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CASE REPORT

CLINICAL CASE

Hypertension and Brachydactyly Syndrome

Genetic Insights and a Novel Presentation

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ABSTRACT

Phosphodiesterase 3A (*PDE3A*) gene mutations have recently been associated with hypertension and brachydactyly syndrome (HTNB). This report shows how the recent recognition of the role of the *PDE3A* gene in HTNB facilitated the diagnosis of HTNB in a 20-year-old female who could not be diagnosed at her initial presentation at 6 years of age. (J Am Coll Cardiol Case Rep 2024;29:102343) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 20-year-old female presented to the cardiogenomics clinic with worsening dyspnea on exertion. She was referred for genetic re-evaluation by the cardiothoracic surgery service who were assessing her candidacy for aortic valve replacement surgery. Her past medical history included hypertension (HTN), hyperlipidemia, bicuspid aortic valve (BAV), severe aortic insufficiency, aortic root dilation, and a dilated left ventricle with preserved left ventricular ejection fraction.

LEARNING OBJECTIVES

- To understand the role of genetic testing in diagnosing hypertension and brachydactyly syndrome.
- To emphasize the importance of advancing genomic discovery by expanding genomic databases and promoting research.

On presentation, the patient appeared to be well-oriented and lacked dysmorphic facial features (**Figure 1A**). Her height was 58 inches, her weight was 87 pounds, and her body mass index was 18.2 kg/m^2. Her physical examination was unremarkable except for the presence of bilateral brachydactyly of the hands and feet (**Figures 1B and 1C**). Her blood pressure was 137/83 mm Hg.

PAST MEDICAL HISTORY

The female proband was born at 37 weeks of gestation to a 32-year-old G_7P_5 mother. The pregnancy was complicated by gestational HTN. At birth, the patient

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ABBREVIATIONS AND ACRONYMS

BAV = bicuspid aortic valve

cAMP = cyclic adenosine monophosphate

cGMP = cyclic guanosine monophosphate

HTN = hypertension

HTNB = hypertension and brachydactyly syndrome

weighed approximately 4 pounds and measured 19 inches. She was diagnosed with a BAV and aortic insufficiency at 3 months of age. At 4 years of age, she was diagnosed with HTN of an unknown etiology. At 6 years of age, she underwent genetic testing and a skeletal survey to evaluate her short stature, HTN of an unknown etiology, and dysmorphic features. Karyotyping was normal (46, XX). A microarray comparative genomics hybridization (array CGH) was ordered to assess copy number variation and returned negative results. The skeletal survey revealed diffuse brachydactyly.

DIFFERENTIAL DIAGNOSIS

Based on her symptoms, her differential diagnoses included Turner syndrome and hypertension and brachydactyly syndrome (HTNB), but a definitive diagnosis could not be made initially based on genetic testing.

INVESTIGATIONS

Transesophageal echocardiography displayed a BAV (Figure 2), left ventricular ejection fraction of 60%, severe aortic insufficiency with eccentric dilation of the left ventricle, mild aortic stenosis, and moderate mitral regurgitation. Cardiac magnetic resonance imaging showed an enlarged ascending aorta relative to the patient's body habitus. A chest x-ray obtained during the patient's preoperative assessment revealed no signs of pleural effusion, pneumothorax, or consolidation. An electrocardiogram displayed sinus tachycardia with left ventricular hypertrophy.

Given her presentation, a 29-gene aortopathy panel and an 82-gene cardiomyopathy panel were requested. Both panels were negative. Additionally, phosphodiesterase 3A (*PDE3A*) analysis was requested, given the clinical suspicion for HTNB. A heterozygous missense variant in the *PDE3A* gene, c.2584C>T (p.Arg862Cys) in exon 13 was identified which had prior human and animal data for pathogenicity (Figure 3). Based on the patient's symptoms of hypertension and brachydactyly and known missense likely pathogenic variant in the *PDE3A* gene, a diagnosis of HTNB was made. Given the family history provided by the patient, the patient's mother was also suspected to have HTNB, considering her reported short stature, brachydactyly, and HTN (Figure 4).

