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A Novel Heterozygous Splice Donor Variant in *TRIM28* Gene Causing Beckwith-Wiedemann Spectrum: Case Report and Literature Review

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1. Abstract

Background

Beckwith-Wiedemann Syndrome (BWS) is an inborn growth disorder caused by molecular alterations in chromosome 11p15.5. Due to the varying clinical findings of patients with 11p15.5 disturbances, the syndromic entity was expanded to the Beckwith–Wiedemann spectrum (BWSp). BWSp describes a complex heterogeneous and multisystem disease spectrum. It can be diagnosed by clinical assessment and/or molecular testing. The clinical features comprise characteristic developmental anomalies, including midline abdominal defects, macroglossia, overgrowth, hemihypertrophy, and neonatal hypoglycemia. Patients with BWSp patients are predisposed to malignancy during their early childhood.

Methods and Results

We describe a 5-year-old female child with hemihypertrophy, macroglossia and speech delay. Her DNA methylation for 11p15.5 region and chromosomal microarray were unremarkable. Whole exome sequencing revealed a heterozygous variant c.1409+2T>C in the *TRIM28* gene only. Abdominal ultrasound as well as alpha-fetoprotein (AFP) level were done every three months as cancer surveillance and were continued until she reached 5 years of age.

Conclusion

This report adds to the genotype-phenotype correlation, highlighting the clinical importance of considering *TRIM28* gene defects as part of the differential diagnosis for any patient with clinical features mimicking BWS, even without evidence of malignancy.

2. Introduction

Beckwith-Wiedemann Syndrome (BWS) is an inborn growth disorder caused by molecular alterations in chromosome 11p15.5. These molecular changes affect so-called imprinted genes, i.e., genes that underlie a complex regulation linked to the parental origin of the gene copy. Different genetic/epigenetic alterations can affect this fine-tuned expression and result in overexpression (e.g., from biallelic expression) or silencing of imprinted genes [1]. Due to the varying clinical findings of patients with 11p15.5 disturbances, the syndromic entity was expanded to "Beckwith–Wiedemann spectrum (BWSp)" [2]. Several clinical features of BWS overlap with those of other imprinting disorders (i.e., transient neonatal diabetes mellitus, Kagami–Ogata syndrome, pseudohypoparathyroidism type 1B), and this ambiguity is reflected by molecularly overlapping alterations [3].

Molecular alterations in BWSp patients affect one or both imprinted regions in 11p15.5, which comprise the imprinting control regions 1 and 2 (IC1, IC2). Molecular changes in the same region also occur in patients with Silver–Russell syndrome, but in this growth retardation syndrome, the molecular alterations are opposite to those that occur in BWSp [3]. Many genes are described to be associated with BWSp, such as *IGF2, H19, CDKN1C, KCNQ10T1,* and *KCNQ1*.

Clinically, the term BWSp describes a complex heterogeneous and multisystem disease spectrum. It can be diagnosed by clinical assessment and/or molecular validation. The clinical features comprise characteristic developmental anomalies such as midline abdominal defects (e.g., exomphalos, umbilical hernia), enlarged tongue (macroglossia) and overgrowth (gigantism), lateralized overgrowth (hemihypertrophy) and neonatal hypoglycemia. Up to 8% of all BWSp patients develop an embryonal tumor during their early childhood, but the exact tumor risk depends, however, on the precise causative genetic/epigenetic alteration. Thus, depending on the molecular subtype of BWSp, the childhood cancer risk ranges from 1 to 30%. The main tumor types associated with BWSp are Wilms tumor (nephroblastoma), hepatoblastoma, and neuroblastoma [2-3].

In this report, we describe a 5-year-old female child with hemihypertrophy and macroglossia, found to have a heterozygous variant in the *TRIM28* gene inherited from her father.

3. Case Description

Our patient is a female child, currently 5 years old, who was initially evaluated in the genetic clinic at 13 months of age due to an enlarged tongue. The mother noted that her child used to keep her mouth open most of the time due to the large, protruded tongue. She denied shortness of breath, drooling, snoring, or difficulty feeding. An ENT specialist evaluated her, and the mother was reassured that there was no evidence of airway obstruction.

This patient is a product of consanguineous parents. The father has occasional abdominal pain, but it has never been investigated. She is the second child of her parents, and her sibling is healthy with normal developmental milestones. The family denied a history of tumors or developmental delays.

She was born at term by emergency Caesarean section due to fetal distress and bradycardia. She developed one episode of hypoglycemia, for which she was fed and kept for observation and monitoring of her glucose level. There was no concern after 24 hours of birth, so she was discharged home. There was no surgical procedure, and no medical admissions were required. She was meeting her developmental milestones up to her age, apart from speech delay.

