Genetics of aortic aneurysm disease: 10 key points for the practitioner

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Today, understanding genetic evaluation in thoracic aortic aneurysm (TAA) patients is crucial for optimizing clinical practice and patient outcomes. Modern genetic sequencing and its interpretation and application deserve to be clarified for the surgeon so that they can be incorporated in day-to-day management. Additionally, multiple other genetics-related topics besides genetic sequencing can be applicable for the surgeon in clinical management.

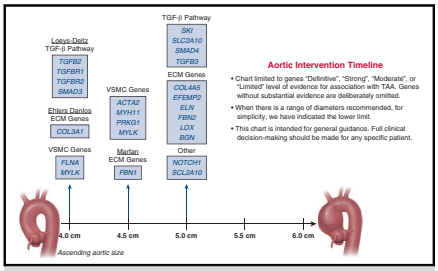
In 1998, our interest in the genetics of aortic disease at Yale University was stimulated by a single family in whom 3 members experienced TAA dissection, including a clinically unrecognized dissection in a 12-year-old girl. In that era, although everyone was aware of Marfan disease, it simply was not anticipated that ordinary, garden variety nonsyndromic TAA could be genetically mediated. Aneurysm disease was thought of as an unfortunate, random occurrence.

We quickly constructed family trees on 100 consecutive dissectors who we had treated and found that a staggering 26% manifested a familial pattern. Figure 1 presents the first 21 positive pedigrees, along with our initial genetics paper published 25 years ago.[1]

For more than a decade, our team has incorporated widespread whole exome sequencing (WES) in our clinical practice. After initial grant support, the WES program for TAA became self-sustaining, economically viable, and of cardinal clinical and academic importance, improving our clinical understanding and decision making and permitting better detection of genetically prone, yet clinically silent, individuals.

TEN POINTS REGARDING CLINICAL APPLICATION OF MODERN GENETICS IN TAA ASSESSMENT AND CARE

The following 10 points are presented to facilitate the practitioner's understanding and use of WES for TAA.



Timeline for surgical intervention for ascending thoracic aortic aneurysms.

CENTRAL MESSAGE

Genetic understanding of thoracic aortic aneurysm (TAA) has advanced immensely in the 2 decades since the landmark initial mapping of the human genome. Aortic surgeons need to be familiar with the genetic landscape of TAA.

Point 1: TAA is inherited predominantly in an autosomal dominant genetic fashion.[1-4] Some recessive inheritance does occur, but the overwhelming modality of inheritance is autosomal dominant. In no instance in Figure 1 are both parents affected. TAA is transmitted mainly from a single parent, male or female, and affects 50% of offspring—all characteristic of dominant pattern inheritance. This makes it imperative to ensure that all offspring of an aneurysm-bearing patient are investigated by imaging. For children, we generally start imaging in the early teenage years.

Point 2: TAA is a "single letter" disease. The genome comprises 3.1 billion genetic "letters" (DNA bases or alleles).[5] The exome, the protein-coding subset of the genome, is composed of 32 million letters (1% of the genome).[5] Striking as this may be, the vast majority of TAA disease is caused by *just one single bad genetic letter* among the billions in the genome. For example, TAA in Marfan disease, Loeys-Dietz syndrome, Ehlers-Danlos disease, and typical familial TAA disease are caused by single letter changes.

Point 3: The cost of genetic sequencing is plummeting. The first human to have genes sequenced was the visionary

