Elastin Polymorphisms Associated with Increased Risk of Thoracic Aortic Aneurysm and Dissection (TAAD)

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Elastin is a polymorphic structural protein, responsible for elastic properties of many tissues including lungs, skin and large arteries. It constitutes approximately 30% of the dry weight in arteries. Elastin fibers are remarkably stable with little or no normal turnover over the life-span of an individual therefore; they should be able to withstand millions of cycles of extension and recoil in tissues such as arteries without mechanical failure. We hypothesize that any subtle variation in Elastin sequence can impact Elastin durability in arteries and consequently increase susceptibility to cardiovascular diseases.

Initial searches of public Single Nucleotide Polymorphism (SNP) databases revealed the presence of 264 common SNPs in the elastin gene (ELN), of which 13 are non-synonymous. One of these (rs2071307 - Gly422Ser) which converts a glycine to a serine was found to significantly impact the self-assembly and elasticity properties of elastin-like polypeptides. In a more focused study we are examining the functional consequences of sequence variants in elastin on cardiovascular disease. Applying the Solexa next generation sequencing platform, we have sequenced the ELN from 800 subjects diagnosed with thoracic aortic aneurysm and dissection (TAAD) in addition to 400 control samples from Ontario residents.

Our initial analyses identified an additional 50 SNPs present in TAAD samples, including 13 novel non-synonymous SNPs in exons 3, 14, 21, 24 and 26. Currently we are genotyping 20 of these SNPs in order to confirm their frequency in our samples. Finally the impact of selected subset of these SNPs on elastin integrity will be evaluated using recombinant elastin-like polypeptides.