# The Phenotypic-to-Genotypic Association of Novel Single-Nucleotide Polymorphisms in the Collagen Matrix-Encoding Gene ZNF469 in Arterial Aneurysmal Diseases

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## RESEARCH QUESTION

**In patients with a strong personal and or family history of aortic and or aneurysmal events, in the absence of known syndromic mutations, are there novel genes that cause this disease state?**

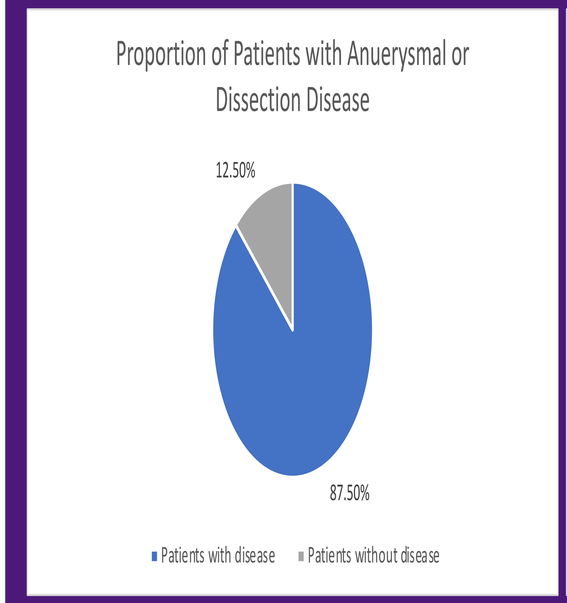
## BACKGROUND

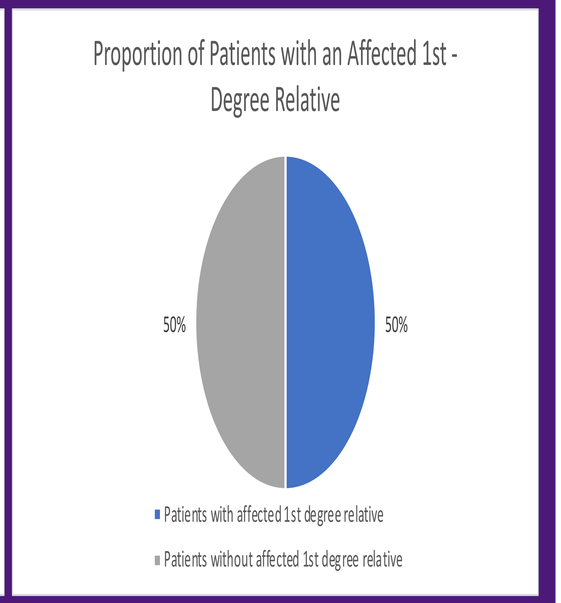
**Aneurysms and dissections are vascular pathologies which are increasingly recognized to have a genetic basis. In this report we share novel mutations in ZNF469 in eight patients in our program who have arterial aneurysms, arterial ectasia, and/or arterial dissections. ZNF469 is responsible for the production of a collagen-related zinc-finger protein involved in multiple aspects of the development and regulation of major extracellular matrix components.**

## METHODS

**Patients in our program with significant personal or familial history of aneurysmal or dissection diseases underwent clinical genetic testing to assess mutation status of genes associated with vasculature, extracellular matrix, and aneurysmal/dissection disease to guide clinical management. Those with mutations in ZNF469 are included as subjects in this study.**

**This study significantly strengthens the association of variants in ZNF469 with vascular aneurysmal and dissection related disorders in a cohort of unrelated patients, with the interesting finding of an age-associated difference in localization of mutations.**




## RESULTS

**All subjects in our cohort had single nucleotide variants (SNVs) in ZNF469, with 4/8 mutations residing in Exon 1 and 4/8 mutations residing in Exon 2. 7/8 mutations were variants of unknown significance, and 1/8 demonstrated a known pathologic mutation associated with brittle cornea syndrome. Of our eight patients, 5/8 (62.5%) have ectasia/aneurysmal disease, 3/8 (37.5%) have experienced vascular dissection, and 4/8 (50.0%) have a family history of one or more first-degree relatives with aneurysmal or dissection disease. Furthermore, 4/8 patients with mutations in Exon 1 had an average age of 46 and those with mutations in Exon 2 had an average age of 68 (p=0.02).**

## FUTURE DIRECTIONS

**As we strengthen this association through familial genotyping of each proband, we hope to further define ZNF469 as a causal, pathogenic gene for non-syndromic vascular aneurysmal disease. We are conducting confirmatory studies that may help define this as a causal genetic vasculopathy, including immunohistochemical characterization of aortic samples recently obtained from one subject during aortic surgery, conducting population level genomic database assessments, and beginning detailed mechanistic study in animal model systems.**