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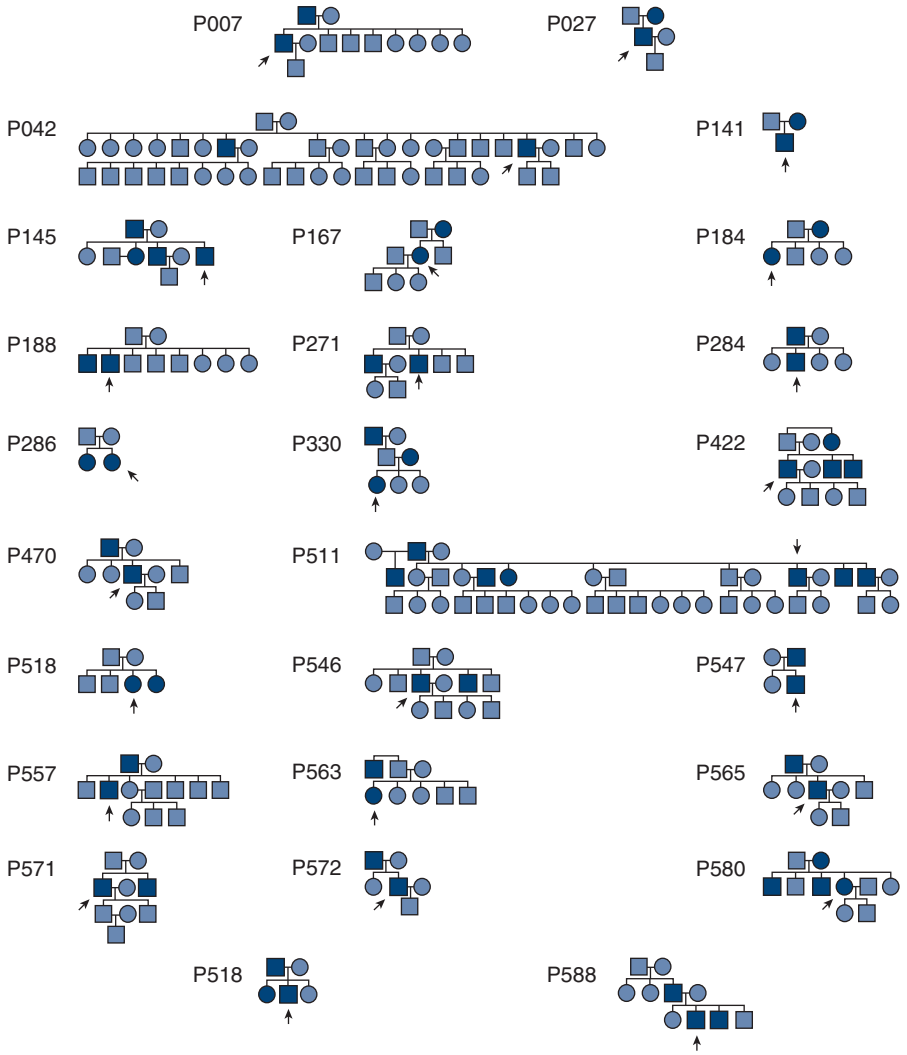

FIGURE 1. Nonsyndromic thoracic aortic aneurysm (*TAA*) family pedigree of 26 patients and their first-order relatives. *Squares* represent the men; *circles*, the women. An *arrow* indicates the proband (the specific patient being studied) with a TAA. Blackened *squares* or *circles* represent affected patients with aortic aneurysms. We suspect that in those cases without a known affected parent, a parent may well have harbored an undiagnosed TAA, as CT imaging had not yet proliferated widely in those years. Also, some of these pedigrees are suggestive of x-linked dominant and recessive modes. Reproduced with permission from Coady MA, Davies RR, Roberts M, et al.[1]

President of Celera Genomics, Craig Ventor. This landmark in human history was achieved in 1999. It is estimated that the first sequencing cost approximately $3 billion. Today, the exome is sequenced for $250; the genome, for $600. The drop in cost follows the well-known Moore's Law for technology and gives more patients access to molecular genetic testing.

Point 4: WES permits individualized genetic care and decision making. As we discuss below, specific aortic diameters that warrant aneurysm resection have been articulated for many specific genes. Also, knowing the aberrant gene allows gene-specific expectations for clinical behavior of TAA (eg, disease virulence, tendency to dissect, age of onset of dissection). We surgeons long have used aortic size as a criterion for surgical intervention, but in terms of the role of genetics, all patients resided in one single bucket.

Figure 2 presents the 70 genes known to cause thoracic aortic aneurysm, color-coded by the strength of causative evidence.[6] Heretofore, these disparate patients were treated quite similarly, in one single decision making "bucket."

Currently, WES permits individualized care based on the clinical characteristics of patients with each specific disease-causing gene. WES is widely available at major medical institutions, so incorporation of genetic information into clinical practice is practically feasible.

