The Clinical Manifestations and Genetic Implications of Baraitser–Winter Syndrome Type 2

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Abstract

An 18-year-old Caucasian male was born by cesarean section weighing 2.6 kg (5 lb 14 oz) at birth after an uncomplicated pregnancy with no perinatal complications. Around 4 to 5 months of age, the patient's mother initially became concerned as he was experiencing signs of developmental delay and a mild floppy tone, in addition to facial features that resembled some form of mental retardation. The patient's older brother also experienced similar developmental symptoms and facial features that presented around the same age period as our patient. It was initially thought to be Down syndrome; however, both the patient and his brother tested negative for Down syndrome on chromosomal analyses. There was also a question of whether the patient had some form of autism spectrum disorder, but doctors were unable to specifically confirm this. Now at the age of 18 years, the patient has no understandable speech with distinctive facial features such as a broad nasal bridge and prominent epicanthic folds, lissencephaly, smaller than average head size, intellectual disability, and hearing loss. It was discovered, through trio-based exome sequencing, that the patient had a de novo missense mutation (p.Ser155Phe) in the *ACTG1* gene, which has been linked to the rare syndrome known as Baraitser–Winter syndrome type 2. Baraitser–Winter syndrome 2 is a unique variant that is clinically similar to Baraitser–Winter syndrome type 1; however, only seven previous cases have been reported.

Keywords

- ▶ Baraitser–Winter syndrome type 2
- ▶ *ACTG1* gene mutations
- ▶ de novo

Introduction

Baraitser–Winter syndrome type 2 is a condition affecting the development of many parts of the body, particularly the brain and face, with only seven previously reported cases in medical literature.¹ There are many distinctive clinical characteristics that help distinguish Baraitser–Winter syndrome type 2 from phenotypically similar genetic conditions. The striking dysmorphic craniofacial features include hypertelorism, arched eyebrows, a ridged metopic suture, congenital non-myopathic ptosis, and a broad nose with a large tip and prominent root.² In addition to these distinct craniofacial

features, anterior predominant lissencephaly, microcephaly, intellectual disability, sensorineural deafness as well as seizures are commonly reported. Early muscular involvement may develop over time, occasionally accompanied by congenital arthrogryposis.² There is variation in the findings among individuals with Baraitser–Winter syndrome type 2, such that not all individuals with this diagnosis have all of the findings or the same degree of involvement.

These abnormalities are related to impaired neuronal migration, a process in which nerve cells move to their proper positions in the developing brain.² Literature has reported that, with the exception of one case, all reported patients with

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Baraitser–Winter syndrome type 2 have been associated with de novo mutations.¹

We report a young male patient with distinct craniofacial features consistent with Baraitser–Winter syndrome type 2 in which trio-based whole genome sequencing discovered de novo mutations in the *ACTG1* gene.

Case Study

An 18-year-old Caucasian male was born by cesarean section weighing 2.6 kg (5 lb 14 oz) at birth after an uncomplicated pregnancy with no associated perinatal problems. At birth, the patient was found to have facial features resembling a multitude of congenital genetic mutations, such as Down syndrome, Dandy–Walker malformation, and cardiofaciocutaneous syndrome. After 4 to 5 months, there was an increasing concern as the patient was experiencing some developmental delays and a notable mild floppy tone. Similar developmental symptoms and craniofacial features were noted in the patient's older male sibling, initially presenting around the same age period. The patient was thought to have a form of Down syndrome; however, chromosomal analyses specific for Down syndrome were negative for both the patient as well as his older brother. Per the patient's mother, there was suspicion as to whether autism spectrum disorder had a component in the patient's developmental and intellectual status; however, physicians were unable to specifically confirm this.

Now at the age of 18 years old, the patient has no understandable speech with distinctive craniofacial features such as a broad nasal bridge and prominent epicanthic folds, lissencephaly, microcephaly, intellectual disability, and hearing loss. The patient's older brother exhibited similar developmental symptoms and craniofacial features; however, differences were noted as the older sibling experienced periodic seizures and did not suffer from hearing loss. The patient's older sibling also exhibited contractures in all four extremities that started a year or so after birth, worsened with age, and eventually led to the sibling requiring a wheelchair for a majority of his life. Our patient consistently demonstrated a floppy tone, whereas the patient's older sibling was noted to exhibit alternating episodes of floppy tone and stiffness. ▶**Fig. 1** illustrates the previously mentioned craniofacial features in both the patient as well as his older sibling a few months after birth and at his current age of 18 years.

