Received: 22 December 2021 | Revised: 10 May 2022 | Accepted: 8 June 2022

DOI: 10.1002/mgg3.2009

Molecular Genetics & Genomic Medicine Open Access WILEY

CLINICAL REPORT

Ten-year follow-up of Nicolaides–Baraitser syndrome with a de novo mutation and analysis of 58 gene loci of SMARCA2-associated NCBRS

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Funding information
National Natural Science Foundation of China, Grant/Award Number: 81904251; Tianjin Health and Family Planning Industry High-level Talent Selection and Training Project, Grant/Award Number: Jinmen Elite Program; Traditional Chinese Medicine Inheritance and Innovation Millions of Talents Project (Qihuang Project) Qihuang Scholars, Grant/Award Number: 2018

Abstract

As a clinical subtype of SWI/SNF-related intellectual disability syndromes, Nicolaides–Baraitser syndrome (NCBRS, OMIM601358) has a unique genotype–phenotype. Due to the scarcity of the number of cases reported and the limitations of diagnosis methods, so far only more than 80 cases have been reported worldwide. In this article, a new patient with a de novo mutation was followed up for 10 years; it includes the epilepsy treatment process, the characteristics of NBCRS with seizures, typical faces, sparse hair, prominent interphalangeal joints, and intellectual disability, and we also summarized the genotype–phenotype of the 80 reported cases for comparison. Due to insufficient studies and lack of attention paid to the syndrome, it is believed that the actual number of cases should be far more than the reported number. The syndrome is phased and progressive. The genotype–phenotype correlation of the disease is related to the location of the gene locus, especially closely related to the SNF2 ATPase domain.

Conclusions: The understanding of NCBRS is lagging, we need to strengthen the screening process of the phenotypic disease with intellectual disability, and perfecting multiple types of diagnostic techniques will help the discovery of the disease; its clinical features are staged and are slowly progressive, and long-term prognosis must be taken precautious with long-term follow-up required.

KEYWORDS

evolving features, genotype, Nicolaides–Baraitser syndrome, SMARCA2

Xilian Zhang and Hanjiang Chen are co-first authors. Rong Ma and Ping Rong are co-corresponding authors.

1 | INTRODUCTION

Nicolaides–Baraitser syndrome (NCBRS, OMIM601358) is a rare congenital multiple malformations syndrome, first reported by Nicolaides and Baraitser (1993) and well delineated in 2009 (Sousa et al., 2009). The syndrome has unique clinical phenotypes and genotypes, manifested by different degrees of developmental delays, especially in speech delay; it is also accompanied by epileptic seizures, distinctive facial morphology, and distal limb anomalies (Van Houdt et al., 2012). This syndrome is mainly caused by a mutation in the SMARCA2 gene (SWI/SNF-Related Matrix-Associated Actin-Dependent Regulator of Chromatin Subfamily A Member 2, OMIM 600014) located in chromosome 9. So far, nearly 80 cases have been reported worldwide, while only three cases have been reported in China. This case we followed for 10 years belongs to the fourth case that had been reported in China. This patient's condition manifested with classic features in stages and the mutation gene was located at Exon24, c.3313C>T, p.(Arg1105Cys), belonging to de novo mutation. Meanwhile, we searched nearly 20 years of articles from 2000 to 2021, collected 88 patients (58 de novo mutations), and summarized their genetic characteristics below (Table 1).

2 | CASE PRESENTATION

A male patient, 1 year and 6 months old, was admitted to the hospital in October 2011 due to intermittent convulsions for more than 2 months. The onset of the symptoms was at the age of 1 year and 3 months, manifested as binocular vision and limb convulsion during sleep, which resolved spontaneously after 1–2 min. Symptoms occurred again at the age of 1 year and 5 months, and the number of attacks increased to every 2–3 days, 2–3 times per day; the pattern also changed, manifested by paroxysmal nodding with shaking upper limbs, occasionally with falling objects in the hands, screaming before convulsion. All seizures occurred during sleep and lasted anywhere from a few seconds to about 1 min. Brain MRI showed that the bilateral parietal area had a patchy hyperintensity shadow. Twenty-four-hour EEG showed paroxysmal, diffused, and high-potential sharp spikes and multiple spikes in sleep. After 24 EEG results were released, epilepsy was diagnosed. He began to take "Levetiracetam 0.1875g bid and Vitamins B1 and B6" for 2 weeks. However, he still had intermittent seizures about once every 7–10 days, with 2–8 convulsions each time. After increasing the dose of "levetiracetam to 0.1875g, 0.25g", the seizure did not relieve, and the seizure pattern was the same as before. After 1 month, 2 ml bid of valproic acid was added and incorporated with traditional Chinese herbal medicine treatment, and the number of seizures began to gradually decrease to 1–2 times in a month, seizure pattern also changed, manifested as frequent blinking, followed by double gazing, loss of consciousness, and twitching of the limbs, which relieved spontaneously after several seconds. With his weight gain, the dosage of valproic acid was gradually increased to 3.5 ml bid, and no seizure occurred at age of 3. Levetiracetam was gradually reduced, valproic acid was maintained for 3 years, and then eventually withdrawn. So far, no recurrence of seizure had happened. Re-examination of 24-h EEG and brain MRI at age of 4 showed normal results.

