Degenerating Heart Valves
Fill Them up With Filamin?

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The intellect is always fooled by the heart.
- La Rochefoucauld

Myxoid valvular heart dystrophies are a frequent cause of valvular diseases. They affect approximately 3% of the population and are the most common cause of isolated mitral regurgitations that require surgical repair.1,2 These valvular diseases are a heterogeneous group of disorders and include isolated nonsyndromic valvular diseases, such as idiopathic mitral valve prolapse and the X-linked myxomatous valvular dystrophy (XMVD), and syndromic entities, such as Marfan syndrome. In this issue of Circulation, Kyndt et al3 report their surprising finding that specific mutations in filamin A (FLNA), a gene previously associated primarily with neurological and skeletal disorders, actually cause XMVD.

XMVD is a rare form of inherited nonsyndromic valvular dystrophy that was identified more than 30 years ago by Monteleone and Fagan.4 Initial reports suggested that only men could be affected, but a subsequent study revealed that the disease has heterogeneous presentations and that women can have milder manifestations.5 Histologically, the valves classically display abnormalities of myxomatous degeneration, with fragmentation of collagen bundles within the valve fibrosa and accumulation of proteoglycan and secondary calcification. The clinical spectrum of XMVD ranges from isolated mild valve defects to severe multivalvular lesions, but XMVD usually affects the mitral and/or aortic valve. The result is mitral valve prolapse and mitral and/or aortic regurgitation. Affected individuals are usually asymptomatic until valvular lesions progress to significant hemodynamic impairment and heart failure. Complications can include endocarditis, spontaneous chordal rupture, and sudden death.5,6

Mutations of fibrillin and collagen genes have been correlated with syndromic cases of myxoid valvular heart dystrophies (eg, as part of Marfan and Ehlers–Danlos syndromes),7,8 but until now, no specific gene had been identified for nonsyndromic valvular dystrophies. Idiopathic mitral valve prolapse exhibits an autosomal dominant inheritance with reduced penetrance and variable expressivity. It has been linked to 3 different loci, at 16p11-p12, 11p15.4, and, recently, 13q31-32.9,10,11 In 1998, Kyndt et al12 mapped XMVD to chromosome Xq28 in a large French family. In this issue of Circulation, Kyndt et al3 identify FLNA mutations in 4 unrelated families with XMVD. Their demonstration that FLNA mutations can cause nonsyndromic myxomatous valvular dystrophy provides novel insight into the origins of cardiovascular defects.

Filamins (A, B, and C) were first described as nonmuscle actin-binding proteins. They are large cytoplasmic proteins consisting of an amino-terminal actin-binding domain and a rodlike domain of 24 repeated antiparallel beta-sheets interrupted by 2 flexible loops that form hinge structures. More than 30 different proteins have been reported to interact with the filamins, suggesting that filamins have a wide role as structural components of the cytoskeleton. Through interactions with both actin and membrane proteins, filamins link the cytoskeleton to the plasma membrane and are believed to be essential in cell motility and membrane stability.

Many of the filamin A interacting proteins are receptors for critical cellular signaling molecules. For instance, the transforming growth factor-β (TGF-β) receptor–activated Smads and the dopamine receptor interact with filamin A. Thus, FLNA is implicated in the regulation of different cellular signaling pathways. FLNA gene defects have previously been associated with developmental disorders of the brain and skeleton.13,14

FLNA mutations were initially identified in patients with an X-linked brain malformation called periventricular heterotopia (PH). In PH, neurons fail to migrate to the correct cortical site during early brain development. The cardinal clinical manifestation is epilepsy presenting during the second decade of life. Perhaps foretelling the new findings of Kyndt et al,3 some women with PH also exhibit congenital cardiovascular abnormalities such as persistent ductus arteriosus and aortic aneurysms. PH is largely diagnosed in women who give birth to few male offspring and who experience miscarriages. This observation suggests X-linked dominant inheritance with prenatal lethality of the hemizygous males. Although FLNA missense mutations can be seen, PH is generally believed to reflect loss of function of one FLNA allele with decreased FLNA dosage.15,16

Interestingly, missense mutations clustered in a unique FLNA domain cause a spectrum of distinct phenotypes that comprise a series of syndromes referred to as otopalatodigital syndrome types 1 and 2, frontometaphyseal dysplasia, and...
Melnick–Needles syndrome. These skeletal dysplasia syndromes are characterized by morphogenetic bone defects and share similar clinical manifestations, including generalized bone dysplasia and facial malformations. They are often distinguished by their associated phenotypes, such as microcephaly and mental retardation in otopalatodigital syndrome type 2. In each syndrome, the expressivity is variable, and more severe clinical manifestations occur in males than females. However, these syndromes do not seem to be associated with PH or with signs of defective neural-cell migration. These genotype–phenotype correlations and the wide range of organ systems affected highlight the critical role of FLNA throughout multiple aspects of human embryonic development.

