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CONSEQUENCES OF ELASTIN GENE MUTATIONS IN AUTOSOMAL DOMINANT CUTIS LAXA AND SUPRAVALVULAR AORTIC STENOSIS

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ABSTRACT

Extracellular matrix (ECM) and associated molecules have a myriad of roles comprising cell-cell communication, cell proliferation, migration, cell differentiation, development and survival. Elastic fibers are major insoluble components of ECM that are vital for connective tissues including large arteries, skin, lung, ligaments, and auricular cartilage. Their function is to provide elastic stretch and recoil to the conncevtive tissues. Elastin (ELN) is the key insoluble protein in the elastic fibers and it is the primary provider of elasticity and resilience. Structural abnormalities in elastin lead to a decrease in the integrity of elastic tissues including skin, lungs and large blood vessels. Therefore, elastin gene mutations lead to several skin, cardiovascular and pulmonary phenotypes including Williams Beuren syndrome, autosomal dominant cutis laxa (ADCL) and supravalvular aortic stenosis (SVAS). ADCL is characterized by loose and inelastic skin, pulmonary emphysema, aortic root dilation, and peripheral pulmonary aortic stenosis. SVAS is characterized by narrowing of the ascending aorta. While ADCL is caused by the frameshift mutations at the 3' end of the ELN gene, missense and truncation mutations throughout the ELN gene lead to SVAS. In this review, we discussed and compared the latest information including clinical presentation, mutational spectrum and molecular mechanisms in ADCL and SVAS.

Keywords: *elastic fibers, elastin, autosomal dominant cutis laxa, supravalvular aortic stenosis*

INTRODUCTION

Elastic fibers are components of the extracellular matrix that contribute resilience to tissues and bind and regulate transforming growth factor beta (TGFβ) [1]. Elastin is the crucial part of elastic fibers. Elastin gene (*ELN*) mutations cause several phenotypes including WBS, SVAS and ADCL. The purpose of this review is to describe heritable diseases caused by elastin gene mutations. First, this review discusses the extracellular matrix, elastic fibers and the elastin protein. In the final section, the review focuses on the inherited diseases caused by elastin mutations including ADCL and SVAS and describes the clinical presentation, mutational spectrum and molecular mechanisms of each disease.

EXTRACELLULAR MATRIX

The ECM acts as a scaffold that supports cells in all tissues and organs. The ECM is comprised of a fibrous material, including collagen fibers, microfibrils and elastic fibers and ground substance surrounding the fibers, including proteoglycans and glycoproteins.

The ECM has roles in cell-cell communication, cell proliferation, migration, cell differentiation, development, and survival. The ECM is also crucial for the storage of growth factors, cytokines and ECM-remodeling enzymes [1].

Collagen fibers are a major component of ECM, which provide tensile strength and have roles in cell adhesion, chemotaxis and migration and tissue morphogenesis [2]. Elastic fibers complement collagen fibers to provide resilience to the tissues, whereas glycoproteins contribute to tissue cohesiveness. Proteoglycans are bulky polysaccharides (glycosaminoglycans, GAGs) covalently attached to relatively smaller core proteins, which counteract compressive forces and are important in cell signaling and wound healing [3].

Elastic fibers

Elastic fibers are major insoluble components of ECM that are vital for connective tissues including large arteries, skin, lung, ligaments, and auricular cartilage. Elastic fibers show tissue-specific and morphologically distinct networks based on the elasticity requirements of tissues [4]. Elastic fibers are composed of two primary components: an inner core of cross-linked elastin and microfibrils [4]. In addition, several 'accessory' molecules interact with microfibrils and elastin as well as its precursor, tropoelastin [4].

The thick elastic fiber networks in the reticular dermis and thin fibers in the papillary dermis provide skin elasticity. Highly branched networks of elastic fibers that provide respiratory expansion and recoil are main providers of pulmonary elasticity. Arterial elastic fibers form lamellar layers for vascular elasticity [5]. Elastic fibers also have a crucial role in vascular smooth muscle cell differentiation during arterial development [6]. In addition, elastic fibers also regulate the bioavailability of TGFβ family [7].