As multiple physicians were unable to provide a definitive diagnosis, a genetic specialist was approached and testing was performed on blood samples from both the patient as well as from his recently deceased older sibling. After multiple years of testing, de novo missense changes in the *ACTG1* gene (p.Ser155Phe) were found using trio-based (the patient and his unaffected parents) whole-genome sequencing, which was discovered to be the mutation associated with Baraitser–Winter syndrome type 2. The specific study assessed three probands and their unaffected parents using two different platforms and additional subjects, including the patient's deceased brother, with similar phenotypic features,

were added to the research study. De novo missense changes in the cytoplasmic γ -actin gene *ACTG1* and in the β -actin gene *ACTB*, all of which were tested by Sanger sequencing,³ were identified in a subset of cases, one of which included the patient from this case; however, the patient's brother did not exhibit either of these discovered missense mutations despite demonstrating phenotypic similarities with the patient.

The results of this analysis confirmed that parent–child trio-based exome sequencing is a powerful approach to discover genes causing sporadic developmental disorders. The genetic analysis performed also emphasized the overlapping roles of cytoplasmic actin proteins in the development of an individual, further suggesting that Baraitser–Winter syndrome type 2 is the predominant phenotype associated with mutation of the *ACTG1* gene.

Discussion

Baraitser–Winter syndrome was first described in 1988 by two researchers, M. Baraitser and R. M. Winter, who presented a seemingly distinct syndrome of iris coloboma, bilateral ptosis, hypertelorism, a broad nasal bridge, prominent epicanthal folds, short stature, and mental retardation in a girl with unrelated parents.² Since then, fewer than 50 additional cases of children with the characteristic clinical features resembling that of Baraitser–Winter syndrome have been reported in the medical literature.^{4–6} Consequently, the phenotypic spectrum has broadened and now includes microcornea, microphthalmia, arched eyebrows, gyral malformation, seizures, hypotonia, sensorineural deafness, congenital arthrogryposis, and progressive joint stiffness.³

The most frequent brain abnormality associated with Baraitser–Winter syndrome is pachygyria, which is characterized by an area of the brain that has an abnormally smooth surface with fewer folds and grooves. It is less common for affected individuals with Baraitser–Winter syndrome to present with lissencephaly, which is similar to pachygyria, but involves the entire brain surface.⁴ It is these structural brain abnormalities that have the potential to lead to the severe intellectual disability, developmental delay, and seizures commonly seen in Baraitser–Winter syndrome.⁴

Baraitser–Winter syndrome type 2, a unique variant that is clinically similar to Baraitser–Winter syndrome, has only seven previous cases that have been reported in the literature as shown in ▶**Table 1**.¹ The patient reported in this case is listed as patient 4 in ▶**Table 1** for comparison to the previously reported cases.¹ A smooth brain malformation involving the entire surface of the brain, commonly referred to as “lissencephaly,” appears to be more consistent in those with an *ACTG1* mutation in comparison to those with an *ACTB* mutation.³ Due to the small number of cases of reported Baraitser–Winter syndrome type 2, the presence of lissencephaly cannot be definitively associated with Baraitser–Winter syndrome type 2 alone; however, given the prevalence of this brain malformation in those with an *ACTG1* mutation, it is suggestive as a clinical diagnostic feature of Baraitser–Winter syndrome type 2. It is important to note that there is variation in the findings among individuals with Baraitser–Winter

Fig. 1 Photographs of the patient. (A) Patient with older sibling few months after birth. (B) Patient at age 18. (C) Patient (right) with older sibling (left). (D) Patient at age 18.

syndrome 2, such that not all individuals with this diagnosis have all of the findings or the same degree of involvement.¹ It is this marked phenotypic variability that explains why there were multiple previous cases reported as distinct clinical entities before the discovery of the *ACTG1* and *ACTB* mutations and their involvement in cytoplasmic actin development.³