His medical history showed that he was rather a healthy baby, G1P1 (Gravida 1, para 1), parents were healthy, nonconsanguineous married, the mother gestated at 29 years old and had a healthy pregnancy, and denied any family genetic history. She had a full-term cesarean section; the baby was born 3000 g in weight and 49 cm in length. He was born as a lovely baby, with beautiful big eyes, thick eyebrows, and prominent eyelashes, while his hair was sparse, his parents did not think anything was out of the ordinary. But also had feeding difficulties, vomiting, slow weight gain, and restless sleep as a baby. At 1 year old, frequent convulsions began and continued for 3–4 years, her parents started to notice his peculiar facial morphology and limb anomalies (Figure 1). At 2 years old, he still could not speak, also needed support when climbing up and downstairs because he could not stand steadily, expressed a horrible feeling when he looked at his photos, had a poor chewing ability, and had an inability to defecate. At 3 years old, he could walk independently but vacillated side to side, he was easy to get excited and irritated, and his chewing function had improved. At 4 years old, he was able to go up and down stairs independently without any assistance. Although he was still unable to express himself, he had an increased desire to do so. With the help of the rehabilitation training, his understanding capacity increased, but his expression and concentration still had not improved. At the age of 5–6 years old, his facial skin began to look rough, and he had ptosis, increased skin wrinkles, broadened palpebral fissures, and drooping lower lips. By the age of 7–10 years old, he appeared to have hirsutism, broad neck, scoliosis, and widely spaced nipples. Followed up till now, the child's height, weight, and general motor abilities were closed to normal; his secondary sexual characteristics have begun to develop; and the most notable features are mental retardation, language delay, and social impairment. Although still lagging in speech, he could understand the instructions of relatives and would communicate with "haha" or laughed when he was excited or wanted to communicate. His parents once let him try to attend a special school, but he did not cooperate well

TABLE 1 The table of 58 de novo sites related to NCBRS

Number	Mutation stype	Amino-acid change	Gene symbol	Variation	Reference DOI	Reference version	Transcription
1	De novo 6-bp deletion	p.(Asp1153_Leu1154del)	SMARCA2	De novo	10.1007/s00439-015-1535-8	GRCh37/hg19	NM_003070.3
2	In-frame deletion	20-26 deletion	SMARCA2	De novo	10.1159/000337323	hg18	NM_003070.3 and NM_139045.2
3	Missense +frame shift	p.Pro624Hisfs 44	SMARCA2	De novo	10.1093/hmg/ddt366	GRCh37/hg19	NM_003070.3
4	Missense +frame shift	p.Gln1196Profs 14	SMARCA2	De novo	10.1093/hmg/ddt366	GRCh37/hg19	NM_003070.3
5	Mutation in potential splice donor (GT) of intron 24	intron	SMARCA2	Mutation is absent in one available parent	10.1038/ng.1105	hg19	NM_003070.3
6	Nonsense mutation	p.Gln1144	SMARCA2	NA	10.1093/hmg/ddt366	GRCh37/hg19	NM_003070.3
7	Missense mutation	p.Ala1188Glu	SMARCA2	De novo	10.1159/000337323	hg18	NM_003070.3 and NM_139045.2
8	Missense mutation	p.Gly1132Asp	SMARCA2	De novo	10.1159/000337323	hg18	NM_003070.3 and NM_139045.2
9	Missense mutation	p.Arg1213Trp	SMARCA2	NA	10.1038/ng.1105	hg19	NM_003070.3
10	Missense mutation	p.Gly1202Cys	SMARCA2	De novo	10.1038/ng.1105	hg19	NM_003070.3
11	Missense mutation	p.Arg1159Gln	SMARCA2	De novo	10.1038/ng.1105	hg19	NM_003070.3
12	Missense mutation	p.Asp1158Val	SMARCA2	De novo	10.1038/ng.1105	hg19	NM_003070.3
13	Missense mutation	p.Arg1159Gly	SMARCA2	De novo	10.1038/ng.1105	hg19	NM_003070.3
14	Missense mutation	p.Gly881Val	SMARCA2	De novo	10.1038/ng.1105	hg19	NM_003070.3
15	Missense mutation	p.Arg1162His	SMARCA2	De novo	10.1038/ng.1105	hg19	NM_003070.3
16	Missense mutation	p.Arg1159Leu	SMARCA2	De novo	10.1038/ng.1105	hg19	NM_003070.3
17	Missense mutation	p.Pro883Leu	SMARCA2	De novo	10.1038/ng.1105	hg19	NM_003070.3
18	Missense mutation	p.Ala1201Val	SMARCA2	De novo	10.1038/ng.1105	hg19	NM_003070.3
19	Missense mutation	p.His939Tyr	SMARCA2	De novo	10.1038/ng.1105	hg19	NM_003070.3
20	Missense mutation	p.Thr756Ile	SMARCA2	NA	10.1038/ng.1105	hg19	NM_003070.3
21	Missense mutation	p.Arg1105Cys	SMARCA2	De novo	10.1038/ng.1105	hg19	NM_003070.3
22	Missense mutation	p.Glu852Asp	SMARCA2	Mutation is absent in one available parent	10.1038/ng.1105	hg19	NM_003070.3
23	Missense mutation	p.Gly881Arg	SMARCA2	NA	10.1038/ng.1105	hg19	NM_003070.3
24	Missense mutation	p.Leu1135Pro	SMARCA2	De novo	10.1038/ng.1105	hg19	NM_003070.3

