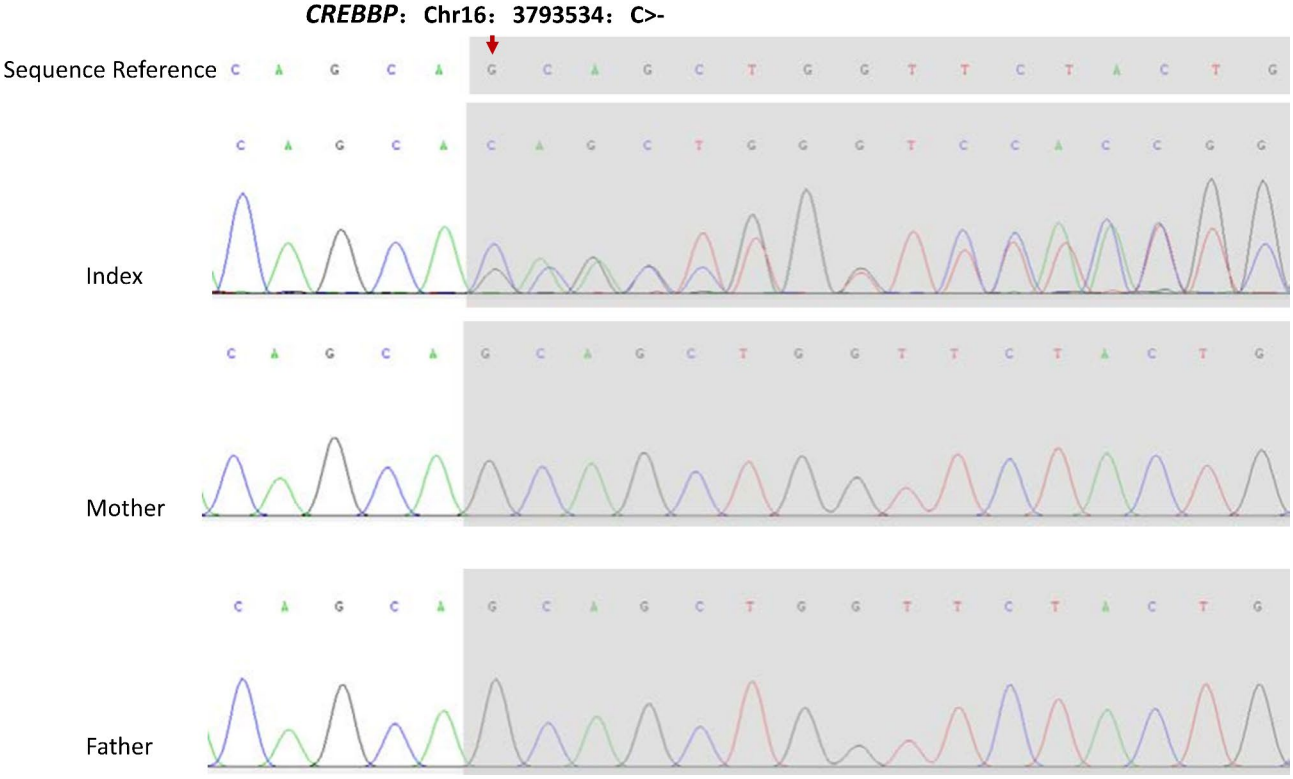

Fig. 1 Sanger sequencing chromatograms of *CREBBP* index's family

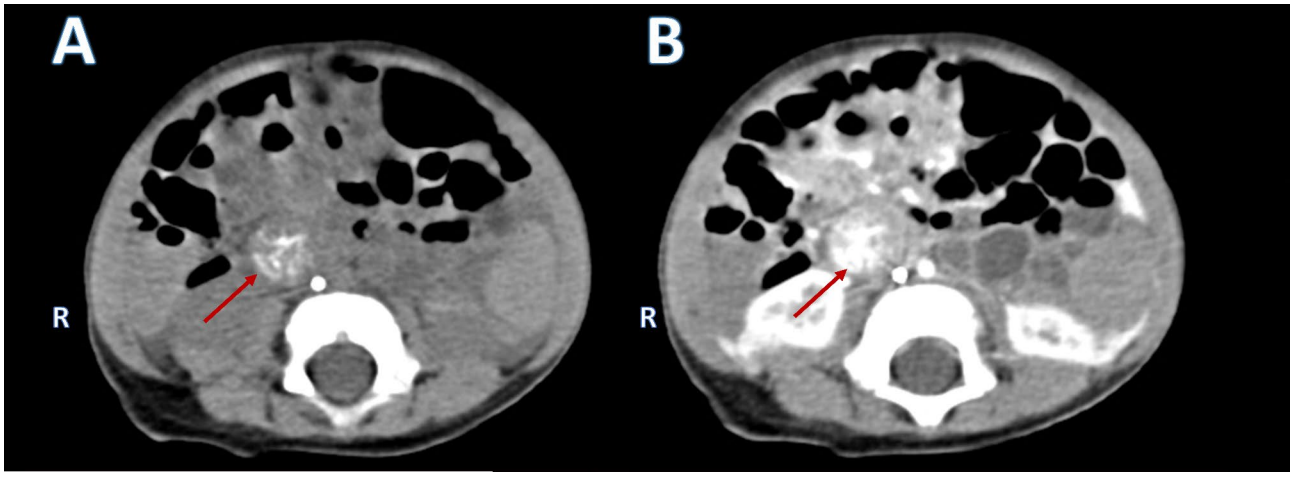

Fig. 2 Computed tomography the mass was located retroperitoneum. (**A**) plain CT scan (**B**) contrast-enhanced CT scan. (The red arrow indicates the position of the tumor)

were within normal limits, and echocardiography was unremarkable. The patient's fever did not improve after a prolonged treatment with Ceftriaxone Sodium at a dosage of 50 mg/kg. Following a two-week hospitalization for investigation, the child remained undiagnosed and was classified as having a fever of unknown origin (FUO). The patients were re-evaluated, which included a detailed medical history, a thorough physical examination, and laboratory screening that ruled out common infections, connective tissue disorders, and other factors typically associated with FUO. Tumors were considered as a potential cause, as they represent the third largest group of causes for unexplained fever in children. A computed tomography scan revealed a mass of mixed density with multiple punctate calcifications on the right side of the abdominal aorta, measuring approximately 3.2 × 2.1 cm. The mass exhibited significant inhomogeneous enhancement on the enhancement scan Fig. 2.