Not all patients with an identified likely causative genetic mutation need surgical intervention. The genetic "timeline" (Figure 3) provides up-to-date guidance on appropriate

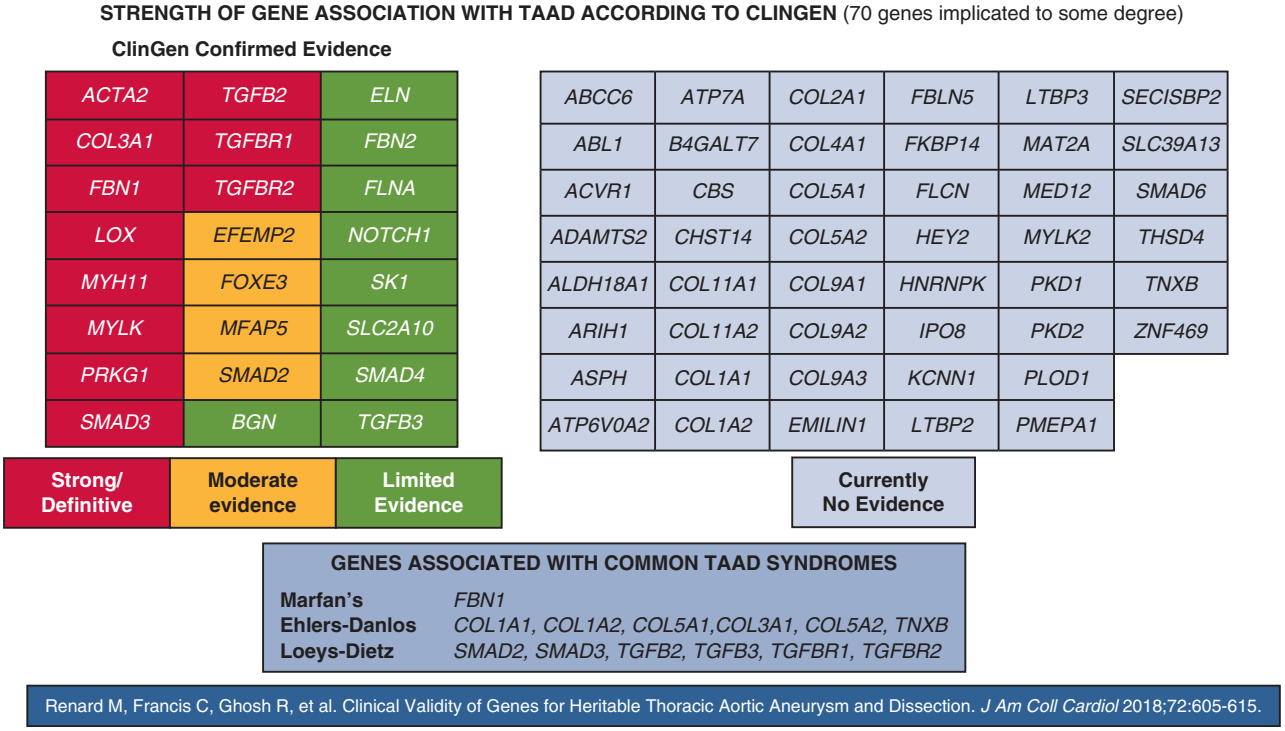

FIGURE 2. Seventy genes associated with thoracic aortic aneurysm and dissection, grouped by the strength of association according to CLINGEN.

aortic dimensions for surgical intervention. These diameters are only suggested general intervention guidelines for specific identified genes; the decision for surgery should be based on clinical judgment after considering the entire picture presented by the specific patient.

Also, current genetic sequencing identifies potential causative genes in only 20% of cases tested. The remainder of patients are treated without a molecular genetic strategy. Furthermore, genetic sequencing is time-consuming (requiring the reading of 3.2 million genetic "letters"). Acute care of ruptures and dissections must be provided without delay for genetic data. If there is no time for genetic testing before urgent surgery, testing can be done later to guide further management.

In terms of genetic surveillance, new genes are discovered every year. If a patient's WES was initially negative, consideration should be given to repeating the testing in 3 to 5 years.