Interestingly, the patient's sibling, with similar craniofacial features and developmental delays, was not found to have a missense *ACTG1* or *ACTB* mutation after trio-based whole genome sequencing. As mentioned above, the patient's older sibling exhibited some contrasting features such as diffuse contractures ultimately leading to being wheelchair bound, periodic seizures, occasional episodes of stiffness alternating

Table 1 Eight patients were reported by Rivière with Baraitser–Winter syndrome carrying heterozygous missense mutations in the *ACTG1* gene; in seven patients the mutation was proven to have occurred de novo. One mutation was recurrent in three patients, a ser-to-phe substitution at codon 155. One of these three, patient 5 was originally reported by Baraitser and Winter (1988)¹

Patient	Chromosome	Amino acid change	Inheritance	Gene
1	17	p.Thr120Ile	De novo	<i>ACTG1</i>
2	17	p.Ala135Val	De novo	<i>ACTG1</i>
3	17	p.Ser155Phe	De novo	<i>ACTG1</i>
4	17	p.Ser155Phe	De novo	<i>ACTG1</i>
5	17	p.Ser155Phe	No parents	<i>ACTG1</i>
6	17	p.Thr203Lys	De novo	<i>ACTG1</i>
7	17	p.Arg254Trp	De novo	<i>ACTG1</i>
8	17	p.Arg256Trp	De novo	<i>ACTG1</i>

Note: Patient 4 is discussed in this article.

with floppy tone, and no hearing loss. It is important to note that it is difficult to distinguish syndromes with overlapping phenotypic features. The patient's older sibling's blood samples are continually analyzed to definitively diagnose his condition; however, genetic studies have yet to confirm a specific mutation and syndrome that lead to his phenotypic features and developmental delay. There are currently no reported cases in the literature of Baraitser–Winter syndrome (type 1 and type 2) in siblings or relatives as these mutations are classified as sporadic in nature.

The genetic mechanism behind the autosomal dominant Baraitser–Winter syndrome has recently been associated with gain-of-function de novo mutations in the actin-encoding genes *ACTB* (Baraitser–Winter syndrome) and *ACTG1* (Baraitser–Winter syndrome-2) genes that encode β - and γ -actins.¹ Actins are a family of essential cytoskeletal proteins that have been implicated in nearly all cellular processes and are critical for cell division, cell movement, and signaling.⁷ The cytoplasmic β - and γ -actins are present in all cell types and are nearly identical to each other, only differing by four amino acids.⁷ Although the β - and γ -actins are similar in structure, it has been proposed that these actins have partially distinct physiological functions based on their relative special and temporal enrichment in neurons and other cell types.^{8–10} Heterozygous *ACTG1* and *ACTB* mutations have been previously reported, suggesting a more severe phenotype for *ACTB* mutations.^{11–13} Previous studies have also found that *ACTG1* mutations may have a more central role in neuronal migration, although there was no statistical significance due to the small number of *ACTG1* cases.

Whole genome sequencing has been recently documented as identifying sporadic and disease-causing genetic mutations in rare syndromes.^{14,15} However, for disorders that are thought to arise from de novo mutations, trio-based whole genome sequencing narrows the number of candidate mutations, which has successfully identified de novo point mutations in intellectual disability, autism, and schizophrenia.^{7,16,17} Baraitser–Winter syndrome type 2 has been successfully identified through the use of trio-based whole genome sequencing, in which heterozygous missense changes in the cytoplasmic actin-coding gene *ACTG1* have been discovered, a majority of which occurred de novo.¹

Conclusion

Baraitser–Winter syndrome type 2 is a rare complex genetic condition with craniofacial, muscular, and visceral involvement due to missense mutations in *ACTG1* and with dysregulation in the function of cytoplasmic actin, there are a wide range of effects in cranial neural crest derivatives during development. We herein presented a patient with dysmorphic craniofacial features and whole-genome parent–child trio-based exome sequencing detecting de novo missense changes in the *ACTG1* gene, which is consistent with Baraitser–Winter syndrome type 2. We concluded that without trio-based exome sequencing, it is difficult to distinguish Baraitser–Winter syndrome type 2 from similar phenotype syndromes such as Baraitser–Winter syndrome type 1 and Noonan syndrome.

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