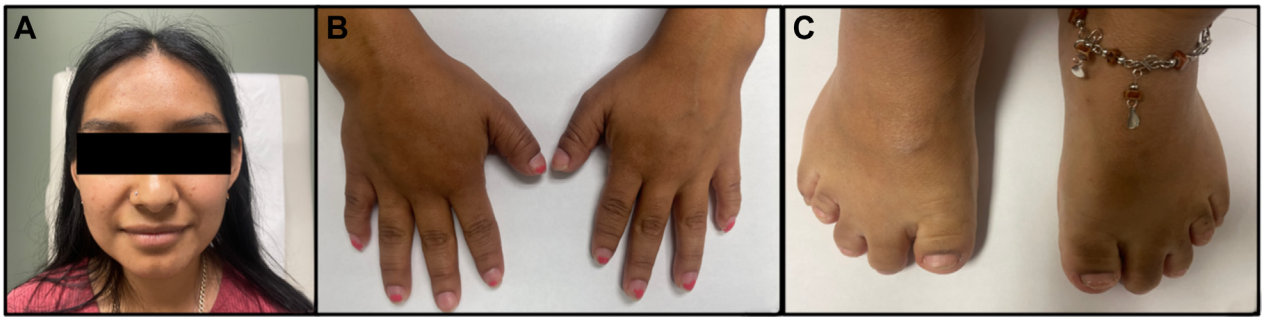
MANAGEMENT

Given the likely diagnosis of HTNB, the patient was initiated on antihypertensive treatment to control her hypertension. She was initiated on enalapril and metoprolol for her hypertension and low-dose aspirin to prevent adverse cerebrovascular events. *PDE3A* gene testing was offered to the proband's mother.

DISCUSSION

HTNB (also known as Bilginturan syndrome) is a rare autosomal dominant syndrome with a prevalence of less than 1 in 1 million individuals.[1] Given the rarity of HTNB, the gene associated with the development of HTNB was previously unknown.

FIGURE 1 Phenotypic Manifestations of the Proband



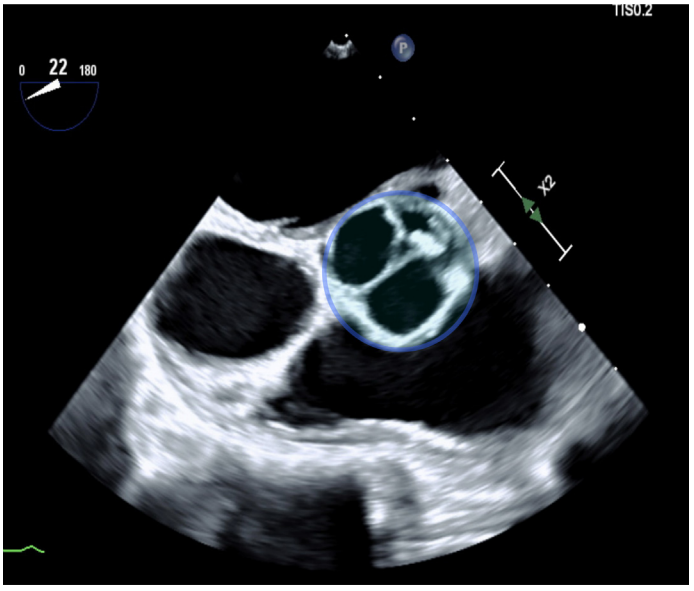
(A) Normal/lack of facial dysmorphic features. (B, C) Bilateral brachydactyly of the hands and feet.

Advances in genomics allowed the use of whole-genome sequencing to identify gain-of-function mutations in the *PDE3A* gene among individuals with HTNB in 2015.[2] The role of mutations in the *PDE3A* gene in HTNB was further supported by in vitro and animal-based studies.[2,3] The *PDE3A* gene encodes phosphodiesterase, which catalyzes the degradation of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP).[1,2,4] cAMP and cGMP are secondary messengers that regulate various cardiometabolic and chondrogenic pathways.[1-4] *PDE3A* pathogenic variants are associated with increased phosphodiesterase activity, resulting in lower cAMP and cGMP levels.[3,4] The lower cAMP and cGMP levels have been associated with symptoms such as brachydactyly, short stature, and age-dependent HTN.[1,2]

Patients with HTNB are at an increased risk of death by stroke before the 50 years of age if their HTN remains untreated.[1,5,6] Early identification of HTN in patients with HTNB is critical as timely intervention with antihypertensive medications can mitigate the risks of stroke and hypertension-related organ damage.[5,6] Considering that HTNB is attributed to a gain of function mutation in the *PDE3A* gene, it is plausible that inhibition of *PDE3* in individuals with HTNB may be beneficial. Therefore, there is a need to investigate the role of phosphodiesterase-3 inhibitors such as dipyridamole in the management of HTNB.