Laboratory tests revealed an elevated serum neuron-specific enolase (NSE) level of 35 ng/ml (reference range: 0-16.3 ng/ml). The patient was referred for surgical removal of the tumor. Immunohistochemical examination of the tumor pathology demonstrated positive expression of chromogranin A (CgA), synaptophysin (Syn), neural cell adhesion molecule (CD56), INI1, and a Ki-67 proliferative index of 5%. NeuN and glial fibrillary acidic protein (GFAP) showed negative expression. The pathological diagnosis confirmed the presence of ganglioneuroblastoma intermixed (GNBI), as verified by immunohistochemistry. Fluorescence in situ hybridization (FISH) did not demonstrate MYCN amplification in the patient's tumors. Based on a comprehensive evaluation of clinical, imaging, laboratory, and pathological results, GNB was diagnosed and identified as the definitive cause of fever in this patient. Follow-up abdominal CT examination conducted one year post-surgery showed no signs of tumor recurrence or metastasis. At the age of two, the child was able to walk independently and could pronounce simple words. The patient's last visit occurred at the age of 2 years and 5 months, revealing a length of 83 cm (< 25th percentile), weight of 11.5 kg (< 10th percentile), and head circumference of 45 cm (< 3rd percentile). His DQ was 41, indicating a moderate developmental anomaly. The child exhibited delays in language and adaptability, only able to speak several single words and unable to form sentences, with poor attention span.