(Continues)

TABLE 1 (Continued)

Number	Mutation stype	Amino-acid change	Gene symbol	Variation	Reference DOI	Reference version	Transcription
25	Missense mutation	p.Ala1188Pro	SMARCA2	Mutation is absent in one available parent	10.1038/ng.1105	hg19	NM_003070.3
26	Missense mutation	p.Arg1105Pro	SMARCA2	NA	10.1038/ng.1105	hg19	NM_003070.3
27	Missense mutation	p.Gly752Ala	SMARCA2	NA	10.1038/ng.1105	hg19	NM_003070.3
28	Missense mutation	p.Glu852Lys	SMARCA2	Mutation is absent in one available parent	10.1038/ng.1105	hg19	NM_003070.3
29	Missense mutation	p.His854Leu	SMARCA2	NA	10.1038/ng.1105	hg19	NM_003070.3
30	Missense mutation	p.Leu946Ser	SMARCA2	NA	10.1038/ng.1105	hg19	NM_003070.3
31	Missense mutation	p.Asp1205Gly	SMARCA2	NA	10.1038/ng.1105	hg19	NM_003070.3
32	Missense mutation	p.His854Arg	SMARCA2	De novo	10.1038/ng.1105	hg19	NM_003070.3
33	Missense mutation	p.Lys755Arg	SMARCA2	De novo	10.1038/ng.1105	hg19	NM_003070.3
34	Missense mutation	p.Ser1146Arg	SMARCA2	NA	10.1038/ng.1105	hg19	NM_003070.3
35	Missense mutation	p.Leu946Phe	SMARCA2	NA	10.1038/ng.1105	hg19	NM_003070.3
36	Missense mutation	p.Asp851His	SMARCA2	De novo	10.1038/ng.1105	hg19	NM_003070.3
37	Missense mutation	p.Arg855Gly	SMARCA2	De novo	10.1038/ng.1105	hg19	NM_003070.3
38	Missense mutation	p.Glu852Gln	SMARCA2	De novo	10.1002/humu.22394	NA	NM 003070.3
39	Missense mutation	p.Gly1098Asp	SMARCA2	De novo	10.1002/humu.22394	hg19	NM 003070.3
40	Missense mutation	p.Arg1105His	SMARCA2	De novo	10.1002/humu.22394	NA	NM 003070.3
41	Missense mutation	p.Arg366Cys	SMARCA2	De novo	10.1093/hmg/ddt366	GRCh37/hg19	NM_003070.3
42	Missense mutation	p.Thr880Ile	SMARCA2	De novo	10.1093/hmg/ddt366	GRCh37/hg19	NM_003070.3
43	Missense mutation	p.Arg855Gln	SMARCA2	De novo	10.1093/hmg/ddt366	GRCh37/hg19	NM_003070.3
44	Missense mutation	p.(Gly881Glu)	SMARCA2	De novo	10.1007/s00439-015-1535-8	GRCh37/hg19	NM_003070.3
45	Missense mutation	p.(Ala1219Pro)	SMARCA2	De novo	10.1007/s00439-015-1535-8	GRCh37/hg19	NM_003070.3
46	Missense mutation	p.Gln1074Glu	SMARCA2	De novo	10.1016/j.braindev.2014.08.009	GRCh37/hg19	NM_003070.3
47	Missense mutation	p.Gly1129Arg	SMARCA2	De novo	10.1016/j.braindev.2014.08.009	GRCh37/hg19	NM_003070.3
48	Missense mutation	p.Thr1126Arg	SMARCA2	De novo	10.1016/j.braindev.2014.08.009	GRCh37/hg19	NM_003070.3
49	Missense mutation	p.Ala1156Pro	SMARCA2	NA	10.1016/j.braindev.2014.08.009	GRCh37/hg19	NM_003070.3
50	Missense mutation	p.Val1198Gly	SMARCA2	De novo	10.1016/j.braindev.2014.08.009	GRCh37/hg19	NM_003070.3
51	Missense mutation	p.Gln1165Lys	SMARCA2	De novo	10.1002/ccr3.425	NA	
52	Missense mutation	p.Gln1241Glu	SMARCA2	De novo	10.1002/ajmg.a.37935	hg19	NM_0030703
53	Missense mutation	p.Asn787Lys	SMARCA2	De novo	10.1002/ajmg.a.37672	hg19	NM_003070.4

