

ELN-Associated Supravalvular Aortic Stenosis With a Williams Syndrome-Like Cardiovascular Phenotype in a Neonate: A Case Report

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Abstract

Williams syndrome (WS) is a rare microdeletion disorder affecting chromosome 7q11.23, including the *ELN* gene, which encodes elastin. Haploinsufficiency of *ELN* leads to vascular abnormalities, such as supravalvular aortic stenosis (SVAS), pulmonary stenosis, and coronary artery disease. SVAS can also occur in isolation due to heterozygous loss-of-function variants in *ELN*, independent of the broader WS deletion.

We present a case of a term neonate with a Grade 4/6 systolic ejection murmur who underwent echocardiography, revealing severe supravalvular pulmonary stenosis, branch pulmonary artery stenosis, and mild SVAS. Due to these WS-like features, a chromosomal microarray was performed, which ruled out WS. Cardiac catheterization for pulmonary artery balloon angioplasty was complicated by ventricular fibrillation, requiring resuscitation. Angiography identified coronary artery stenosis. Intraoperative cardiac instability raised concerns for an *ELN*-related vasculopathy. Whole-exome sequencing (WES) revealed an *ELN* frameshift mutation in exon 6.

This case describes a neonate with a WS-like cardiovascular phenotype but no WS-associated deletion, instead harboring a heterozygous pathogenic *ELN* loss-of-function variant consistent with isolated SVAS, thereby challenging genotype-phenotype correlations.

Categories: Cardiology, Genetics, Pediatrics

Keywords: *eln* gene, genotype-phenotype correlation, pediatric congenital heart disease, supravalvular aortic stenosis, williams syndrome

Introduction

Williams syndrome (WS) is a rare microdeletion disorder that results in the loss of a set of genes on chromosome 7q11.23 [1]. These genes include the *ELN* gene, which encodes elastin. The loss of *ELN*, resulting in vascular abnormalities, plays a crucial role in the development of supravalvular aortic stenosis (SVAS) and diffuse arteriopathy associated with valvular and supravalvular pulmonary stenosis, aortic arch coarctation and hypoplasia, and mitral valve stenosis. Additional vascular abnormalities include coronary artery stenosis, hypertension, and vessel stiffness, all of which contribute to significant cardiac complications. The underlying genetic basis is strongly linked to deletions in the *ELN* gene, which is responsible for the vascular and connective tissue manifestations of the syndrome [2]. Due to these cardiovascular abnormalities, individuals with WS are at an increased risk of complications, particularly with anesthesia, necessitating careful perioperative management.

This case report describes a rare case of a neonate with supravalvular pulmonic stenosis, severe branch pulmonary artery stenosis, and SVAS, which are typically seen in WS. However, genetic testing ruled out WS and instead identified a pathogenic heterozygous variant in the *ELN* gene. This unique presentation challenges the conventional understanding of the relationship between *ELN* mutations and vascular abnormalities and opens the door to further discussions of the pathophysiology and clinical manifestations of non-syndromic *ELN* gene mutations.

Case Presentation

Our cardiac clinic was consulted by the newborn nursery for the evaluation of a systolic murmur in a term appropriate-for-gestational-age (AGA) female infant, born via uncomplicated vaginal delivery to a 35-year-old multigravida mother with adequate prenatal care. A review of systems revealed no significant abnormalities or family history of any genetic disorder.

Physical examination was unremarkable aside from a Grade 4/6 systolic ejection murmur without a thrill, best auscultated at the left upper sternal border and radiating to the bilateral axillae. An echocardiogram performed at 24 hours of life revealed mild SVAS with a peak gradient of 15 mmHg, significant supravalvular

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pulmonary stenosis with a peak gradient of 48 mmHg, elevated gradients in the left pulmonary artery (up to 95 mmHg) and the right pulmonary artery (58 mmHg), right ventricular hypertrophy with septal flattening, insufficient tricuspid regurgitation to estimate right ventricular systolic pressure, a small bidirectional patent foramen ovale (PFO), and aortic coarctation with a gradient of 25–30 mmHg.

