Aortic aneurysms and dissections are a major source of morbidity, mortality, and medical expenditure in the United States, accounting for approximately 20,000 deaths each year. Aortic aneurysms are typically classified by location; abdominal aortic aneurysms are the most common, followed by thoracic aortic aneurysms. An aortic dissection can occur following the progressive dilatation of an aortic aneurysm or can occur without a predisposing aneurysm. Familial thoracic aortic aneurysms and dissections (TAAD) can occur in conjunction with a known genetic syndrome, such as Marfan syndrome, or in the absence of any known genetic syndrome. Recent studies have mapped two loci for familial TAAD, one at 5q13-14 (TAAD1) and one at 3p24-25 (TAAD2). This study aimed to identify and compare clinical phenotypic features both within and between the two loci using 76 individuals who carried the affected haplotype for their respective locus. Of the study population, 96.7% have been affected by thoracic aortic disease; 93.8% have had an aneurysm greater than 2 standard deviations above the expected size, 31.6% have had an aortic dissection, and 25% have had surgical repair of the aorta. There was an increased occurrence of additional cardiovascular findings (68%), skeletal anomalies (28.9%), and inguinal hernias (17.1%) in the study population. In comparing clinical features observed between individuals linked to the two loci, men linked to TAAD1 weighed significantly more than men linked to TAAD2 (p=0.032), individuals linked to TAAD1 had a higher occurrence of aortic dissections than
individuals linked to TAAD2 (p=0.023), and individuals linked to TAAD2 had a higher occurrence of skeletal anomalies than individuals linked to TAAD1 (p=0.016).

Individuals known to carry the TAAD2 haplotype had 87 children, 55 (63.2%) males and 32 (36.8%) females, suggesting the gene(s) at the 3p24-25 locus may be involved in embryologic development in favor of the male gender (p=0.018). Women who inherited the affected haplotype at either locus had decreased penetrance for aortic disease (p=0.028) compared to men. For all subjects, the mean age of onset for aortic disease was 42.82 years (+/-19.38), for aortic repair was 44.38 years (+/-16.11), and for aortic dissection was 46.11 years (+/-13.89). There is an anticipatory effect in the age of onset of aortic disease; using three generation families, the age of onset for generation I was 60.73 years (+/-16.42), the age of onset for generation II was 45.08 years (+/-9.83), and the age of onset for generation III was 22.5 years (+/-6.99) (p<.001). Regression analysis demonstrated that generation has a major effect on the age of onset (r²=0.65, p<.001), but other contributing factors such as hypertension, body surface area, and gender play a synergistic role (r²=0.947, p<.001). Elucidating the clinical phenotype for individuals linked to these loci will provide useful clinical information for the care and management of aortic disease in these families and other families linked to these loci.