TABLE 1 (Continued)

Number	Mutation stype	Amino-acid change	Gene symbol	Variation	Reference DOI	Reference version	Transcription
54	Missense mutation	p.Leu1070Gln	SMARCA2	NA	10.1186/s12920-019-0555-y	hg19	NA
55	Missense mutation	p.Thr829Ile	SMARCA2	De novo	10.1186/s12920-019-0555-y	hg19	NA
56	Missense mutation	p.Ser1208Cys	SMARCA2	De novo	10.1186/s12920-019-0555-y	hg19	NA
57	Missense mutation	p.Ser783Trp	SMARCA2	De novo	10.1186/s12920-019-0555-y	hg19	NA
58	Missense mutation	p.Gly1130Val	SMARCA2	De novo	10.1097/MCD.0000000000000336	hg19	NM_003070.5

Note: Consistent with Figure 2, we list the detailed information of the 58 de novo mutation sites related to NCBRS, contains mutation stereotypes, amino acid change, gene symbol, variation, reference DOI, version, transcription.

with the teachers' instructions, often left his seat without permission, laughed involuntarily, and could not get along well with his classmates, so he spent most of his time with his parents. Meanwhile, he was timid, shy, restless, and interested in music and video games. Several Intelligence Quotient (IQ) tests floating between 45 and 55, indicated mild to moderate intellectual disability. Fortunately, it is good news that before this manuscript submission, his mother informed us that she had given birth to a healthy baby this year (Figures 2 and 3).

According to the above clinical features, our team considered it should belong to a certain clinical syndrome. So, genetic screening was performed for him at the age of 7; the result (KingMed Diagnostic, NP18D932) showed that a heterozygous SMARCA2 mutation located at Exon24, c.3313C>T, p. (Arg1105Cys) (Figure S1). His parent's genetic analysis did not detect pathogenic genes, so it was considered a de novo mutation. Combined with the child's clinical features, mutation gene loci, the diagnosis of Nicolaides–Baraitser syndrome was established. In order to have systematic research for NCBRS, we searched almost all of the available articles from 2000 to 2021. Enriched indexes contained exons, amino acids, protein locations, mutation stereotypes, transcript, and reference gene numbers. Most of the articles were case reports, and only a few were research articles. We searched 88 mutation locations in total and excluded 29 repeated sites and a variant site that belonged to Coffin–Siris syndrome (CSS, OMIM135900), we found 58 de novo sites related to NCBRS. Among them, 52 sites are missense mutation, the other sites are in-frame deletion (two cases), frameshift mutation (two cases), intron mutation (one case), and nonsense mutation (one case), respectively. We also studied the distribution of gene loci; all sites (Figure S2) are distributed at exon 25 (27 cases), exon 18 (23 cases), exon 24 (12 cases), exon 15 (8 cases), exon 19 (4 cases), exon 26 (2 cases), exon 23 (2 cases), and the exons 4, 8, 12, 14, 16, and 17 (1 case, respectively). Most of the sites are located exons15–25.

3 | DISCUSSION AND CONCLUSIONS

Nicolaides–Baraitser syndrome (NCBRS, OMIM601358) is a rare (prevalence 1/1,000,000) congenital multiple malformation syndromes (Kosho et al., 2013). It is characterized by a unique phenotype–genotype. Its gene mutation in the SMACRA2 gene on chromosome 9, is located in chromosome 9.p24.3 region, contained 34 exons, and encoded a protein composed of 1590 amino acids (Sousa et al., 2015). With the rapid development of second-generation gene analysis technology, the case numbers