Point 5: We sequence everyone. We have found WES to be so informative and clinically useful that we sequence everyone (more specifically, everyone whose insurance or personal funds are able to absorb the increasingly affordable testing). Sequencing not only permits gene-specific decision making, but also enables testing of family members for susceptibility. In addition to the benefits for specific sequenced patients and families, widespread WES dramatically advances medical knowledge in the field of aortic diseases.

Point 6: Newly discovered genes. Dr Ziganshin from our team (with Dr Chung at Columbia) has just identified 2 new TAA candidate risk genes, based on advanced computerized analysis of 1278 of the senior author's surgically excised human aortic tissue specimens.[7] We call to your attention VPS8, which appears to be quite common and, based on our preliminary patient record review, a very nasty gene, causing high-grade aortic dilatation and behaving in malignant fashion, often with sudden dissection as the presenting modality. The more genes medical science discovers, the greater the proportion of TAA patients who can be treated in a gene-specific pattern.

Point 7: Genetic timeline for aortic intervention. The aortic timeline (which is really a "sizeline") shown in Figure 3 indicates the suggested size for surgical intervention for each specific causative gene. Around every 2 years, this timeline is updated with the most current information on the appropriate size for surgery for each causative gene.[8-14] Please note that many malignant mutations require surgery quite early in terms of aortic diameter. We publish an updated timeline with regularity, as genetic data change and accumulate rapidly.

Point 8: Three genes to remember. Please remember the names of 3 relatively common genes that behave badly, with