Discussion and conclusions

Although RSTS does not typically affect life expectancy, MILLER R et al. [4] identified 36 individuals (5%) with tumors among 724 patients with RSTS. Similarly, BOOT MV et al. [3] conducted a retrospective analysis of 86 individuals diagnosed with RSTS in the Netherlands from 1986 to 2015, finding that 26 individuals (30%) were associated with tumors. Additionally, Naye Choi reported that 12% of Korean RSTS patients had tumors [9]. In contrast, our previous study on RSTS summarized 60 cases diagnosed with *CREBBP* pathogenic variants in China and found no reports of concurrent tumors [10]. *CREBBP* is involved in transcriptional regulation and epigenetic modification, and variations in this gene affect at least half of RSTS individuals. Consequently, studying RSTS individuals with *CREBBP* variants presents a unique opportunity to analyze the correlation between tumors and RSTS.

Including the present study, tumors have been reported in 44 individuals with RSTS due to *CREBBP* variations, all of whom have been confirmed through genetic testing. An overview of all reported tumors in RSTS is presented in Tables 1 and 2. Among these patients, 13 cases were identified as malignant tumors (Table 1). The median age for malignant tumors was 9 years (age range: neonatal period to 57 years), with 7 males and 6 females, and 54.8% of the patients were children. Among these RSTS patients, hematological malignancies (5/13) and neurological malignancies (3/13) predominated, which aligns with the types of malignant tumors observed in the general pediatric population. Leukemias represent approximately 30–40% of pediatric malignancies, lymphomas account for about 12%, and neuroblastoma is the most prevalent among childhood extracranial solid tumors [25, 26].

The mutation types of malignant tumors included frameshift variants (5/13), microdeletions (3/13), splice site mutations (3/13), a nonsense mutation (1/13), and a missense mutation (1/13).

Benign tumors were identified in 31 cases (Table 2).

The median age was 13 years (age range: 1 year period to 49 years) 7 male, 22 femal, and 53.4% were childrens and adolescents. Pilomatricoma was identified as the most common benign tumor (10/31), followed by hemangioma (7/31) and meningioma (5/31). The mutation types associated with benign tumors included microdeletions (13/31), frameshift mutations (6/31), duplications (5/31), nonsense mutations (3/31), missense mutations (3/31), and a splice site mutation (1/31). Notably, duplication variants have only been reported in RSTS patients with benign tumors. We observed that the same variant may correspond to different tumor types in RSTS individuals. For instance, deletions of exons 9 to 31 have been reported in individuals with meningioma, neuroma, and dermatofibroma. Additionally, duplications of exons 4 to 23 have been observed in individuals with meningioma, naevus, and fibroadenoma of the breast. The c.1011dupA variant has also been reported in individuals with meningioma and hemangioma. Unfortunately, due to the limited sample size, we were unable to identify a correlation between genotype and tumor type characteristics, which is consistent with the conclusions of previous studies [3].

CREBBP was first identified as a member of the KAT3 family of histone acetyltransferases (HAT), alongside its association with myeloid leukemia (AML) [26]. Although the mechanisms underlying oncogenesis in the absence of CREBBP protein remain unclear, it is proposed that CREBBP may function as a tumor suppressor, participating in various tumor-suppressor pathways [27]. Somatic mutations in *CREBBP* have been shown to affect H3K18 acetylation, which plays a significant role in the development of malignant tumors, including relapsed acute lymphoblastic leukemia and lymphoma [28–30]. GNB

Table 1 Genotypes and tumor types of 13 patients with *CREBBP* variants who have RSTS co-morbidities and malignant tumors