Elastin

Elastin is the key insoluble protein in the elastic fibers (90%) [7] and it is the primary provider of elasticity and resilience. At first, elastin is synthesized as tropoelastin, a precursor protein of 60-70 kDa secreted from elastogenic cells such as fibroblasts, smooth muscle cells (SMCs) and auricular chondrocytes [7]. Its primary structure includes valine-, proline-, and glycine-rich hydrophobic domains and hydrophilic cross-linking domains, which are rich in lysine and alanine **(**Hydrophobic domains are important during the self-aggregation of tropoelastin by coacervation [8]. Coacervation brings tropoelastin monomers together, and their association is stabilized by cross-links, known as desmosines or isodesmosines [9]. The asymmetric structure of elastin includes an N-terminal part that provides spring-like properties and a C-terminal part that has a role in cell adhesion by αvβ3 integrin and cell surface proteoglycans [10]. The human elastin gene is localized to chromosome 7q11.2 and has 34 exons spanning 45 kb of the genome [11]. Human elastin primary transcript undergoes alternative splicing leading to many different mRNA isoforms.

Elastin is a crucial protein in the aorta and great arteries. $ELN^{-/-}$ mice die immediately after birth due to the vascular obstruction, caused by an enhanced proliferation of smooth muscle cells [12]. In contrast, $ELN^{+/-}$ mice survive until adulthood and show systemic hypertension, enhanced a number of elastic lamellae, the elastin layers associated with SMCs [12, 13] and a thinner wall of blood vessels [14].

INHERITED DISEASES CAUSED BY ELASTIN MUTATIONS

Elastin gene mutations result in several skin, cardiovascular and pulmonary phenotypes. Elastinopathies, including Williams-Beuren Syndrome (WBS), supravalvular aortic stenosis (SVAS), and autosomal dominant cutis laxa (ADCL) are all caused by the mutations in the *ELN* gene [15, 16, 17] **(Table 1)**. Familial SVAS and ADCL are caused by two distinct groups of point mutations within the elastin gene. In contrast, WBS is caused by the microdeletions of the region on 7q11, which includes the *ELN* gene [15] and approximately 26-28 other neighboring genes [18]. The clinical characteristics include intellectual disability, connective tissue defects, metabolic defects, and cardiovascular malformations, including SVAS.

Table 1. *Elastinopathies*

Disease	Mutations	Clinical presentations	Molecular mechanisms
SVAS	Heterozygous loss-of-function mutations	Narrowing or obstruction of the aorta	Haploinsufficiency
WBS	Microdeletions of the region on chromosome 7q11.23; 25-28 genes including *ELN*	Connective tissue and metabolic defects, cardiovascular abnormalities	Haploinsufficiency
ADCL	Heterozygous frameshift mutations	Loose skin, aortic stenosis, pulmonary emphysema	Dominant-negative or toxic gain of function

SVAS: supravalvular aortic stenosis; WBS: Williams-beuren synrome; ADCL: autosomal dominant cutis laxa

Autosomal dominant cutis laxa

Cutis laxa (CL) is a heterogeneous group of connective tissue disorders caused by the elastic fiber abnormalities [19]. Acquired and inherited forms of cutis laxa patients show loose, inelastic, redundant and sagging skin. There are autosomal dominant, autosomal recessive and X-linked recessive inherited forms of CL and each has different clinical manifestations [19]. Human genetic studies have identified several genes in different forms of cutis laxa comprising A*LDH18A1, ATP6V0A2, ATP7A, EFEMPS/FBLN4, ELN, FBLN5, LTBP4, PYCR1* and *RIN2* [19].

Clinical presentation

The ADCL (OMIM #123700) is mostly diagnosed during early childhood, however, it might appear in late childhood or early adulthood. An aged-appearance as a result of redundant and inelastic skin, prominent ears, long philtrum, high forehead, hoarse voice and beaked nose are the most important facial characteristics of ADCL patients [19]. Clinical characteristics of ADCL can be mild to benign [19]. However, severe systemic manifestations can be present including pulmonary emphysema [20,21], aortic root dilation (ARD) [22], hernia [22] and peripheral pulmonary aortic stenosis [17]. The pulmonary and aortic lesions can result in significant morbidity and mortality and to date only symptomatic treatments are available. For example, severe pulmonary emphysema was addressed in at least one patient with ADCL using lung transplantation with satisfactory results [21]. Aortic root dilatation can be delayed by administration of beta-adrenergic blockers and rupture of aneurysms can be prevented by timely aortic root replacement [22].

Mutational spectrum

ADCL is mostly caused by frameshift mutations within the last five exons of the *ELN* gene which result in C-terminally elongated and secreted tropoelastin [20, 22,17, 23, 24, 25]. Unusual mutations include a heterozygous mutation in exon 25 of the elastin gene [28] and tandem duplication in the elastin gene [21]. A recent *de novo* intronic mutation has been found in intron 31 of a young ADCL patient [29]. Approximately 30% of the ADCL patients have *de novo* dominant *ELN* mutations. Recessively inherited missense mutations in *ELN* have been described in one family with cutis laxa to date, suggesting heterogeneity in terms of inheritance patterns in *ELN*-related cutis laxa [30]. Furthermore, identification of a heterozygous tandem duplication in the fibulin-5 gene of a cutis laxa patient raised the possibility of locus heterogeneity in ADCL [31].

