Supravalvular aortic stenosis (SVAS), a localized narrowing of the aorta just distal to the aortic valve, has been encountered sporadically for over 130 years. In 1961, Williams reported 4 patients with SVAS who shared syndromic features, including short stature, mental retardation, peripheral pulmonary artery stenoses, and a characteristic facies. Beuren et al reported additional cases, and this syndrome is now known both as Williams syndrome (WS) and Williams–Beuren syndrome. Familial clustering of nonsyndromic SVAS and WS was later identified, bolstering the notion that both WS and SVAS are genetically based.

Williams hypothesized that SVAS was caused by a combination of medial hypertrophy and aortic wall constriction, but proposed no underlying mechanisms. Others proposed intimal fibrous thickening, due to hyperplasia and excessive collagen deposition (Figure [A]), as potential pathogeneses. However, the mechanisms that might account for cell proliferation and fibrosis remained uncertain. In 1993, Keating’s group discovered that (1) individuals with both familial and sporadic WS were hemizygous at the elastin locus and (2) members of a family with SVAS had a balanced translocation that disrupted the elastin gene and cosegregated with the SVAS phenotype. Because elastin is a major component of the aortic wall, comprising ~50% of total protein, and because aortas of individuals with SVAS have decreased elastin content and abnormal elastin architecture, elastin deficiency seemed the obvious underlying cause of SVAS. This conclusion was solidified by detection of elastin point mutations in individuals with SVAS. Keating’s group speculated that SVAS associated with elastin deficiency was caused by decreased aortic elasticity leading to endothelial dysfunction, and that this nondenuding endothelial injury led to intimal proliferation, fibrosis, and stenosis (Figure [B]).

By knocking out elastin in the mouse germ line, Li et al established an animal model with potential to reveal mechanistic connections between elastin haploinsufficiency and SVAS. An initial surprising finding was that mice with complete elastin deficiency (Eln−/− genotype) died perinatally of obstructive arterial stenosis, and reorientation of aortic SMC from a circumferential to an axial pattern. These impressive phenotypes were unaccompanied by evidence of endothelial damage or dysfunction, arguing against the mechanism originally proposed by Keating’s group. In contrast, haploinsufficient Eln+− mice (potentially a more authentic model of human SVAS and WS) were viable, with thinner aortic elastic laminae and significantly more lamellar units (lamellar unit—an elastic lamina with an adjacent layer of SMC) than Eln−/− mice. In support of clinical relevance of the Eln+− mouse model, aortic samples of 2 humans with SVAS (taken from regions without stenosis) also had far more lamellar units than controls. However, Eln+− mice had neither aortic wall thickening nor SVAS. These studies established elastin as a major regulator of aortic development and structure; however, they did not reveal how elastin deficiency causes SVAS.

Increased aortic SMC proliferation in Eln+− mice seemed to offer the best clue to SVAS pathogenesis (Figure [C]). A key role for SMC proliferation in aortopathy related to elastin deficiency was supported by the hyperplastic appearance of SVAS tissue, in vitro evidence of increased proliferation in SMC cultured from aortas of patients with WS and nonsyndromic SVAS, and experiments showing that elastin blocks cell proliferation in vitro and intimal growth in vivo. More recent reviews concurred that excessive SMC proliferation and migration triggered by low levels of aortic elastin were the most likely cause of vascular stenosis associated with human elastin haploinsufficiency. However, ex vivo comparison of aortas of Eln+− and Eln−/− mice revealed that—when normalized to blood pressure—Eln+− aortas had smaller inner and outer diameters along with thinner—not thicker—walls. These findings suggested that—in mice—elastin haploinsufficiency impairs aortic distensibility but does not increase SMC proliferation. These results—along with the absence of SVAS in Eln−/− mice—also raised concern that the Eln−/− mouse might not accurately model SVAS associated with elastin deficiency in humans. This concern is supported by a lower than average similarity of human and murine elastin proteins (64% identity at the amino acid level) as well as different numbers of exons and variations in elastin exon content and abnormal elastin architecture, elastin deficiency seemed the obvious underlying cause of SVAS. This conclusion was solidified by detection of elastin point mutations in individuals with SVAS. Keating’s group speculated that SVAS associated with elastin deficiency was caused by decreased aortic elasticity leading to endothelial dysfunction, and that this nondenuding endothelial injury led to intimal proliferation, fibrosis, and stenosis (Figure [B]).

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To resolve this problem and potentially produce a more authentic mouse model of human SVAS, Hirano et al rescued perinatal lethality of the Eln−/− genotype by breeding in a human ELN transgene. The human ELN transgene was a genomic clone inserted into the mouse genome with aid of a bacterial artificial chromosome (an approach intended to achieve physiological expression and regulation of human elastin in mice). Eln+− ELN−/− mice were viable, with aortic elastin levels only ~35% of those in Eln−/− aortas. The potential
for \( \text{Eln}^{-/-} \ \text{ELN}^{+/-} \) mice to better model human elastin haploinsufficiency was suggested by genotype-specific increases in elastic lamina breaks and medial thickening, as well as modestly reduced pressure-normalized ex vivo outer aortic diameters.\(^{23}\) However, no luminal stenoses were reported in these mice, and SMC proliferation was not investigated.