Malignant Neoplasm	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10	Patient 11	Patient 12	Patient 13
Tumor site	Neurological			Hematological					Gastroenterology	Hepatology	Respiratory	Breast	Genital
Tumour types	Medulloblastoma	Neuroblastoma	Ganglioneuroblastoma	lymphoblastic leukemia		Lymphoma			Colon carcinoma	Hepatoblastoma	Lung carcinoma	Breast adenocarcinoma	Germ cell tumor testis
Gender	M	M	M	M	F	M	F	F	M	F	F	F	M
Age at evaluation	9 Y	newborn	1 Y	10 Month	6 Y	57 Y	34 Y	28 Y	58 Y	4 Y	34 Y	31 Y	5 Month
Variants	c.1941 + 3 A > T	c.605dup	c.1068del	c.2469_2470del	c.4442 A > G	c.4837delG	c.2842 C > T	deletion exon 22 to exon 23	c.4561–2 A > G	c.4650_4654delAGAGA	Microdeletion	Microdeletion	c.1824-1G > A
Predicted protein effect	/	p.Gln203fs	p.Gln356Hisfs*33	p.Gln823Hisfs*8	p.Asp1481Gly	p.Val1613Cysfs*22	p.Gln948*	/	/	p.Glu1551Hisfs*2	/	/	/
References	[3]	[5]	Present study	[9]	[11]	[3]	[12]	[13]	[3]	[14]	[3]	[3]	[15]

M: male; F: female; Y: year

Table 2 Genotypes and tumor types of 31 patients with *CREBBP* variants who have RSTS co-morbidities and benign tumors

Benign tumors	**Patient 14**	**Patient 15**	**Patient 16**	**Patient 17**	**Patient 18**	**Patient 19**	**Patient 20**	**Patient 21**	**Patient 22**	**Patient 23**	**Patient 24**	**Patient 25**	**Patient 26**
Tumor site	Neurological								Genital	Skin			
Tumour types	Meningioma					Ganglioglioma	Cutaneous neuromas	Neuroma	HSIL	Dermatofibroma	Naevus		
Gender	F	F	F	F	F	F	F	F	F	F	F	F	M
Age at evaluation	29	36	37	41	46	3	3	29	49	32	6	25	9
Variants	microdeletion	deletion of exons 9 to 31	deletion of exons 9 to 31	c.1011dupA	duplication of exons 4 to 23	c.4134G > T	c.5838_5857dup20	deletion of exons 9 to 31	c.4340 C > T	deletion of exons 9 to 31	c.2199delG	duplication of exons 4 to 23	duplication of exons 4 to 23
Predicted protein effect	/	/	/	p.Gln338Thrfs*12	/	no AA changes	p.Pro1953Hisfs*30	/	p.Thr1447Ile	/	p.Gln733Hisfs*5	/	/
References	[3]	[3]	[3]	[3]	[3]	[16]	[17]	[3]	[3]	[3]	[18]	[3]	[3]
Benign tumors	**Patient 27**	**Patient 28**	**Patient 29**	**Patient 30**	**Patient 31**	**Patient 32**	**Patient 33**	**Patient 34**	**Patient 35**	**Patient 36**	**Patient 37**	**Patient 38**	**Patient 39**
Tumor site	Skin and appendage											Vascular	
Tumour types	Pilomatricoma										Hemangioma		
Gender	F	F	F	F	M	M	F	F	F	M	M	NI	NI
Age at evaluation	NI	49 Y	12 Y	7 Y	15 Y	2 Y	5 Y	6 Y	9 Y	14 Y	1 Y	NI	NI
Variants	c.6122-6125delCCAT	c.6127 C > T	c.5837dupC	c.4627G > T	c.4394 +–4 A > C	microdeletion	microdeletion	microdeletion	microdeletion	duplication of exons 12 ro 19	del(16)(p13.3p13.3)	c.778 C > T	microdeletion
Predicted protein effect	p.Ser2041Cysfs*33	p.Glin2043*	p.Pro1947Thrfs*19	p.Asp1543Tyr	/	/	/	/	/	/	/	p.Gln260*	/
References	[19]	[20]	[21]	[22]	[3]	[3]	[3]	[3]	[3]	[3]	[23]	[24]	[22]
Benign tumors	**Patient 40**	**Patient 41**	**Patient 42**	**Patient 43**	**Patient 44**								
Tumor site	Vascular				Breast								
Tumour types	Hemangioma				Fibroadenoma breast								