Molecular mechanisms

The mutations in ADCL have several cellular and biochemical effects. Alternative splicing of exon 32 of the ELN gene and mutation-induced exon skipping often result in several mutant mRNA isoforms, and this makes harder to analyze the molecular consequences of the ADCL mutations in exons 30-32 [32]. ADCL mutations produce stable mutant mRNAs, and their protein products are secreted into the extracellular space [17, 23, 20, 21, 22], albeit with reduced efficiency in some cases [17, 21]. The histological abnormalities in ADCL include a disorganized and reduced amount of elastic fibers that result in loss of elasticity in the connective tissue [22]. The weak fibrillin-binding capacity of mutant tropoelastins leads to increased compliance and reduced stiffness of lung tissue [32].

A transgenic mouse model expressing human ADCL mutant elastin was generated using a human elastin cDNA with a c.2114_2138del mutation in exon 30 of ELN [32]. ADCL transgenic mouse had healthy skin and blood vessels. However, lung disease including airspace enlargement and severe emphysema was observed. Also, ADCL mice had enhanced endoplasmic reticulum stress, activation of the unfolded protein response (UPR), enhanced apoptosis and increased TGFβ signaling [32]. Similar findings were found in ADCL patient dermal fibroblasts with exon 30 mutations with longest missense

peptide sequence [25]. Lower amounts of insoluble elastin were found as a result of increased coacervation and elastin globule formation [25]. The partially secreted mutant tropoelastin hinders the binding of tropoelastin to fibulin-5 and fibrillin-1 and results in changes in elastic fiber assembly such as abnormalities in elastin accumulation on microfibrils in ADCL cells [26].

A human ADCL mutation (c.2012delG) in exon 30 was introduced into the human elastin bacterial artificial chromosome (BAC), then the mutant BAC was expressed as a transgene in mice with the wild-type human gene [34]. The mutant protein was incorporated into elastic fibers in the skin and lung resulting in some abnormalities, however, relatively low levels of the mutant protein was found in the aorta suggesting tissue-specific effects on elastin assembly [34]. These findings suggest different mechanisms of elastin assembly in aorta and lung and skin [34].

Enhanced TGFβ signaling has been found in patient fibroblasts [25] and in a transgenic mouse model [33], however, the precise mechanisms of TGFβ signaling alterations remain unclear, as does the possible contribution of these changes to the development of ADCL. The exact molecular mechanisms of how ELN mutations cause ADCL are still unknown, but dominant negative and toxic gain-of-function mechanisms have been proposed as molecular mechanisms for ADCL [33, 25].

Supravalvular aortic stenosis

Clinical presentation

SVAS (OMIM # 185500) occurs approximately 1 in 5,000 individuals. SVAS can occur as an isolated vascular disease that characterized by narrowing or obstruction of the ascending aorta [35] or as part of the WBS with identical clinical and structural characteristics [36, 37]. Segmental narrowing of major arteries such as pulmonary, carotid, cerebral, renal and coronary arteries may also be part of SVAS [38, 39]. In children, SVAS might result in more severe conditions, such as myocardial infarcts and sudden death [40]. Systemic hypertension, cerebrovascular accident, myocardial infarction and obstructive cardiomyopathy are the most severe and life-threatening clinical characteristics. Severe forms of SVAS may result in dyspnea, angina, systemic murmur and left ventricular hypertrophy. The primary treatment of SVAS is vascular surgery, which has an increased risk of morbidity and mortality.

Mutational spectrum

SVAS can be a part of WBS, a complex developmental genomic disorder, caused by microdeletions of the region on chromosome 7q11.23 encompassing 26-28 genes surrounding *ELN* [15, 18] or might be isolated. Several mutations consisting translocations [41, 42], gene deletions [43, 44, 45] and point mutations in the *ELN* [45, 46, 47, 48, 49] lead to the isolated form of SVAS. SVAS is inherited in an autosomal dominant manner. Most of the mutations produce premature termination codons and

result in haploinsufficiency through nonsense-mediated decay (NMD) [48]. If left untreated, SVAS might result in progressive heart failure and death.