Given the echocardiographic findings, a chromosomal microarray analysis was performed to rule out WS and other genetic anomalies. The microarray did not show abnormalities consistent with WS but revealed a benign gain-of-function mutation on chromosome 14q32.33. The patient was then referred to a tertiary care center for catheterization, balloon pulmonary angioplasty, and stenting of the pulmonary arteries. The catheterization was complicated by ventricular fibrillation due to guidewire manipulation in the right ventricle. The patient was converted back to sinus rhythm after chest compressions, a dose of epinephrine, and synchronized cardioversion. During catheterization, angiography revealed severe supralvalvular pulmonary stenosis, significant bilateral branch pulmonary artery stenosis, mild SVAS, critical left main coronary artery stenosis, and brisk filling of the right coronary artery (Figures 1–2). These findings, in addition to the cardiac arrest under general anesthesia, raised concerns for WS despite the previous chromosomal microarray findings of a benign gain-of-function mutation on chromosome 14q32.33. Therefore, whole-exome sequencing (WES) was performed and revealed a novel autosomal dominant heterozygous frameshift mutation in exon 6 of the ELN gene. Specifically, the variant was c.281dup: p.(Gly95Trpfs*4) in exon 6, resulting in the altered sequence CCTG[dupG]TGGA. This duplication mutation leads to a novel frameshift variant of the ELN gene that is predicted to result in protein truncation or nonsense-mediated decay, a known mechanism of disease associated with loss of function of this gene. It was stated in the report that this mutation had not previously been identified as either a pathogenic or a benign variant in the literature. It was interpreted as a pathogenic variant.



FIGURE 1: Aortic angiogram showing critical left main coronary artery stenosis and the normal right coronary artery.

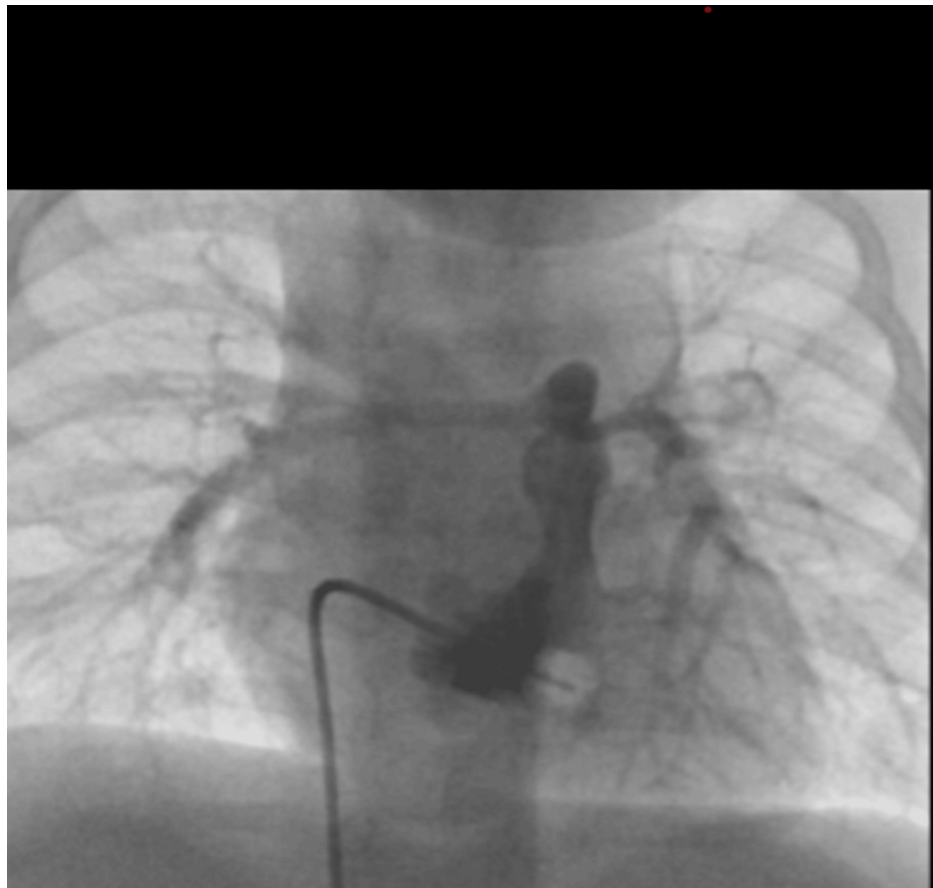


FIGURE 2: Right ventricular angiogram showing severely hypoplastic right and left pulmonary arteries.