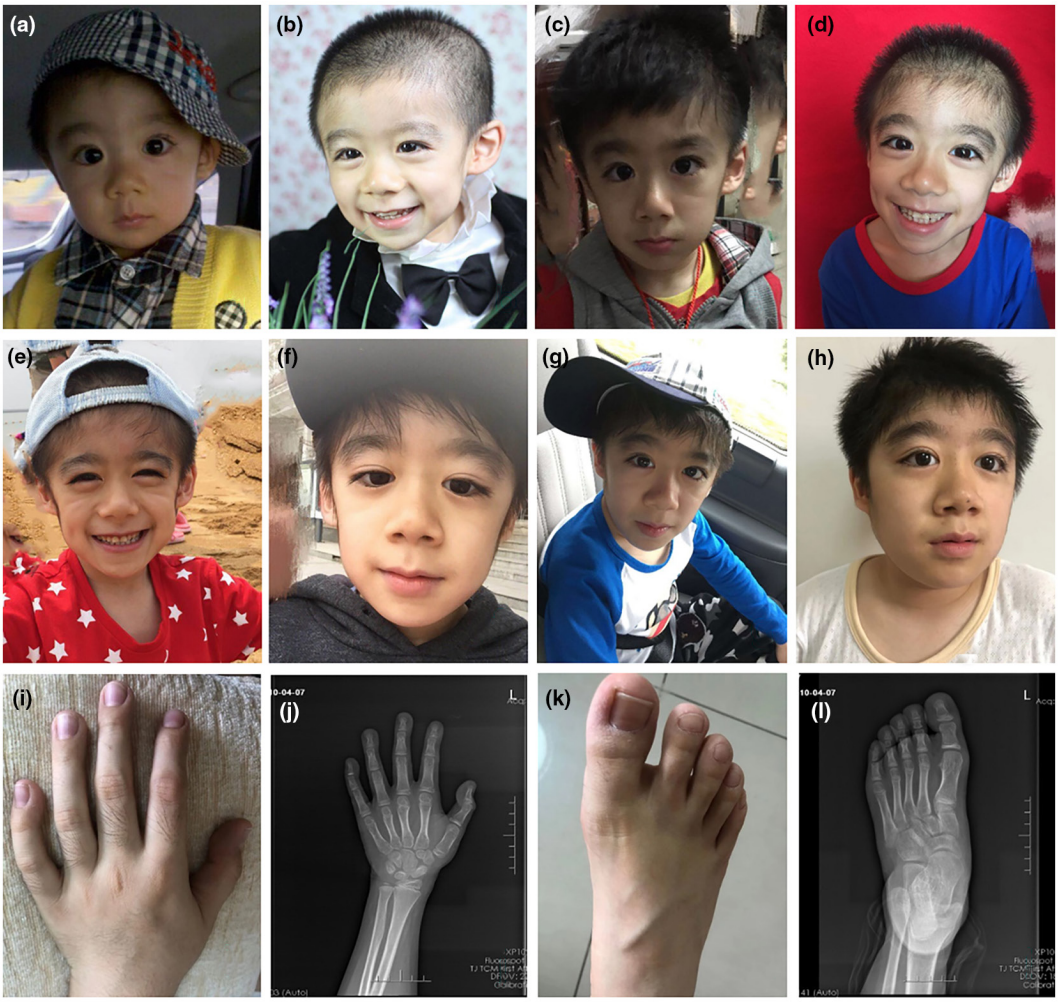

FIGURE 1 The changes in facial morphology and distal limbs in 10 years. (a) 1 year, (b) 2 years, (c) 4 years, (d) 5 years, (e) 6 years, (f) 7 years, (g) 8 years, (h) 10 years. These photos showed this child with a narrow forehead, low anterior hairline, wide nasal bridge, broad nasal base, broad and long philtrum, large mouth and thin upper vermillion at different periods, and facial skin began to be rough, ptosis, increased skin wrinkling with aged. Foot and hand images (i–l) showed that prominent interphalangeal joints and distal phalangeal, foot sandal gap, and nail anomalies.

gradually increased. Also, there has been a clear and systematic understanding of the structures, functions, families, and pathogenesis of this syndrome in recent years.

3.1 | The evolving features of NCBRS in stages

Distinctive facial morphology, seizures, distal limb anomalies, and intellectual disability are the notable features of NCBRS, and they are also key features to differentiate it from other syndromes. Distinctive facial morphology is usually manifested as prominent eyelashes, ptosis, wide nasal bridge, broad and long philtrum, largemouth, coarse facial features, and so on. Most of these features were atypical at a young age but gradually became more pronounced with age. Facial skin gradually became rough and began to wrinkle and sag, especially obvious when smiling. Because the subcutaneous fats were very thin, the children all showed loose and sagging skin, especially on expressed areas, such as the faces and fingertips. Most children with NCBRS have sparse hair, especially at birth, and decreases with age; they also have low hairlines, thick eyebrows, and wider eyebrow spacing, partly with hirsutism, more in the neck and back. Distal limb anomalies were another important feature of NCBRS. Mainly manifested as prominent interphalangeal joints, prominent distal phalanges, sandal gap, and nail anomalies (small nails, generally limited to the fifth finger/toe). Seizures accounted for about 50% of NCBRS; the initial onset age was about 7 months to 7 years old. There were various types of seizures such as absence, tonic-clonic, atonic, spasm, partial status epilepticus, and so on. Most EEGs could detect abnormal discharges. The vast majority of brain MRIs are normal. Related studies suggested that seizures were resistant to multiple antiepileptic drugs, some of which may