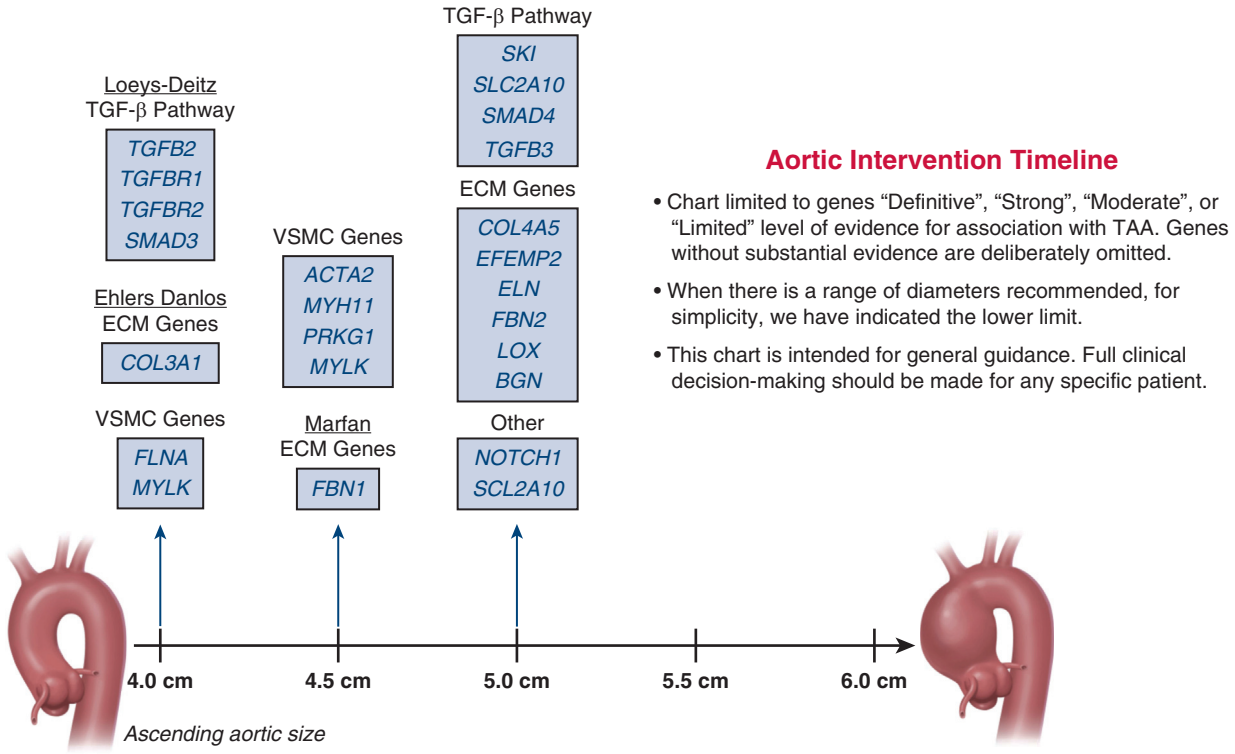

FIGURE 3. Timeline for surgical intervention for ascending thoracic aortic aneurysm (*TAA*). This chart lists the documented genetic mutations known to cause TAA. The *arrows* indicate the general aortic size threshold for surgical intervention in patients harboring each mutation. This chart is meant to serve as only one component of clinical decision making.

dissection at <5 cm or even without any aortic dilatation at all: *ACTA2*, *MYLK*, and *MYH11*.[15-19]

Point 9: Gene-specific age ranges for dissection. Keep in mind that age has a gene-specific role, in addition to diameter. In Figure 4, note the clustering of aortic events not only by size, but also by age. The age clustering should be taken into account in surgical decision making. When an aneurysm-causing gene has been identified, this graph can

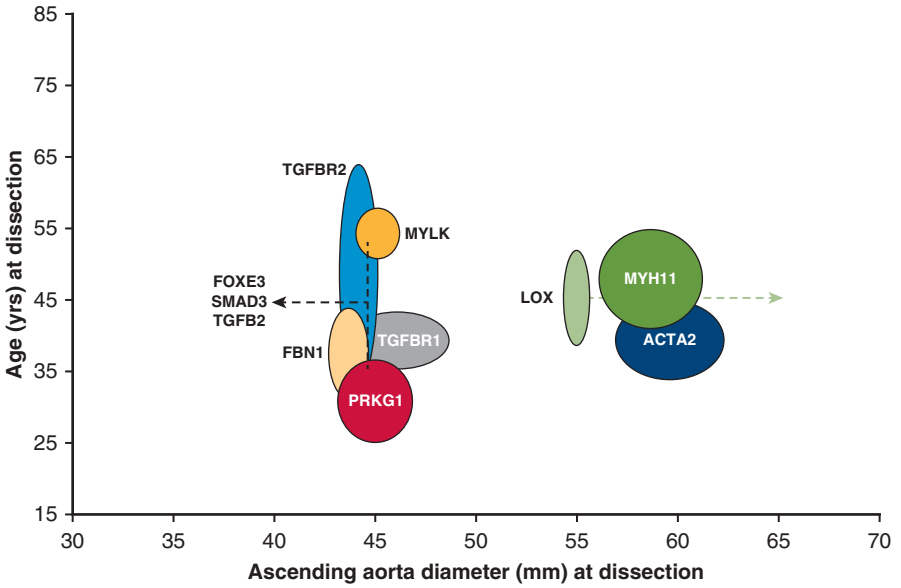

FIGURE 4. Schematic representation of genetic mutations with age and ascending aorta diameter at dissection. Widening of the circles/lines represents SD in terms of age and diameter. Reproduced with permission from Mariscalco G, Debiec R, Elefteriades JA, et al.[20]

be consulted; thus, in addition to aortic diameter, patient age can be taken into account when considering whether to operate. It usually is unwise to allow the patient to wade too deeply into the gene-specific age range in which dissections commonly occur.

Point 10: The conundrum of "variants of unknown significance": Despite explosive advancements in the genetics of TAA, for many patients WES yields inconclusive results. The geneticist often indicates that a "variant of uncertain significance" (VUS) has been identified. A report of suspicious but inconclusive findings can be very stressful for patients. Compassionate counseling is warranted, by the surgical team or genetic counselors. In response to the unsettling problem of VUS, our team and several others developed a model of TAA in the zebrafish that shows promise in providing prompt additional evidence regarding the true pathogenicity of VUS.[21,22]

This VUS conundrum can provide a quandary for patients and caregivers alike. Geneticists want to be scientifically accurate—specifically, to not report a gene as "causative" without strong data. Geneticists weigh a number of factors in their assessment of pathogenicity. First is the frequency of the variant in the general population. A high frequency argues against pathogenicity, because a frequently occurring gene would be more plentiful than the entire spectrum of patients affected by TAA of all types. Second is preservation in phylogeny. A gene conserved up and down the phylogenetic tree is likely to be clinically important, and thus disease-causing. Third is in vitro analysis (ie, computerized analytic techniques). The specific genetic variant can inform the geneticist about the likelihood that reading the remainder of the gene (beyond the variant "letter") will be disturbed. Obviously, disturbance of the entire gene read is highly deleterious.

