Table e-1. Genetic causes of vasculopathy affecting Smooth Muscle Cell Contractile (SMC) function.

Gene	Clinical syndrome and additional features	Possible mechanism involving SMC function
ACTA2 (Actin, Alpha 2, Smooth Muscle, Aorta)	Thoracic aortic aneurysm and dissections (TAAD) Moyamoya like cerebrovascular disease Patent ductus arteriosus Aortic coarctation Pulmonary hypertension Congenital mydriasis Hypoperistalsis and malrotation of the gut Hypotonic bladder	*ACTA2* mutations are predicted to alter the dynamics of actin assembly into filaments, by either disrupting the actin-actin interaction sites or interfering with ATP hydrolysis. Analysis of SMCs explanted from patients heterozygous for *ACTA2* mutations demonstrated reduced ACTA2-containing fibers and therefore confirmed that *ACTA2* missense mutations disrupt actin fiber assembly or stability.
COL3A1(Collagen Type III Alpha 1 Chain)	Ehlers-Danlos syndrome (EDS) type IV Widespread vasculopathy Facial features (acrogeria), translucent skin with highly visible subcutaneous vessels on the trunk and lower back, easy bruising, and severe arterial, digestive and uterine complications	Mutations in type III collagen may disrupt SMC contractility by binding SMCs to type III collagen in the matrix.
FBN1(Fibriliin 1)	Marfan Syndrome	*FBN1* missense mutations disrupt the polymerization of fibrillin-1 monomers into microfibrils, resulting in a decrease in the amount of fibrillin-containing microfibrils. *FBN1* mutations may also disrupt SMC contraction through disruption of the SMC mechanotransduction complex.
MFAP5(microfibrillar-associated protein 5)	TAAD Atrial fibrillation, mitral valve prolapse and arterial tortuosity	MFAP5 is a component of fibrillin-containing microfibrils and therefore mutations may affect SMC function in a similar manner such as in *FBN1*mutations.
MYH11(Myosin Heavy Chain 11)	TAAD Moyamoya like cerebrovascular disease PDA	Loss of regulation, leading to constitutive ATPase activity in the mutant myosin filaments and energetic overload on the SMCs, in addition to impairment of myosin motor function and decreased contraction.
MYLK(Myosin Light Chain Kinase)	TAAD	The contraction of smooth muscle begins with the phosphorylation of the light chain of myosin, a reaction catalyzed by MYLK that is itself activated by the binding of calcium-calmodulin.

PRKG1(Protein Kinase, CGMP-Dependent, Type I)	TAAD Coronary artery aneurysm/dissection and arterial tortuosity in some patients	*PRKG1* is a cyclic GMP and cyclic GMP-dependent protein kinase and has important roles in physiologic processes such as relaxation of vascular smooth muscle and inhibition of platelet aggregation.
TGFB2 (Transforming Growth Factor Beta 2)	Loeys-Dietz syndrome Abdominal aortic aneurysms and/or intracranial and other arterial aneurysms and/or dissections	TGF-β signaling plays a major role in the differentiation of SMCs, including the expression of contractile proteins. Almost all the *TGFBR2* and *TGFBR1* missense mutations alter amino acids in the intracellular domain of the receptor and are predicted to disrupt kinase activity of the receptors, and thus likely prevent proper signaling, thereby disrupting the differentiation of neural crest and mesenchymal cells into vascular SMCs. The lack of contractile units in the vascular SMCs owing to disruption of differentiation would be predicted to lead to altered SMC contractility.
TGFB3 (Transforming Growth Factor Beta Receptor 3)	Rienhoff syndrome or Loeys-Dietz syndrome type 5	
TGFBR1 (Transforming Growth Factor Beta Receptor 1)	Loeys-Dietz syndrome Abdominal aortic aneurysms and/or intracranial and other arterial aneurysms and/or dissections	
TGFBR2(Transforming Growth Factor Beta Receptor 2)	Loeys-Dietz syndrome Abdominal aortic aneurysms and/or intracranial and other arterial aneurysms and/or dissections	
SMAD3	Aneurysms osteoarthritis syndrome Loeys-Dietz syndrome	

SMC=smooth muscle cells