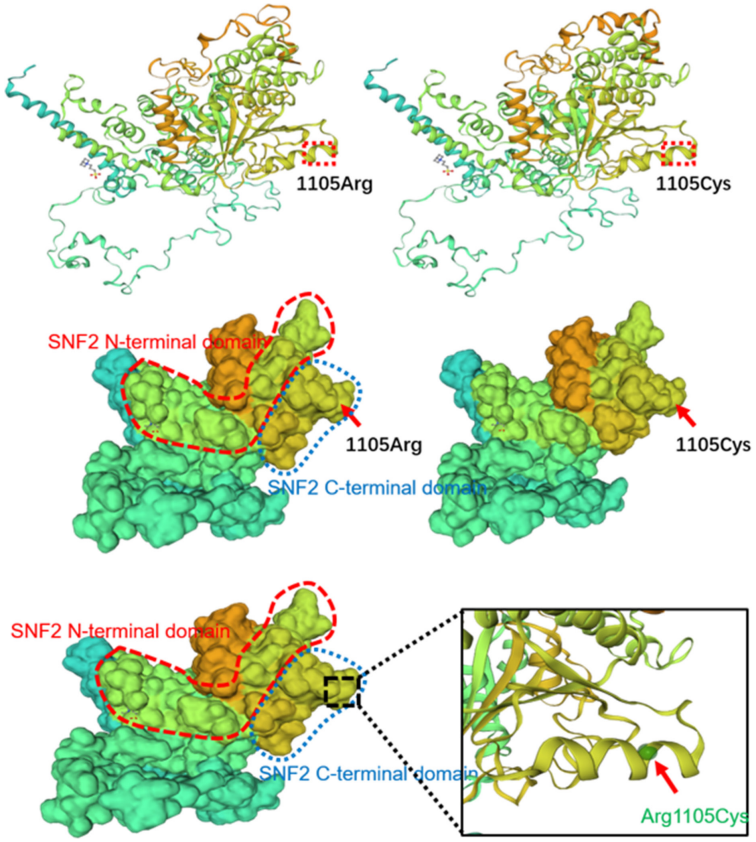

FIGURE 2 The three-dimensional structure diagram of NM_003070.4:c.3313C>T. (KingMed Diagnostic, NP18D932) showed that the mutation was located at Exon24, c.3313C>T, p. (Arg1105Cys). His parents' genetic analysis did not detect pathogenic genes. The 3D protein structure was predicted by the Swiss-Prot web tool to check the effect of amino acid change in position 1105 resultant from the variation of c.3314G>A. The 15–25 exons region is the SNF2 ATPase domain, it contains the N-terminal domain and C-terminal domain. The 508–1305 amino acids (structure in the figure) of SMARCA2 have 58.25% similarity with SNF2-family ATP-dependent chromatin remodeling factor-like protein; the 1105th amino acid is located in the α-helix structure of the helicase C-terminal domain. The start and end amino acids of the α-helix are 1102–1113. No matter whether the 1105th amino acid is Arg or Cys, it does not change the shape of the helix structure.

effective for the valproic acid, but without concrete data supporting it. Mental development retardation and abnormal behaviors were the main features of NCBRS at a later stage of this disease. Almost all patients had varying degrees of intellectual disability; serious intellectual disability accounted for the majority of the cases. Among them, speech delay was its distinctive feature, almost 80% of reported cases had a severe speech delay, which was closely related to the deficit of development of the language center in the cortical. However, it was shown nearly no effect on general motor development, such as the capacity of sitting, standing, and walking. Behavioral disorders such as hyperactivity, aggressiveness, psychosis, autism, attention deficit hyperactivity disorder, social disorder, narrow interest range, and enuresis had been reported. One patient been followed up for over 20 years also highlighted the evolving features, including feeding problem, coarse facial features, absent speech, moderate or severe spectrum intellectual disability, and behavior problems. But it also pointed out that it was difficult to be made with certainty in the correlations of genotype–phenotype and need to take a long time to fully manifest and assess these features in different ages (Ejaz et al., 2016).

3.2 | The location of genetic mutation directly affected the phenotype–genotype of NCBRS

With the widespread use of trio-based whole-exome sequencing (WES) screening, we had a deeper understanding of its mechanism. We found that the phenotype is closely related to variant stereotypes, exon location, epigenetics, and DNA methylation (Wieczorek et al., 2013). Most of the sites were located in the 15–25 exons; this region was the SNF2 ATPase domain, which contained two important functional regions, helicase ATP binding, and helicase C-terminal. TAPase domain highlights the seven canonical helicase-related sequence motifs (I, Ia, VI) characteristics of the SNF2 group of proteins, and 14 additional conserved