Her physical examination revealed that her growth parameters are within the centiles for age and gender. There were no dysmorphic features apart from macroglossia. There were no ear pits or tags, abdominal distention, or abdominal wall defects. Her systemic examination was unremarkable, apart from a 1 cm discrepancy in length between lower limbs.

Due to the presence of macroglossia and hemihypertrophy, the possibility of Beckwith-Wiedemann syndrome was entertained; both DNA methylation studies and copy number analysis (for sequences within 11p15.5) by chromosomal microarray were done, and both returned unremarkably.

Abdominal ultrasound and alpha-fetoprotein (AFP) levels were done every three months as screening for Wilms tumor and other malignancies per recommended guidelines, and this continued until the patient reached five years of age. Whole exome sequencing (WES) revealed only a heterozygous variant c.1409+2T>C in the *TRIM28* gene.

Genetic Analysis

After WES variant filtering, the same heterozygous (GenBank NM_005762.2: c.1409+2T>C) in the *TRIM28* gene was identified in the patient and her father only.

4. Discussion

BWS is the most prevalent overgrowth syndrome, characterized by a genetic imprinting anomaly. This condition exhibits a diverse range of clinical manifestations and comes with an inherent risk of early childhood tumor development. Therefore, it is crucial to promptly identify the syndrome during the prenatal or neonatal stage to facilitate vigilant monitoring and timely intervention for potential complications [3-5].

The diagnosis of BWS relies on clinical criteria and can be further verified through molecular or cytogenetic testing [1]. Nevertheless, due to the diverse nature of this disorder, there is no universally agreed-upon set of criteria, and most experts concur that these criteria should not replace individual clinical assessment on a case-by-case basis [6]. Similarly, it's important to note that a lack of confirmation through diagnostic testing does not necessarily rule out the possibility of BWS [6]. Our patient's early-life presentations of hypoglycemia, macroglossia, and hemihypertrophy all strongly indicated a diagnosis of BWS, despite negative methylation at 11p15.5, negative chromosome microarray and whole exome sequencing did not show any pathogenic/likely pathogenic variant in genes known to cause BWS.

The predominant portion of tumors associated with BWSp consists of nephroblastomas [2]. This, also referred to as Wilms tumor (WT), is a rare kidney tumor primarily found in children [7]. It represents approximately 95% of all kidney tumors in childhood and stands as the most prevalent kidney malignancy in children under the age of 15 years. It affects 1 in 10,000 children globally and is more frequently observed in individuals of African descent [7-8]. Wilms tumor is genetically heterogeneous, and about 40 different genes have been pinpointed as potential contributors to its development [9]. Substantial evidence suggests that there are probably more genes contributing to this predisposition yet to be identified [7]. Among these, the most frequently altered and well-recognized drivers include *WT1, WTX/AMER1, CTNNB1, SIX1, SIX2, DROSHA, DICER1, DCGR8*, and *TP53* [10-11].

Recently, the *TRIM28* gene has been identified to be associated with Wilms' tumor (WT) predisposition with pathogenic variations found in about 1% of isolated cases and 8% of familial cases of WT [10].

In children with WT, *TRIM28* functions as a classical tumor suppressor gene, and typically both gene copies are disrupted in the tumor [10]. Therefore, the loss of *TRIM28* protein expression in tumor tissue through immunohistochemistry is an effective method for identifying patients who carry pathogenic *TRIM28* variants [10]. As for many of the recently discovered WT predisposition genes, much is needed to know how pathogenic *TRIM28* variants lead to WT development [10].

5. Conclusion

This report adds to the genotype-phenotype correlation, highlighting the importance of considering *TRIM28* gene defects as part of the differential diagnosis for any patient with clinical features mimicking BWS, even without evidence of malignancy. Keeping in mind that this gene is associated with Wilms tumor, we recommend tumor surveillance with abdominal ultrasound for the liver, adrenal glands, and kidneys every three months until 4 years of age, followed by kidney ultrasound only every 3 months from age 4 to 8 years. Serum AFP levels should be performed every 3 months until 4 years of age. Physical examination by a pediatrician, geneticist, or pediatric oncologist twice a year is also recommended.

6. Declarations

Consent for publication

Consent for publication was obtained from the reported family.

7. Ethical compliance

This study was approved by the Abu Dhabi Health Research and Technology Committee (ADHRTC). Ref. No.: ADHRTC-2024-149

Availability of data and materials

All data generated during this study are included in this published article.

8. Competing interests

The authors declare that they have no competing interests.

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9. Authors' contribution

The authors contributed to the conception and design. All authors contributed to the acquisition and

revised manuscript and agreed to be accountable for all aspects of the work, ensuring integrity and

accuracy. All authors read and approved the final manuscript.

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