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Prenatal ultrasound detection of a DACT1 pathogenic variant overlapping Townes-Brocks Syndrome: A case report with asymptomatic maternal carrier

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Abstract

Townes–Brocks syndrome (TBS) is a rare autosomal dominant disorder typically caused by SALL1 mutations. Variants in DACT1 may produce overlapping phenotypes but are rarely described prenatally. We report a 32-year-old primigravida referred at 20th weeks for severe fetal growth restriction. Ultrasound revealed hyperechogenic bowel, abdominal calcifications, saddle-shaped nasal profile, cortical development anomalies, and triphalangeal thumbs. Amniocentesis with trio exome sequencing identified a heterozygous pathogenic DACT1 variant, also present in the asymptomatic mother. The pregnancy was terminated at 23 weeks due to poor prognosis. Postmortem confirmed imperforate anus and limb anomalies. This case highlights the value of detailed fetal imaging combined with advanced molecular testing for rare genetic syndromes, and the complexity of counseling in autosomal dominant disorders with incomplete penetrance.

Keywords: Autosomal dominant, Fetal growth restriction, Townes–Brocks syndrome

Introduction

Townes-Brocks syndrome (TBS; OMIM #107480) is a rare autosomal dominant genetic disorder with an incidence of approximately 1 in 250,000 live births. It is classically characterized by anorectal malformations, external ear anomalies, and thumb malformations, although its clinical spectrum is highly variable, including renal, cardiac, auditory, and genitourinary anomalies [1,12].

Pathogenic variants in the *SALL1* gene are responsible for the majority of reported TBS cases. However, recent studies have identified mutations in the *DACT1* gene, a regulator of the Wnt signaling pathway, that can result in phenotypes partially overlapping with classical TBS. These *DACT1*-related disorders are still poorly defined, with only a limited number of cases described in the literature, highlighting the importance of reporting new cases to refine the genotype-phenotype correlation [2].

Prenatal diagnosis of TBS and TBS-like syndromes is particularly challenging due to the lack of specific sonographic markers. Subtle morphological anomalies such as limb abnormalities, renal dysplasia, or growth restriction can be the only detectable signs during routine ultrasound examinations. Advanced genetic testing techniques, including chromosomal microarray analysis (CMA) and next-generation sequencing (NGS), are often required to achieve a definitive diagnosis, enabling proper genetic counseling and perinatal management [3,10].

Here, we present a prenatal case characterized by severe fetal growth restriction (FGR) and distinct morphological findings that led to the identification of a rare *DACT1* mutation. Interestingly, the same variant was also detected in the asymptomatic mother, expanding the phenotypic spectrum associated with *DACT1* mutations and underscoring the clinical complexity of interpreting variants with incomplete penetrance.

Case

A 32-year-old primigravida was referred to our maternal-fetal medicine unit for routine second-trimester screening. The pregnancy had been

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uneventful until that point, and the patient's medical and family history were unremarkable. First-trimester ultrasound at 12 weeks' gestation showed normal nuchal translucency and no structural anomalies, with the crown-rump length (CRL) measuring only 4 days behind the estimated gestational age, making a dating error unlikely.

At 19 weeks and 6 days of gestation, a detailed fetal ultrasound revealed severe fetal growth restriction (FGR). Biometric measurements were significantly reduced, with head circumference (HC) at the 17th percentile, transverse cerebellar diameter (TCD) at the 12th percentile, and both abdominal circumference (AC) and long bone lengths below the 3rd percentile. Additional findings included hyperechogenic bowel, punctate calcifications at the umbilical cord insertion site, and a saddle-shaped nasal profile (figure 1). The insula was not clearly visualized, although this could have been attributable to the relatively early gestational age. Non-invasive prenatal testing (NIPT) for common aneuploidies returned low-risk results.

Given the constellation of findings—particularly the severe early-onset growth restriction and abnormal bowel echogenicity—genetic counseling was offered, and invasive prenatal testing was recommended. At 20 weeks, an amniocentesis was performed. Fetal genetic workup included conventional karyotyping, chromosomal microarray analysis (CMA), and trio exome sequencing via Next-Generation Sequencing (NGS), which also involved parental samples.

At 22 weeks and 3 days, while awaiting genetic results, a follow-up ultrasound documented further progression of FGR. Although the cerebral biometric parameters (HC and TCD) remained relatively stable, AC and long bone measurements were markedly reduced compared to previous scans. Neurosonography revealed a normal-appearing corpus callosum but showed bilateral absence of the parieto-occipital fissures and marked hypodevelopment of the Sylvian fissure, raising concerns for cortical development anomalies. The previously observed hyperechogenic bowel and abdominal calcifications were reconfirmed. A retrospective review of ultrasound cine-loops from 19 and 22 weeks revealed bilateral thumb abduction and triphalangeal thumbs, highly suggestive of Townes-Brocks syndrome (TBS). (figure 2).

Genetic analysis results, reported at 22+5 weeks, identified a heterozygous pathogenic variant in the *DACT1* gene (NM_001079520.2), which was also detected in the asymptomatic mother. The finding was consistent with a TBS-like phenotype caused by *DACT1* mutations, known to exhibit variable expressivity and incomplete penetrance. Following multidisciplinary counseling, which included discussions of the poor fetal prognosis and future reproductive implications, the couple opted for voluntary termination of pregnancy (TOP) at 23 weeks' gestation.

