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Whole exome next-generation sequencing identifies novel disease genes in primary vascular aneurysms

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Objective: Non-atherosclerotic arterial aneurysm is a morbid condition and its etiology remains unclear outside the spectrum of an identifiable heritable connective tissue condition (e.g. Marfan or Ehlers-Danlos Syndromes). We identified a cohort of unrelated patients lacking a heritable connective tissue diagnosis despite manifesting multiple aneurysms and/or pseudoaneurysms in medium-sized arteries. We termed the condition multiple aneurismal pseudoaneurysmal syndrome (MAPS) and hypothesized that MAPS may be due to a novel disease gene. We utilized exome sequencing and bioinformatics to identify disease geneswhich contribute to risk for MAPS.

Methods: Next-generation exome sequencing was performed for 15 MAPS patients and one family with multi-generational arterial aneurysms. Bioinformatics filtering of identified putative 'mutations' and Ingenuity Pathway Analysis of suspicious genes were performed.

Results: The familial MAPS phenotype was targeted by exome sequencing to identify candidate MAPS genes. For sporadic MAPS cases, Ingenuity Pathway Analysis (IPA) software was used to search literature describing biochemical pathways between known vascular disease genes and bioinformatics-filtered candidate genes. Analysis of familial MAPS yielded 15 candidate genes, of which *PCDH*12 was the most promising candidate due to its respective mutation being located in an extremely conserved gene region with a high score for predictive phenotypic damage. Analysis of sporadic MAPS using IPA software identified 6 candidate genes including *BAG6, PRKCD, CTNNA1, JAG1, FN1, and MMP13.*

Conclusion: Exome sequencing with bioinformatics filtering in the novel aneurysm phenotype, MAPS, identified several promising aneurysm candidate genes. Knock-out/knock-in animal models are being developed to further explore the relationship between candidate genes and phenotypic expression.

Biography

Ryan D'souza is a 3rd year medical student currently completing his MD degree at the University of Colorado School of Medicine. He was born in India, and moved to the United States to complete his undergraduate education in molecular and cell biology at the University of Connecticut. He currently conducts cardiovascular research, with projects specifically focusing on genetic causes of aneurysms, and biomarkers of heart transplant rejection. He is also an artist who specializes in pencil shading and painting, with several published pieces in the Human Touch Anthology. He aspires to become an interventional cardiologist.

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