We suggest that practicing surgeons take VUSs seriously. Many currently proven causative genes started out as a VUS, and many (but not all) current VUSs eventually will be shown to be disease-causing.

Beyond the modern genetics described above, achieving definitive proof of pathogenicity of a variant may require demonstration of a genotype–phenotype correspondence over generations. We surgeons cannot wait generations, however—our concern is keeping our patients alive and rupture-free now.

In this regard, concerning rapid assessment of pathogenicity of genetic variants disclosed by WES, we are excited by our zebrafish modeling of specific TAA genetic variants[21] (see Figure 5). Note the periaortic hemorrhage in this mutant fish. We are becoming increasingly convinced that the zebrafish model can provide rapid initial assessment of the pathogenicity of specific variants.

We close with additional key observations. First, today there is no reason for parents with a genetically inherited aortopathy to pass that genetic defect on to their children.

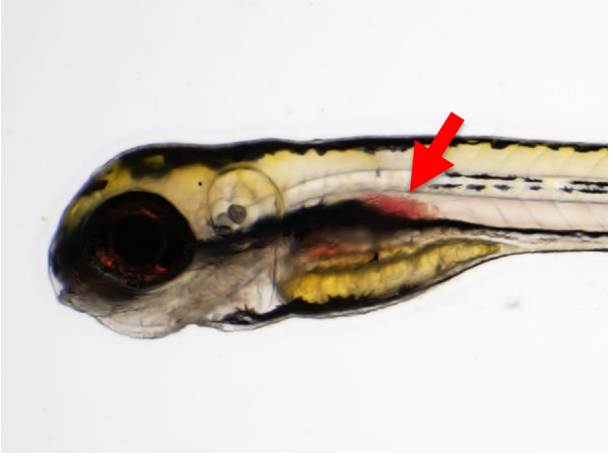

FIGURE 5. Closeup brightfield image of a 6 dpf *COL5A1* knockout fish with visible aortic hemorrhage (*red arrow*; scale bar: 500 μm). Reproduced with permission from Prendergast A, Ziganshin BA, Papanikolaou D, et al.[21]

In vitro fertilization (IVF) can select a nonaffected embryo. Not only will the child be well, but also, by genetic selection we will decrease the prevalence of that genetic defect in the general population. The frequency of that mutation in the population, and the aneurysm disease that it causes, should dwindle over time.

Second, the era of CRISPR gene therapy is upon us. In other diseases, CRISPR editing of the human genome has begun.[23-25] Soon we should be able to edit that single genetic letter responsible for aortic disease in our patients. Editing a gene is easy for today's brilliant scientists; the problem will be delivering that therapy to cells and tissues within the aortic wall. We are at the exciting cusp of application of widespread IVF to select embryos free of aneurysm-causing mutations and gene editing to remove aneurysm causing mutations. We look forward to the realization of their potential.

Limitations

This paper is intended as a guide to clinical practice, not an exhaustive scientific review of the entire field of TAA genetics. The practical suggestions made in this brief didactic offering reflect our practice patterns at the Aortic Institute at Yale University. Practice patterns in the rapidly progressing field of TAA genetics may vary across institutions, although we believe most of the principles enumerated here are widely applicable to other centers with a strong interest in the genetics of this disease.

CONCLUSIONS

We hope that this common sense description of the applications of modern genetics to TAA can serve to demystify this topic and lead to wider familiarity with these techniques, which can augment surgical care substantially.

Conflict of Interest Statement

Dr Elefteriades is a principal of CoolSpine, LLC. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

It is imperative that we recognize the immense contributions to this field made by Dr Dianna Milewicz and her team at the University of Texas.

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