Kyndt et al\textsuperscript{3} widen the spectrum of clinical syndromes caused by FLNA genetic abnormalities with their identification of FLNA mutations in 1 large and 3 smaller families with XMVD. Diagnosis of XMVD was based on transthoracic echocardiography, and family members were considered affected if the thickness of the free edge of either or both mitral valve leaflets was greater than 4 mm, regardless of the presence or the absence of mitral valve prolapse and mitral regurgitation. Given the difficulty of assessing aortic leaflet thickening by transthoracic echocardiography, patients were also considered affected if mild to severe aortic regurgitation was present. Within these families, the disease was inherited with complete penetrance in males and incomplete penetrance in females. However, there was variable expressivity in both genders. Coupling genealogical surveys of the larger family with linkage analyses, Kyndt et al\textsuperscript{3} refined the previously mapped locus on chromosome Xq28 to a 2.5-Mb region.\textsuperscript{12} Screening of candidate genes revealed a P637Q missense mutation in the FLNA gene in the affected members of the larger family. Mutational analyses of the FLNA gene in the other families identified 3 additional FLNA gene mutations: 2 more missense mutations (G288R, V711D) and a 1944 bp in-frame deletion. Male and female carriers were both affected, but the affected females had a less severe phenotype. No signs of PH, otopalatodigital syndrome, frontometaphyseal dysplasia, Melnick–Needles syndrome, Ehlers–Danlos syndrome, or other extracardiac abnormalities were found.

The mechanism by which these FLNA mutations lead to a cardiac-restricted phenotype remains unknown, and further studies will be required. Helpful tools in these studies will be animal models with mutations in specific domains of the FLNA gene. Hart et al\textsuperscript{17} recently described a mouse model with loss of filamin A. Absence of the FLNA protein in male mice caused embryonic lethality secondary to incomplete septation of the conotruncus (truncus arteriosus), along with craniofacial and other skeletal defects. A proportion of both male and female mutant mice had other cardiac defects, including dysplasia of the mitral valve, ventricular septal defects, and primum atrial septal defects. These findings highlight the diversity of filamin A contributions to heart development.

In the study by Kyndt et al\textsuperscript{3} all 4 XMVD mutations are located within the repeats 1 to 7 of the filamin protein. The 3 substitutions associated with XMVD occur in the same region of the gene, and each replaces a nonpolar amino acid with a polar one within the first, fourth, or fifth repeats. The authors suggest that this change in polarity could cause a significant change in the structural conformation of the beta-pleated sheets of the FLNA protein and could impair binding with other protein partners. On the other hand, the 1944 bp FLNA deletion that Kyndt et al\textsuperscript{3} identified produces a truncated protein that lacks the repeats 5 to 7. Although the number of affected individuals in the relevant family is small, it is interesting to note that the newly produced, truncated FLNA protein causes a polylavulval phenotype in the 2 affected individuals. Further analyses of these patients will highlight the differences in disease severity produced by FLNA-point mutations versus this deletion.

Given that many proteins bind filamin A, it seems reasonable to hypothesize that specific disease phenotypes are driven by the effect of individual FLNA mutations on interactions with different protein partners during embryonic development. To fully appreciate the requirements for filamin A in cardiac valvular morphogenesis, it will be necessary to define the protein(s) that interact with filamin A during cardiogenesis and to dissect the contribution of repeats 1 to 7 in these interactions. During heart valve formation, a subset of endothelial cells overlying the future valve site are programmed to delaminate, differentiate, and migrate into cardiac jelly through a process referred to as endothelial–mesenchymal transformation. Locally expanded swellings of cardiac jelly and mesenchymal cells (referred to as cardiac cushions) undergo extensive remodeling to form the heart valves. Several ligands and signaling pathways are implicated in this process, including vascular endothelial growth factor, Nfatc1, Notch, Wnt/beta catenin, BMP, TGF-\(\beta\), ErbB, and Nfib1/Ras. TGF-\(\beta\) interacts with several of these other pathways to induce endothelial–mesenchymal transformation of epithelial cells during normal embryonic development of the heart.\textsuperscript{18} Filamin A coordinates localization and activation of TGF-\(\beta\) receptor–activated Smads, particularly Smad2, to act as a positive regulator of TGF-\(\beta\) signaling.\textsuperscript{14} One potential mechanism underlying cardiac valvular dystrophy could involve dysregulated/disrupted interaction of Smads with filamin A and inhibition of endothelial–mesenchymal transformation via perturbation of the TGF-\(\beta\) signaling.

As previously noted, women with PH can be afflicted with cardiac defects such as persistent ductus arteriosus and aortic aneurysms. Men with PH are rare but can exhibit severe, usually lethal, vascular malformations. Given the identification of TGF-\(\beta\) receptor mutations in some aneurysm syndromes,\textsuperscript{19} and the association of Smads with filamin A, the TGF-\(\beta\) pathway is an attractive candidate for inducing both valvular and vascular malformations. The dosage of filamin A and TGF-\(\beta\) activity may require precise regulation. Myxomatous mitral valves found in fibrillin-1–deficient mice (which model Marfan syndrome) display excessive TGF-\(\beta\) activation and upregulated expression of FLNA.\textsuperscript{20} It remains to be seen whether the mutations described by Kyndt et al\textsuperscript{3} activate or inactivate filamin A–mediated signaling.

Future research on filamin A and TGF-\(\beta\) signaling holds great promise for deciphering valvular diseases. On the basis of genetic analyses of TGF-\(\beta\) signaling disorders, clinical
trials are now beginning to test new pharmacological interventions for aortic aneurysms. The opportunity to integrate filamin A and events in the cytoskeleton with the TGF-β signaling pathway may present exciting new therapeutic targets for patients with valvular diseases.

Disclosures

None.

References