Postmortem examination confirmed the ultrasound findings, notably the presence of imperforate anus—a hallmark feature of TBS—and the triphalangeal thumbs, in addition to mild dysmorphic facial features.

Discussion

This case highlights the critical role of detailed prenatal ultrasound in identifying subtle yet clinically significant morphological anomalies, which can raise suspicion for rare genetic syndromes and guide the decision toward invasive diagnostic testing. The combination of severe early-onset fetal growth restriction (FGR), hyperechogenic bowel, abdominal calcifications, and limb anomalies—particularly the detection of triphalangeal thumbs—was instrumental in prompting comprehensive genetic analysis through trio exome sequencing (table 1).

Townes-Brocks syndrome (TBS) is classically associated with SALL1 mutations; however, recent evidence suggests that DACT1 variants may lead to overlapping or TBS-like phenotypes [4,11]. DACT1 encodes the Dishevelled-binding antagonist of beta-catenin 1, a regulator of the Wnt signaling pathway crucial for embryonic development, particularly in the formation of the gastrointestinal tract, central nervous system, and limbs. Pathogenic variants in DACT1 have been reported only in a limited number of cases, most of which involve postnatal diagnoses [5,9]. Prenatal detection of DACT1-related phenotypes remains exceedingly rare, with only a handful of reports describing ultrasonographic findings suggestive of this condition.

In our case, the identification of a heterozygous DACT1 mutation, also found in an asymptomatic

mother, underscores the phenomenon of variable expressivity and incomplete penetrance[2]. While the fetus exhibited multiple anomalies consistent with a TBS-like phenotype—including imperforate anus and triphalangeal thumbs—no clinical features were evident in the maternal carrier. Similar cases have been described in the literature, where mild or absent phenotypes in carriers complicate the interpretation of genetic variants and genetic counseling for families. This variability suggests that other genetic modifiers or environmental factors may influence the clinical expression of DACT1 mutations (table 2).

Relevant studies reinforce the diagnostic value of detailed ultrasound combined with advanced genetic testing to accurately identify prenatal TBS-related conditions (Table 3).

Genetic counseling and inheritance

Mutations in DACT1 follow an autosomal dominant inheritance pattern, meaning that each child of a carrier has a 50% probability of inheriting the variant. However, this does not imply that 50% of offspring will necessarily develop the disease, as DACT1-related disorders are characterized by incomplete penetrance and variable expressivity. Incomplete penetrance indicates that some individuals carrying the mutation remain completely asymptomatic, as observed in the mother of our case. Variable expressivity refers to the broad range of phenotypic manifestations, which can vary from minimal anomalies—often undiagnosed—to severe, syndromic presentations involving multiple organ systems.

This variability introduces significant challenges for genetic counseling, since predicting the clinical outcome for an affected fetus or future pregnancies remains uncertain. Couples should be counseled about the 50% recurrence risk in each pregnancy, but also informed that the severity of the condition—if present—cannot be precisely anticipated. This highlights the importance of early prenatal monitoring, comprehensive imaging, and advanced molecular diagnostics in at-risk pregnancies [6,7,11].

Conclusions

This prenatal diagnosis of a rare *DACT1* mutation broadens the current understanding of genetic variants associated with Townes-Brocks syndrome–like phenotypes. It underscores the critical role of high-resolution prenatal imaging combined with advanced molecular diagnostics—including exome sequencing—in the early detection and management of rare genetic disorders. The identification of an asymptomatic maternal carrier highlights the complexity of genetic counseling in autosomal dominant conditions with incomplete penetrance and variable expressivity, posing challenges in predicting the phenotypic outcome for future pregnancies.

Moreover, this case emphasizes the importance of pursuing comprehensive genetic evaluation in the presence of severe early-onset fetal growth restriction—particularly when associated with multiple or atypical structural anomalies—since subtle yet pathognomonic features, such as triphalangeal thumbs, may guide the diagnostic pathway. Early recognition of these findings enables timely and informed parental decision-making, facilitates multidisciplinary counseling, and improves the accuracy of recurrence risk assessment for subsequent pregnancies.

Acknowledgments

None.

Disclosure Statement

The authors declare no conflicts of interest.

Ethics statement

Informed consent was obtained from the patient for publication of this case report and any accompanying images. Ethical approval was not required in accordance with the institutional requirements for single case reports.

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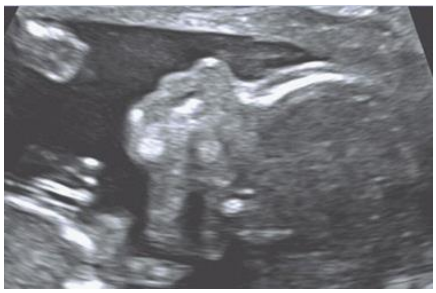

Figure 1. Prenatal ultrasound showing saddle-shaped nasal profile.

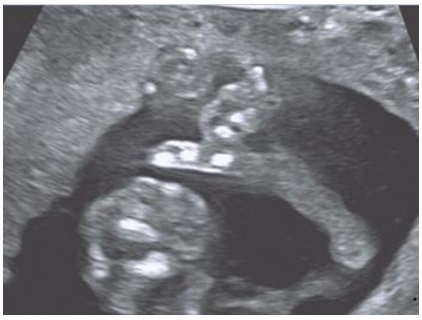

Figure 2. Prenatal ultrasound showing triphalangeal thumbs.