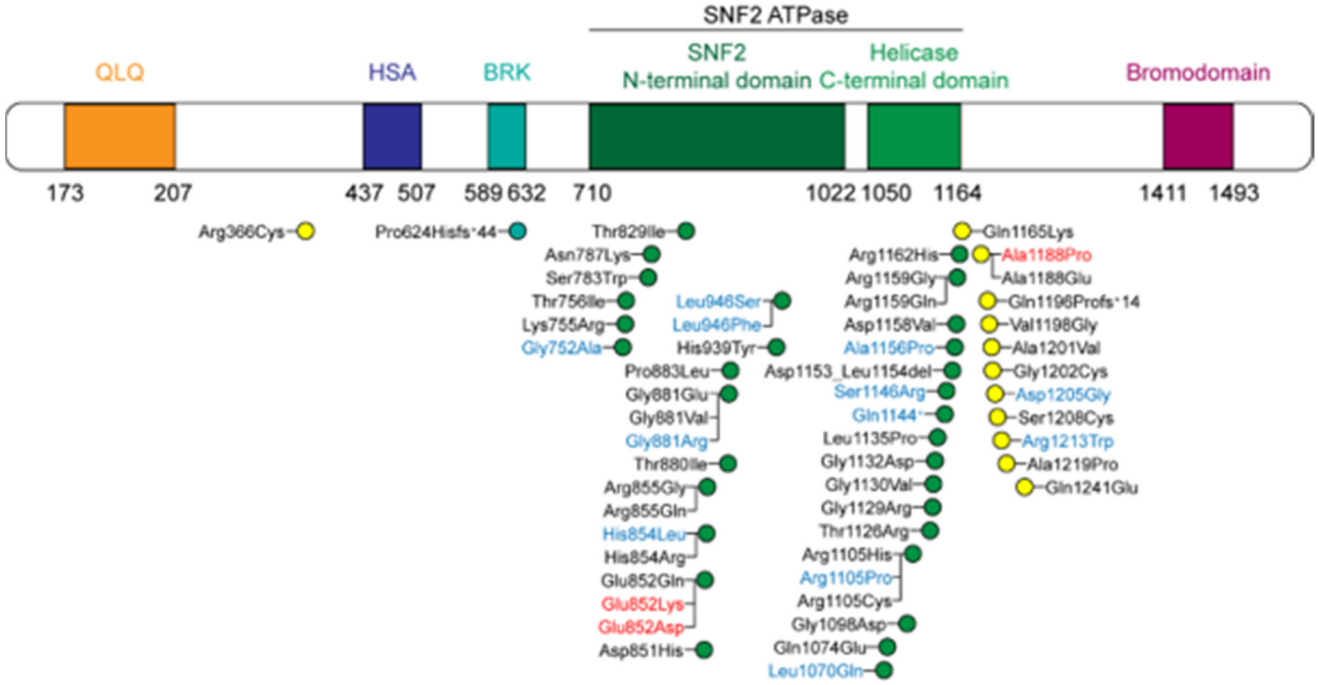

FIGURE 3 The distribution of 58 de novo mutation sites. Among the 58 de novo sites related to NCBRS, 52 sites are missense mutation, the other sites are in-frame deletion (two cases), frameshift mutation (two cases), intron mutation (one case), and nonsense mutation (one case), respectively. Most of de novo sites are located at the SNF2 ATPase domain, which is directly related to phenotypes.

blocks(A-N) (Santen et al., 2013). Over half of the sites were located in the helicase C-terminal region, which was closely related to the severity of intellectual disability and the possibility of seizures. Therefore, the phenotypes of NCBRS are directly related to genetic mutation location. The mutation gene in this case is also located at the exon 24, which was the core of the SNF2 ATPase domain. So, we could explain why this patient had typical features. However, researchers (Gao et al., 2019) also found that deletions encompassing the entire SMARCA2 gene did not cause NCBRS, and mice lacking functional SMARCA2 did not present with major developmental abnormalities, and the solely non-truncating mutations in patients with NCBRS located exclusively in the SNF2 ATPase domain. This phenomenon suggested that mutations did not lead to haploinsufficiency, but had a specific dominant-negative or gain-of-function effect. It may be related to missense mutations in the ATPase domain that lead to the structurally normal and dominant-negative effect of the BAF complex.

3.3 | The inner relationship between the SMARCA2 gene, NCBRS, CCS, SWI/SNF-related intellectual disability syndromes, and tumors

From the above paragraphs, we learned that genetic mutation location affected the phenotype–genotypes. Thus, it was very necessary to understand the functions of the SMARCA2 gene, BAF complex (BRG-/BRM-associated factor complex), and SWI/SNF complex (mating type switch/sucrose nonfermenting). SMARCA2 gene is the catalytic subunit of the BAF complex, BAF is the ATPase active center of SWI/SNF complex, and they changed the structure of chromatin through ATP hydrolysis to generate energy to regulate chromatin remodeling and gene transcription regulation, especially for neural development (Son & Crabtree, 2014). The SWI/SNF complex was composed of more than 10 functional proteins including BRM (encoded by SMARCA2 gene), BRG1 (encoded by SMARCA4 gene), BAF155 (encoded by SMARCC1 gene), BAF170 (encoded by SMARCC2 gene), and INI1(SNF5 or BAF47, encoded by SMARCB1 gene) (Sokpor et al., 2017). Abnormalities of different subunits could cause Coffin–Siris syndrome, Nicolaides–Baraitser syndrome, schizophrenia, and an autism spectrum disorder. Therefore, gene mutations in the components of the SWI/SNF complex can cause a series of neurological symptoms, affect neurodevelopment and specific immune responses, and lead to a series of diseases. Therefore, this disease group was called “SWI/SNF-related intellectual disability syndromes” (Kosho et al., 2014). In this syndrome, NCBRS usually needs to be differentiated from Coffin–Siris syndrome (CCS). For some time, NCBRS was considered to be a clinical subtype of CCS. The clinical distinctions between NCBRS and CSS were often challenging, especially