Molecular mechanisms

Different types of heterozygous loss-of-function mutations in the *ELN* gene lead to SVAS [51]. As a result of point mutations, translocations and partial deletions in the *ELN* gene, premature stop codons, and unstable mRNA has been observed [50, 48]. Decreased levels of elastin mRNA [48, 51] and protein levels as well as the reduced elastin deposition indicate that SVAS is caused by null mutations in *ELN* [51] through haploinsufficiency.

Decreased levels of elastin in SVAS arteries leads to enhanced proliferation of vascular smooth muscle cells [53]. Hyperproliferation of smooth muscle cells (SMCs) in turn yields thicker, narrower arteries that lack flexibility [4]. Similar to SVAS patients, heterozygous elastin knockout mice (Eln+/-) showed hypertension, enhanced lamellar units in all elastic arteries, enhanced number of SMC layers and decreased elastin amount similar to SVAS patients [54]. Ge et al. generated a human induced pluripotent stem cell (iPSC) model of SVAS to study the mechanism of the disease [55]. Their model showed that SVAS SMCs had less organized networks of smooth muscle alpha-actin and increased proliferation rate than control iPSC-SMCs. Adding recombinant ELN or decreasing ERK1/2 activity have been reported as promising therapy, causing inhibition of SMC overproliferation [55]. Another potential SVAS therapy is rapamycin, an inhibitor of mTOR signaling, which rescues increased SMC proliferation and aortic obstruction [56]. Human iPSCs model of SVAS, SVAS patients, and elastin mutant mice showed enhanced integrin β3 expression and activation [57]. In addition, the inhibition of integrin β3 rescued aortic hyperproliferation and aortic stenosis, uncovering a potential therapeutic strategy for SVAS patients [57].

Comparison of ADCL and SVAS

SVAS and ADCL are two phenotypically different autosomal dominant inherited diseases caused by the mutations in the *ELN* gene. The clinical phenotype of ADCL includes predominantly abnormalities in skin and lung including aged appearance, pulmonary aortic stenosis, emphysema and aortic root dilatation and aneurysms. However SVAS patients have mostly stenoses the aorta and other elastic vessels, such as the pulmonary and coronary arteries. Thus, generally, ADCL predisposes to aneurysms whereas SVAS is associated with stenoses, an opposite vascular phenotype. However a shared vascular manifestation of both disorders is pulmonary artery stenosis [58].

Loss-of-function mutations including premature stop mutations, large intragenic deletions in SVAS lead to degradation of mRNA through NMD as a result of haploinsufficiency, whereas ADCL-causing mutations yield stable mRNAs and their protein products are secreted into the extracellular space, where the mutant protein interferes with elastic fiber assembly in a dominant-negative manner [17, 23, 20, 21, 22]. In addition, mutant ADCL tropoelastin also activates the unfolded protein response and apoptosis considered to be a toxic gain of function effects [33, 25]. ADCL is mostly

caused by the mutations within the 3' end of the *ELN* gene while SVAS mutations are broadly distributed in the *ELN* gene.

CONCLUSION

ECM and associated molecules have a myriad of roles comprising cell-cell communication, cell proliferation, and survival. Elastic fibers are integral parts of ECM of the connective tissues such as skin and large arteries. Their function is to provide elastic stretch and recoil to the connective tissues. The elastic fibers are assembled from fibrillin microfibrils and elastin and many accessory molecules facilitate the assembly process such as fibulins, LTBPs and lysyl oxidases. Structural abnormalities in elastin lead to a decrease in the integrity of elastic tissues including skin, lungs and large blood vessels. Therefore, elastin gene mutations lead to several skin, cardiovascular and pulmonary phenotypes. Microdeletions of the chromosome 7q11 including the *ELN* gene lead to WBS [15] and characterized by mental retardation, dysmorphic features, and arterial stenosis. Missense and premature truncation mutations throughout the *ELN* gene lead to SVAS [41]. ADCL is caused by the frameshift mutations at the 3' end of the elastin gene.

This review focused on the clinical presentation, mutational spectrum and molecular mechanisms of SVAS and ADCL. Dominant-negative and toxic gain-of- functions are the most important *ELN*-related ADCL mechanisms and haploinsufficiency is the SVAS disease mechanism. However, the exact molecular mechanisms of ADCL and SVAS are still under investigation. In addition, molecular insights into rare diseases might be relevant to common, complex diseases characterized by elastin degradation including aneurysms, chronic obstructive pulmonary disease and emphysema.

The genetic profile of ADCL and SVAS are known, but the genotype and phenotype spectrum is incomplete, and the genotype-phenotype correlations are unclear. Understanding the disease etiology, genetic profile and molecular and physiological mechanisms of each disease can improve diagnosis and the development of molecularly targeted treatments.

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