In this issue of \textit{ATVB}, a report by Jiao et al\(^8\) enhances our understanding of the pathogenesis of aortic obstruction associated with elastin deficiency. The authors used a combination of meticulous in vivo, in situ, and ex vivo approaches to investigate the size, structure, and mechanical properties of aortas of (elastin-deficient) \( \text{Eln}^{-/-} \ \text{ELN}^{+/-} \) mice (termed human bacterial artificial chromosome [hBAC]-mNull mice by Jiao et al\(^8\)). Compared with controls, hBAC-mNull aortas had smaller external and internal diameters but were significantly longer and heavier. Postnatal time-course data showed that hBAC-mNull aortas had decreased circumferential growth, but significantly increased axial growth. Compared with aortas of mice with higher levels of elastin, hBAC-mNull aortas also had thicker medias. However, their medial cross-sectional areas were normal, with no increase in number of medial cells per cross section. Reduced circumferential growth of hBAC-mNull aortas (accompanied by secondary medial thickening; Figure [D]) resulted in a large (70%) reduction in ascending aortic lumen area compared with mice with normal or near-normal levels of elastin. This is the most impressive aortic stenosis yet reported in an elastin-haploinsufficient mouse. Although hBAC-mNull aortas were less distensible than control aortas in vivo, this deficit could account for only a small percentage of the observed luminal narrowing. Finally, aortic SMC of hBAC-mNull mice had a higher proliferative rate both in vivo and in culture. Jiao et al\(^8\) also examined aortic tissue from a single human WS subject who died suddenly. This aorta had a relatively small external diameter, a thick wall, normal medial area and cell number, loss of elastin, and accumulation of collagen; features that are all shared with the \( \text{Eln}^{-/-} \ \text{ELN}^{+/-} \) aortas. The authors concluded that—contrary to widely held models\(^{9,10,12,17,18,20,24}\)—increased SMC proliferation is likely not the underlying cause of aortic stenosis and lumen loss associated with elastin haploinsufficiency. Rather, aortic lumen narrowing results from deficient circumferential growth, incidentally accompanied by excess axial growth.

Jiao et al\(^8\)’s findings are elegant, exciting, and potentially paradigm shifting. Nevertheless, this article raises 2 major—and related—questions, answers to which will determine the long-term impact of this work. The first question is largely clinical: is aortopathy of the \( \text{Eln}^{-/-} \ \text{ELN}^{+/-} \) mouse an authentic model of the aortopathy in human SV AS and WS? Jiao et al\(^8\) validated their findings in \( \text{Eln}^{-/-} \ \text{ELN}^{+/-} \) mice in relation to only 1 human WS specimen. This \( n=1 \) data set precludes confident conclusions,
especially because WS has substantial phenotypic variability.\textsuperscript{20} The key finding of aortic narrowing with unchanged medial area and cellularity in the single WS aorta is uncertain because aortic diameter was not indexed to body size (these data were not available), and WS individuals are of significantly smaller stature.\textsuperscript{20,25} Moreover, this WS individual does not seem to have had clinically significant SVAS. Noninvasive studies of larger numbers of WS and SVAS individuals using magnetic resonance imaging and examination of additional pathological specimens are needed to determine whether abnormal aortic growth and morphology in Eln\textsuperscript{−/−} ELN\textsuperscript{+/−} mice phenocopy aortic growth patterns in WS humans and—more importantly—in humans with nonsyndromic SVAS.

The second important question raised by Jiao et al\textsuperscript{8} is more complex: are the molecular mechanisms that drive aortopathy in the Eln\textsuperscript{−/−} ELN\textsuperscript{+/−} mouse unique to this mouse model, identical to the mechanisms that drive aortopathy in human elastin haploinsufficiency, and therefore especially likely to reveal mechanisms that underlie aortopathy in human SVAS and WS? The Eln\textsuperscript{−/−} ELN\textsuperscript{+/−} mouse used by Jiao et al\textsuperscript{8} relies on expression of human elastin in a mouse, a setting that might facilitate nonphysiological molecular interactions. The assumption inherent in this work—that the molecular interactions that drive elastin-related human aortopathy are more accurately represented in Eln\textsuperscript{−/−} ELN\textsuperscript{+/−} mice than in Eln\textsuperscript{−/−} mice—is untested because these molecular interactions are not known. Further work is required to define these interactions, thereby facilitating an objective assessment of the fidelity with which the Eln\textsuperscript{−/−} ELN\textsuperscript{+/−} mouse reproduces the pathology of human elastase haploinsufficiency.

If borne out, the novel model of SVAS pathogenesis proposed by Jiao et al\textsuperscript{8} would fundamentally alter our understanding of SVAS and redirect the development of medical therapy. As concerns medical therapy, this new work sounds a cautionary note: significant aortic disease is already present in 3-week-old Eln\textsuperscript{−/−} ELN\textsuperscript{+/−} mice, raising the possibility that postnatal medical therapy may be too late to reverse SVAS. We look forward to continued outstanding work by the Tellides group and others that will further elucidate the physiological and pathogenic roles of aortic elastin and potentially pave the way for medical therapy of SVAS.

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None.

**References**


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What's the Skinny on Elastin Deficiency and Supravalvular Aortic Stenosis?
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