Table 2 (continued)

Gender	M	F	F	M	F	
Age at evaluation	NI	NI	41 Y	15 Y	38 Y	
Variants	Microdeletion	Microdeletion	c.1011dupA	c.406 C > T	duplication of exons 4 to 23	
Predicted protein effect	/	/	p.Gln338Thrfs*12	p.Gln136*	/	
References	[25]	[25]	[3]	[3]	[3]	

AA: amino acid; M: male; F: female; Y: year; HSIL: high-grade squamous intra-epithelial lesion of the cervix; NI: no information available

originates from embryonic neural crest cells and is differentiated from neuroblastoma and ganglioneuroma based on its degree of differentiation and biological behavior. Clinical manifestations of GNB typically include fever, vomiting, and excessive sweating, with a predilection for the retroperitoneum, adrenal gland, and mediastinum. In rare instances, the tumor secretes vasoactive intestinal peptide (VIP), which can lead to chronic diarrhea and persistent hypokalemia and this is our patient was initially diagnosed with the cause of bacterial diarrhoea [31]. Miller and Rubinstein [4] have suggested that tumors of neural crest origin exhibit an increased predisposition in patients with RSTS, with an approximate incidence of 5%. A review of the literature revealed four reported cases of neuroblastoma in patients with RSTS, of which only one case underwent genetic analysis (Fig. 3) [5]. The link between the GNB observed in our patient and a pathogenic CREBBP variant remains inconclusive; therefore, further investigation into the molecular mechanisms underlying this association is warranted. Additionally, CREBBP functions as a key regulator in Wnt signaling and participates in similar cellular replacement activities, such as hair growth, that occur in the human body. Wnt signal transduction is believed to be potentially related to pilomatricoma [32, 33], which may explain the higher incidence of pilomatricoma in patients with RSTS.

In general, benign tumors are more prevalent in patients with RSTS compared to malignant tumors. *CREBBP* frameshift variants were most frequently observed in RSTS patients with malignant tumors, whereas microdeletions were more commonly found in those with benign tumors. In resource-constrained settings, where molecular genetic testing is often unavailable, the diagnosis and management of RSTS patients may rely solely on clinical grounds, potentially leading to a biased estimation of tumor incidence in this population. The 2024 first international consensus statement on Rubinstein-Taybi syndrome indicates that there is currently insufficient evidence to suggest that RSTS elevates the risk of tumors; therefore, routine tumor screening in patients with RSTS is not recommended [34]. However, given the birth prevalence of RSTS and the global population, this risk cannot be entirely dismissed. At present, RSTS lacks precision medicine approaches, and the quality of life for patients can only be improved through multidisciplinary collaboration.

In conclusion, this study presents the first documented case of a patient with RSTS and GNB in China. The diagnosis was established through whole exome sequencing, thereby enhancing our understanding of the gene