Later, surgical repair was performed, including a three-patch aortic repair, homograft patch augmentation of the proximal left coronary artery, and pulmonary artery augmentation. Postoperative transesophageal echocardiography (TEE) showed good cardiac function, mild residual pulmonary stenosis, and adequate coronary artery flow (Figures 3-4). The patient is currently hemodynamically stable and growing appropriately.

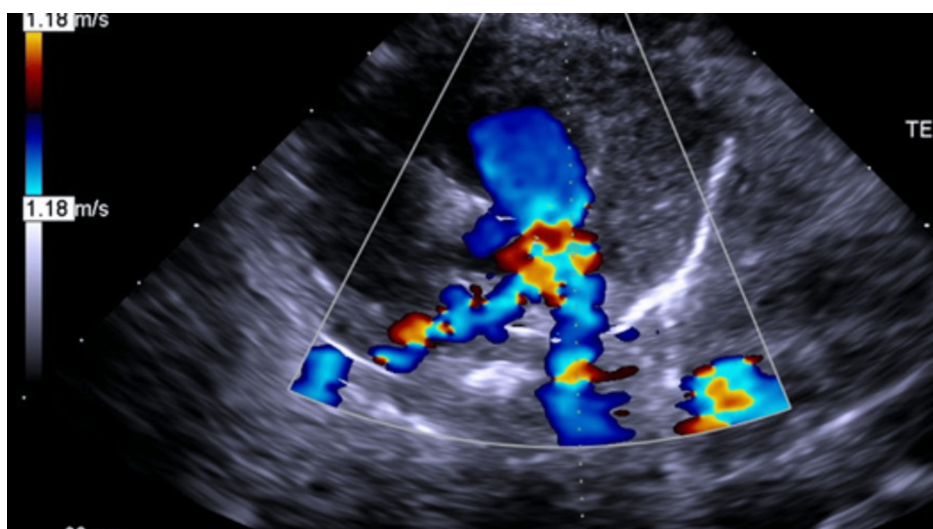


FIGURE 3: Parasternal short-axis view showing turbulent flow in main and branch pulmonary arteries.

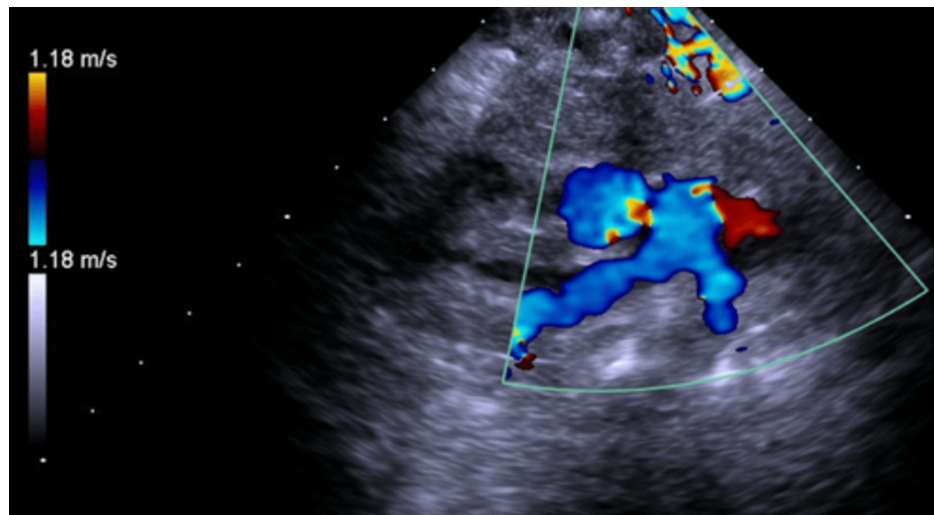


FIGURE 4: Parasternal short-axis view showing non-turbulent flow in main and branch pulmonary arteries post-surgery.

