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Title of Research *	Biological Effects of α -Smooth Muscle Actin Mutations that Cause Thoracic Aortic Aneurysms
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Introduction & Purpose *	Thoracic Aortic Aneurysm and Dissection (TAAD) is a major cause of mortality in the U.S., at 0.5–1% of total deaths/yr. One type of familial TAAD results from mutations in α -smooth muscle actin, a major component of the vascular wall contractile apparatus. Of the nineteen TAAD mutations in α -smooth muscle actin (ACTA2) that have been detected, three (N115T, R116Q, and R256C) cause either aneurysm alone or are coupled with coronary artery disease or stroke. We hypothesize that ACTA2 mutations alter wall integrity or contractility leading to the disease.
Experimental Design *	These mutations may alter wall integrity or contractility leading to the disease. However, the lack of an appropriate model has prevented delineation of a molecular mechanism underlying the effects of these mutations. The actin of the yeast <i>S. cerevisiae</i> , 86% similar to α -smooth muscle actin, provides an excellent alternative model. All three mutations, cloned into yeast actin, cause decreased growth under stress conditions: elevated temperature, hyperosmolarity, and utilization of glycerol as sole carbon source.
Results *	The cells are 20% larger with abnormal vacuole structures and actin cytoskeletal patterns, unaffected nuclei but fragmented and aggregated mitochondria. Mutation-induced F-actin destabilization may alter its susceptibility to cofilin, a major F-actin severing protein. Such destabilization in vivo might be lessened by decreasing cofilin activity. In a cell in which we deleted an enhancer of cofilin action, Aip1p, cell size and actin cytoskeleton abnormalities, most severe in N115T cells, were rescued, consistent with mutation-induced cytoskeletal instability. Mutant cells, in the order WT, N115T, R116Q, and R256H, were increasingly sensitive to latrunculin A, which sequesters G-actin causing depolymerization.
Conclusions *	The similarities in the yeast and vascular muscle actin systems suggest that results with these mutations in yeast may provide molecular insight into the disease mechanisms underlying TAAD and its ultimate treatment.

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