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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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
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 convolution 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 paradoxical nodding with shaking upper limbs, occasionally with falling objects in the hands, screaming before convolution. 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, non-consanguineous 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 3000g 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...
| Number | Mutation type | 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 | | 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 | De novo | 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 |
| Number | Amino-acid change | Mutation type | Gene symbol | Variation | Reference version | Transcription | Reference DOI |
|--------|-------------------|---------------|-------------|-----------|-------------------|---------------|---------------|
| 25     | Missense mutation | p.Ala1188Pro  | SMARCA2     | Mutation is absent in one available parent | 10.1038/rg.1105 | hg19          | NM_003070.3   |
| 26     | Missense mutation | p.Ala1188Pro  | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 27     | Missense mutation | p.Glu821Lys   | SMARCA2     | Mutation is absent in one available parent | 10.1038/rg.1105 | hg19          | NM_003070.3   |
| 28     | Missense mutation | p.Ala1188Pro  | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 29     | Missense mutation | p.Flu821Glu   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 30     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 31     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 32     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 33     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 34     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 35     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 36     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 37     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 38     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 39     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 40     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 41     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 42     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 43     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 44     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 45     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 46     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 47     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 48     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 49     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 50     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 51     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 52     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
| 53     | Missense mutation | p.Leu821Ser   | SMARCA2     | NA        | 10.1038/rg.1105   | hg19          | NM_003070.3   |
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.

TABLE 1 (Continued)

| Number | Mutation type | Amino-acid change | Gene symbol | Variation | Reference DOI | Version | Transcription |
|--------|---------------|-------------------|-------------|-----------|--------------|---------|---------------|
| 54     | Missense mutation | p.Leu1070Gln | SMARCA2 | NA | NA | 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 | 10.1186/s12920-019-0555-y | hg19 | NA |

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.



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
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, large mouth, and thin upper vermilion 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.

![Figure 1: The changes in facial morphology and distal limbs in 10 years.](image)

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 vermilion 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.
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
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 CCS 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; CSS-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 BAFopathies’ 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.

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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.

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