Discussion

Elastin, encoded by the *ELN* gene, plays a fundamental role in maintaining vascular integrity and elasticity. Mutations in *ELN* are well-established contributors to vascular disease, particularly in cases of WS, where microdeletions at chromosome 7q11.23 lead to *ELN* deficiency and result in characteristic cardiovascular abnormalities, such as SVAS and pulmonary artery stenosis [1]. However, our case report presents a novel frameshift mutation in exon 6 of the *ELN* gene (c.281dup: p.(Gly95Trpfs*4)) that mimics the WS cardiovascular phenotype in the absence of the typical chromosomal deletion. This case highlights the need to expand genetic testing beyond microarray analysis in patients with unexplained congenital vascular anomalies.

ELN is a crucial extracellular matrix protein necessary for normal vascular development and function. *ELN* mutations have been implicated in a spectrum of vascular disorders, including autosomal dominant cutis laxa and isolated SVAS [3]. *ELN* haploinsufficiency, as seen in WS, leads to abnormal *ELN* function, increased arterial stiffness, and progressive stenosis of large arteries, predisposing patients to critical cardiovascular complications, whereas dominant-negative variants, often involving late exons, are linked to autosomal dominant cutis laxa [3]. Our patient's phenotype, marked by severe SVAS, severe supraaortic pulmonary stenosis, branch pulmonary artery stenosis, and left main coronary artery stenosis, mirrors the vascular pathology observed in WS but is driven by a novel frameshift mutation rather than a microdeletion.

Previous studies have identified pathogenic *ELN* mutations contributing to SVAS and other vascular pathologies [4-6]. The c.281dup: p.(Gly95Trpfs*4) mutation found in our case introduces a premature stop codon, leading to either protein truncation or nonsense-mediated decay, a mechanism frequently associated with *ELN*-driven vascular disease [7]. This mechanism aligns with other documented *ELN* mutations resulting in non-syndromic SVAS and diffuse arteriopathy [8].

In our case, chromosomal microarray failed to identify WS, highlighting the necessity for comprehensive genetic sequencing when evaluating unexplained congenital vascular stenosis. The patient's severe coronary artery stenosis, an uncommon but life-threatening feature of *ELN*-related disorders, required urgent surgical intervention. The significant perioperative instability observed in this case aligns with the literature documenting anesthetic risks in patients with *ELN* mutations due to abnormal vascular compliance and coronary ischemia.

This case reinforces the importance of WES in neonates with congenital cardiovascular abnormalities when initial microarray testing is unremarkable. Genetic analysis allowed us to establish a definitive diagnosis and guide perioperative decision-making, ultimately leading to successful surgical repair. The findings also prompt further investigation into genotype-phenotype correlations in non-syndromic *ELN* mutations, thereby expanding our understanding of elastinopathies beyond WS.

Conclusions

This case describes an *ELN* exon 6 frameshift mutation presenting with a WS-like cardiovascular phenotype, expanding the spectrum of *ELN* mutations contributing to congenital vascular diseases. This case challenges conventional genotype-phenotype correlations in *ELN*-related arteriopathy and reveals the pathogenic

potential of *ELN* mutations beyond classical WS-associated deletions. The findings highlight the necessity of advanced genetic testing, particularly WES, in neonates with unexplained congenital vascular stenosis to ensure accurate diagnosis and appropriate clinical management.

Furthermore, this discovery provides valuable insight into the molecular mechanisms underlying *ELN*-related vasculopathy. A multidisciplinary approach involving cardiology, genetics, and surgical teams is crucial in managing such complex cases. Future research should explore the prevalence of *ELN* exon 6 mutations in patients with vascular pathologies to improve diagnostic algorithms and optimize personalized treatment strategies.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Supervision: Jamshaid Akhtar, Srilatha Alapati, Rakesh Donthula, Kawthar Faour

Disclosures

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