at a younger age (Bramswig et al., 2015). With the deepening of understanding, researchers found that there were a series of differences between them. The hallmark differences between the two syndromes are limb/trunk anomalies and gene mutation, as typically patients with NCBRS present prominent finger joints and broad distal phalanges, whereas patients with CSS display hypoplasia or aplasia of the fifth fingernails with or without hypoplasia of the terminal phalanges. NCBRS-mutated gene is SMARCA2; CCS-mutated genes contained ARID1B, ARID1A, ARID2, SMARCA4, SMARCB1, SMARCE1, SOX11, and DPF2. Reported that some of the patients represented an intermediate phenotype between them and proposed that these syndromes may represent a disease spectrum rather than two distinct disorders. The newest study (Aref-Eshghi et al., 2018) demonstrated that BAF opathies' DNA methylation epi-signatures can be used as surrogate markers for molecular diagnostics, with performances superior to sequence variant analysis.

In addition to the mutation in NCBRS, SMARCA2 mutation, overexpression, or epigenetic silencing were also found in various human diseases including cancer. So, it was believed that BRM may act as a tumor suppressor or a tumor susceptibility gene. The mechanism may be a BRM-influenced cell cycle, causing repression of E2 promoter binding factor family transcription factors. Cells lacking BRM cannot enter the G1/S phase resulting in growth arrest. BRM function in the cell cycle was probably dependent on the phosphorylation of BRM causing dissociation of Rb from ATPase (Jancewicz et al., 2019). Now there is a question, will SWI/SNF mutation patients have an increased tendency to develop tumors? It is theoretically possible, but so far, the incidence has not increased significantly, which may be related to a lack of long-term clinical follow-up, or it may be because some people have already developed tumors.

3.4 | The road to the future: Diagnosis, treatment, and prognosis

Nowadays, genetic screening is the golden standard of NCBRS diagnosis. Especially with the popularization of trio-based whole-exome sequencing (WES), the case numbers gradually increased, the gene loci are more abundant, and the pathogenesis researches are also more mature. At the same time, genomic DNA methylation assessment has the potential to become part of the clinical screening of patients with broad ranges of developmental disorders; it has the potential to be adapted in molecular diagnosis together with current genomic screening tests. The newest research (Gripp et al., 2016) finds out that a novel facial dysmorphology analysis tool may supplement the clinical phenotype and genotype summaries and provide data independent of the clinician's personal experience and bias. Since then, there have been no effective drugs, mainly focusing on anti-epilepsy and rehabilitation intervention. Regarding the prognosis, in addition to mental retardation and social impairment, most of the children still survive for a long time. Two deaths had been reported. The first British origin patient died of status epileptic and subsequent respiratory complications at the age of 33, the other was a Polish patient reported by Krajewska-Walasek who had died at the age of 25 due to rupture of esophagus varices. Therefore, it can be inferred that this syndrome is progressive and requires a long time to follow-up. It is too early to draw a conclusion about its prevalence, morality, and mechanisms.

AUTHOR CONTRIBUTIONS

Xilian Zhang and Hanjiang Chen: study concept, design, and write; Xuan Liu, Ying Song, Zhaoyuan Chen: search literature and acquisition of data; Rong Ma, Ping Rong: study supervision.

ACKNOWLEDGMENTS

We thank the parents of our patients for their cooperation and for providing consent for publication. Thanks to BGI for the guidance on the drawing.

FUNDING INFORMATION

This work was supported by the National Natural Science Foundation of China grants (81904251) and the Tianjin Health and Family Planning Industry High-level Talent Selection and Training Project (Jinmen Elite Program)

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest in relation to this article.

ETHICS STATEMENT

Not applicable.

INFORMED CONSENT

Written informed consent was obtained from the patient included in this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Zhang, X., Chen, H., Song, Y., Chen, Z., Liu, X., Rong, P., & Ma, R. (2022). Ten-year follow-up of Nicolaides–Baraitser syndrome with a de novo mutation and analysis of 58 gene loci of SMARCA2-associated NCBRS. *Molecular Genetics & Genomic Medicine*, *10*, e2009. https://doi.org/10.1002/mgg3.2009