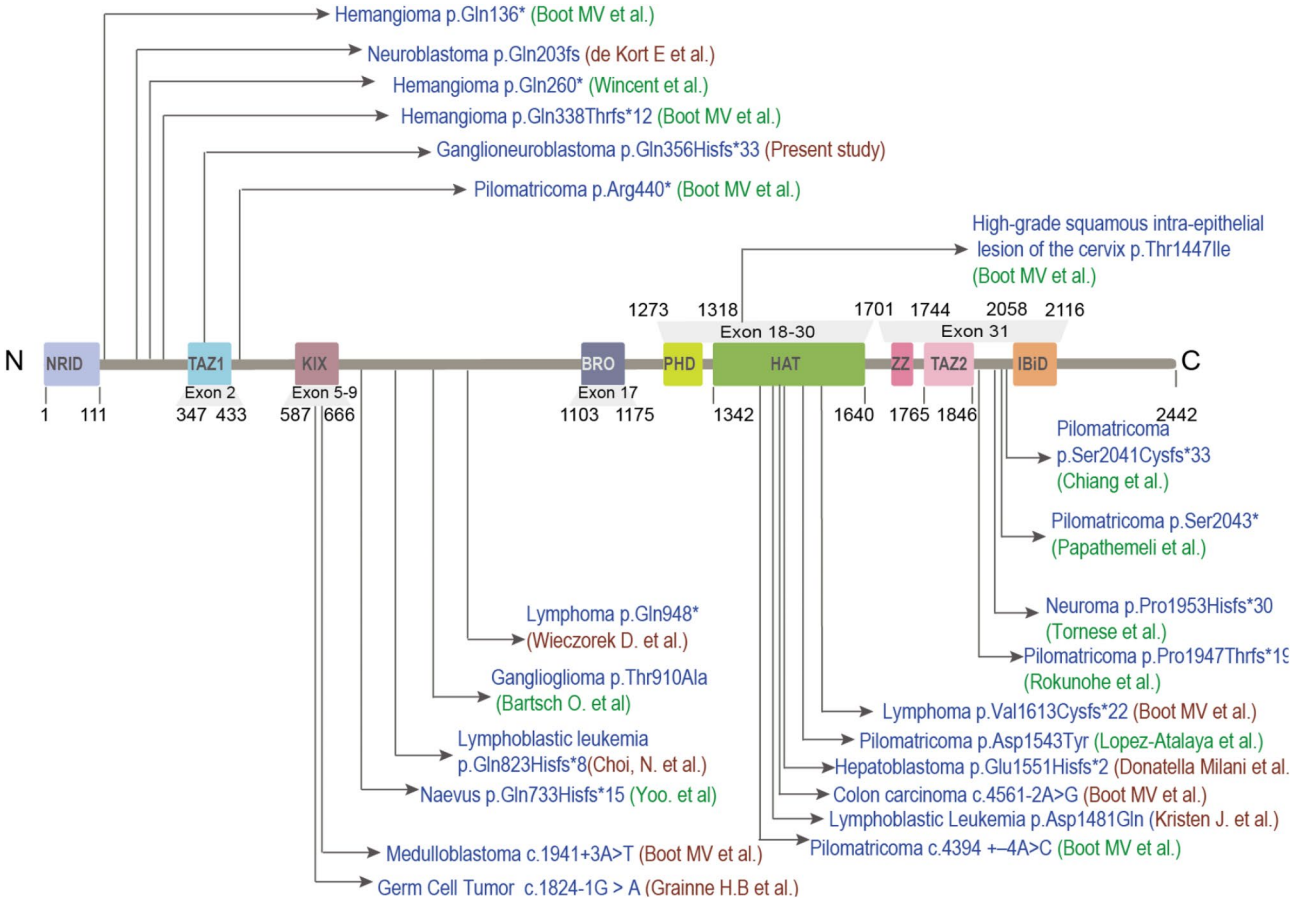

Fig. 3 The report documents 23 cases of variations co-occurring with tumors distributed along the CREEBP protein, except for microdeletion and duplication variants. Green markers indicating benign tumors and red markers indicating malignant tumors

mutations associated with this disease and broadening our knowledge of its phenotypic manifestations.

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Author contributions
Jiaji Zhou, Haiting Liu and Shuyao Zhu conceptualized and designed the study, drafted the initial manuscript, and critically reviewed and revised the manuscript. Dan Tang and Lan Zeng designed the carried out the initial analyses. Fu Xiong, Guanghuan Pi and Ai Chen critically reviewed and revised the manuscript. All authors reviewed the article critically for intellectual content and agreed to the published version of the manuscript.

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Data availability
The datasets generated and/or analysed during the current study are available in the ClinVar repository, VCV002446424.1.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of Sichuan Provincial Maternity and Child Health Care Hospital (Protocol 20230911-225 and date of 2023. 09. 11). Written informed consent was obtained from the parents of the patient.

Consent for publication
Written informed consent was obtained from patient's parents for publication of the details of their medical case and any accompanying images.

Competing interests
The authors declare no competing interests.

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