The current case report highlights the need to promote genomic research to identify pathogenic mutations and understand the pathophysiology of the disease. When the patient initially presented at 6 years of age, the presence of short stature and BAV prompted consideration for Turner syndrome, whereas the presence of HTN and brachydactyly were suggestive of HTNB. Although genetic testing was conducted at that time, the association of mutations in the *PDE3A* gene with HTNB had not yet been discovered, which prevented a definitive diagnosis of HTNB from being made. However, advances in genomics have led to the identification of several novel variants in the *PDE3A* gene associated with HTNB.[2,3] The pathogenicity of the missense mutation our patient harbored is supported by the identification of this variant in a family with HTNB.[3] Additionally, experiments using CRISPR-Cas9 rat models and cardiomyocytes differentiated from induced pluripotent stem cells encoding the variant support the pathogenicity of the variant identified in the patient.[3]

FIGURE 2 **Transesophageal Echocardiogram Showing Bicuspid Aortic Valve in the Proband**



Bicuspid aortic valve highlighted in blue.

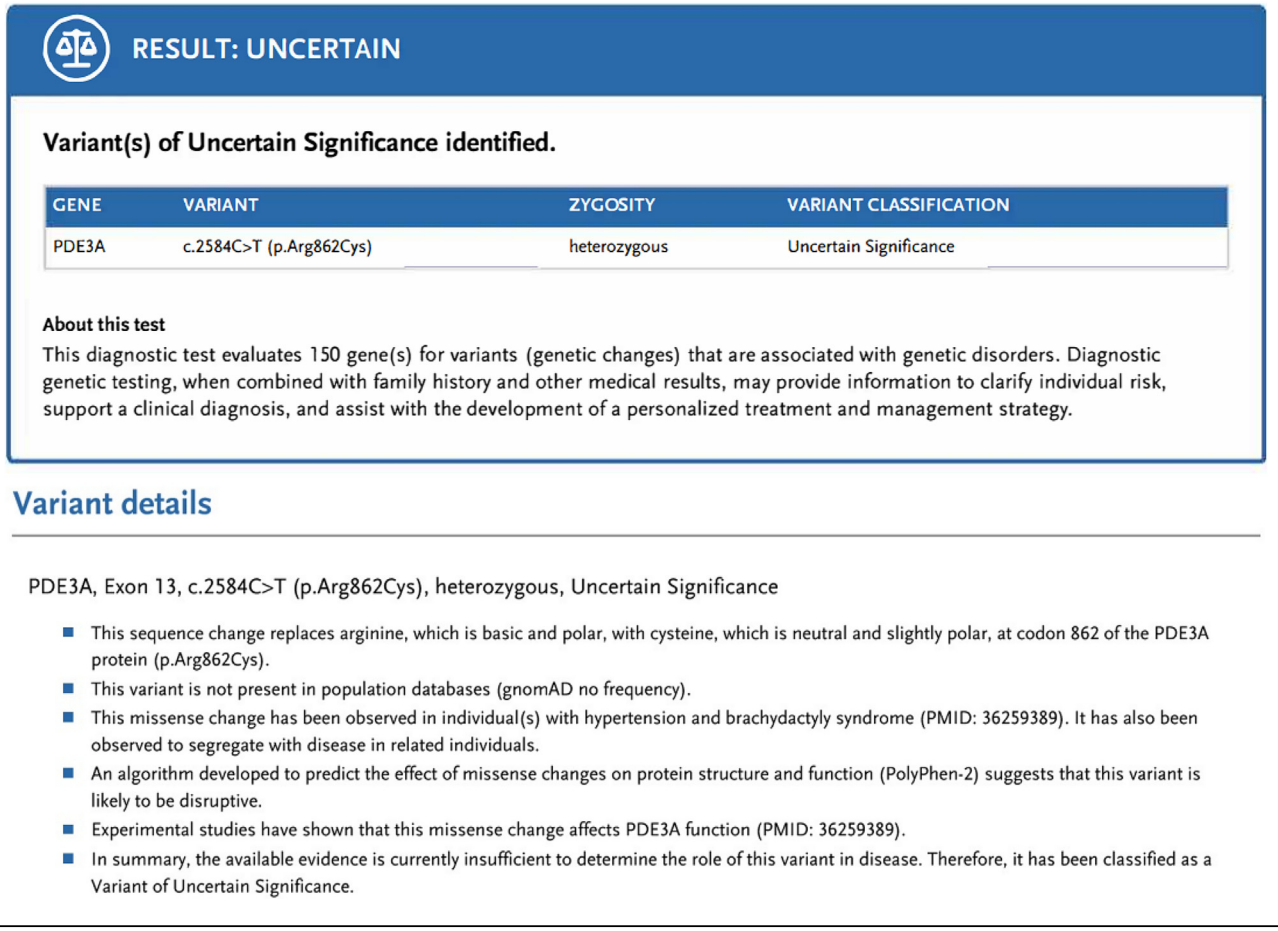
This report is the first to describe a case of HTNB with BAV. The presence of BAV in carriers of a *PDE3A* gene mutation has not been previously described. However, mutations in the *PDE3A* gene are known to decrease cAMP and cGMP levels, which may precipitate endothelial dysfunction.[4] Endothelial dysfunction has been associated with BAV and BAV-related aortopathies.[7] The endothelial dysfunction in carriers of a *PDE3A* gene mutation may play a role in the development of BAV.

The current report is limited by the unavailability of genetic testing in the patient's mother, which precluded the assessment of the segregation of the identified variant in the family.

CONCLUSIONS

This case report emphasizes the importance of genetic testing in the diagnosis of HTNB. The development of large biobanks with genetic data and the promotion of genetic research may lead to the identification of additional novel genetic variants and provide insights into the pathogenesis of disease.

FIGURE 3 Genetic Testing Results



RESULT: UNCERTAIN

Variant(s) of Uncertain Significance identified.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
PDE3A	c.2584C>T (p.Arg862Cys)	heterozygous	Uncertain Significance

About this test

This diagnostic test evaluates 150 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

Variant details

PDE3A, Exon 13, c.2584C>T (p.Arg862Cys), heterozygous, Uncertain Significance

- This sequence change replaces arginine, which is basic and polar, with cysteine, which is neutral and slightly polar, at codon 862 of the PDE3A protein (p.Arg862Cys).
- This variant is not present in population databases (gnomAD no frequency).
- This missense change has been observed in individual(s) with hypertension and brachydactyly syndrome (PMID: 36259389). It has also been observed to segregate with disease in related individuals.
- An algorithm developed to predict the effect of missense changes on protein structure and function (PolyPhen-2) suggests that this variant is likely to be disruptive.
- Experimental studies have shown that this missense change affects PDE3A function (PMID: 36259389).
- In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

Abbreviated genetics report that displays the proband's variant and its clinical significance.

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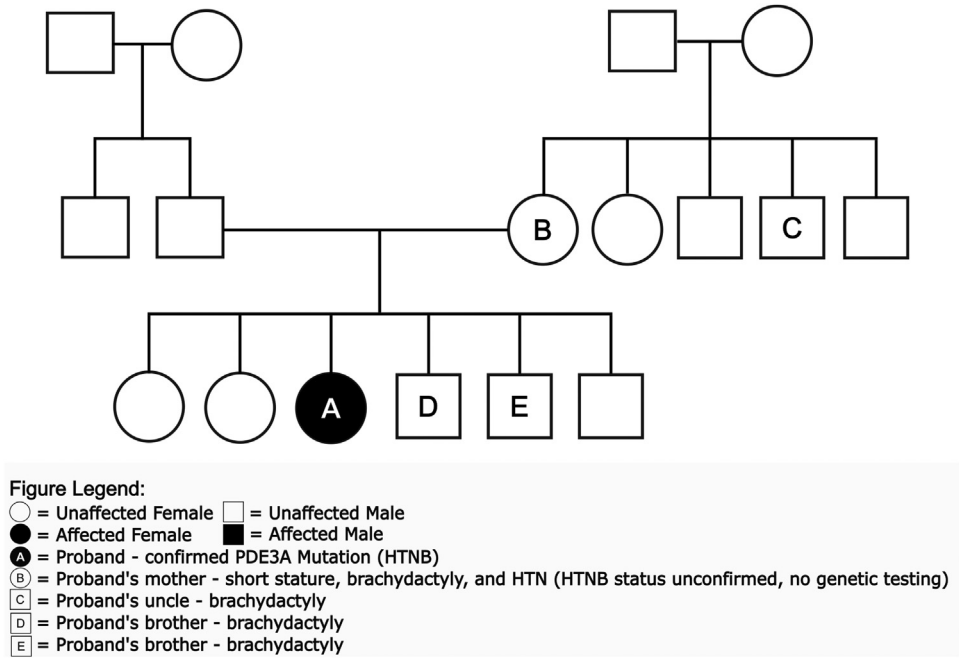
FIGURE 4 **Family Pedigree**



Only the proband underwent genetic testing in the family.

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KEY WORDS **bicuspid aortic valve, Bilginturan syndrome, brachydactyly, hypertension**