Genetics and Hereditary Factors of Aortic Disease: Applying What We Know, Exploring What We Don't

A discussion on the current landscape of genetics research related to diagnosing and treating aortic disease.

WITH DIANNA M. MILEWICZ, MD, PhD

How did you first become interested in exploring the intersection of genetics and aortic pathologies?

When I was a resident in internal medicine at the University of Texas Southwestern Medical School, I saw a 19-year-old man who presented with an acute aortic dissection. Fortunately, this patient survived after surgical repair. It was determined that he had undiagnosed Marfan syndrome. I became fascinated that there was a condition (Marfan syndrome) in which just a change in one nucleotide out of the 3 billion nucleotides in the human genome caused not only the aortic dissection but also the patient's very tall stature, long arms, and long fingers, among other factors.

I began my initial work with genetics during my fellowship in human genetics at the University of Washington. There, my work, along with others, helped to identify the *FBN1* gene as the cause of Marfan syndrome.

When I moved into my first faculty position at the University of Texas Health Science Center in Houston, Texas, I became interested in whether there was a genetic contribution to thoracic aortic aneurysms and acute aortic dissections in patients who didn't have Marfan syndrome. I conducted a very simple clinical study. I had a genetic counselor collect family histories from any patient admitted to the hospitals in the Texas Medical Center with thoracic aortic aneurysms or aortic dissections to determine if they had family members who also had thoracic aortic aneurysms or dissections, specifically targeting patients who didn't have Marfan syndrome. Almost 20% of those patients had a family history of the disease, which indicated that there was a very strong genetic component to thoracic aortic aneurysms or dissections that had gone unrecognized or at least uncharacterized.

At that point, I switched my research to identify the genes that predisposed thoracic aortic aneurysms and acute dissections in individuals who didn't have Marfan syndrome.

How would you describe the current state of research into the genetic predictors of aortic disease?

My research program, along with other groups, have identified 18 genes that, when altered, confer a high risk for thoracic aortic disease and lead to thoracic aortic disease to be inherited in families. Despite finding all of these genes, we can only identify the causative gene in about 35% of affected families. Importantly, only about 20% to 25% of patients have a family history of thoracic aortic disease. We really are only beginning to understand the genetic triggers in people who don't have a family history of thoracic aortic disease and don't have features of Marfan syndrome, which is 75% to 80% of people with thoracic aortic disease.

The goal of my research program is to identify who in the general population is at risk for an acute aortic dissection so that those patients can be managed to prevent the dissection. First, we place them on a drug regimen to slow the rate of growth of the aneurysm and avoid things that we know trigger dissections. Then, when the aneurysm grows to a certain point, we repair it to prevent dissection.

We use genetic triggers to identify who in the general population is at risk for dissection. For those with a family history, we're about 35% of the way to finding all the genes that increase the risk for dissection. We're just starting to understand the genetic factors that predispose patients who present with aortic dissections or aneurysms but don't have a family history of those diseases.

How is research for genetics and aortic disease primarily funded, and what are the challenges to gaining that funding?

Research is primarily funded through the National Institutes of Health (NIH), and the challenge is that NIH funding is very competitive because the NIH only funds about 10% to 15% of the grants that are submitted. First, your grant has to address a serious issue, which is true for aortic dissections. Then, you have to show that you're successful in finding genes, which we are. Finally, you have to make sure the research is exciting and innovative so that the reviewers get excited about funding it. That's the challenge we face right now—convincing the grant reviewers that this is an important disease, that the approach we're using to finding those genetic triggers is correct, and that we will be successful.

We've done very well with acquiring NIH funding for cases where there's a family history; it's been more of a challenge to get funding for genetic studies where there is no family history of disease because it's tougher to find those gene variants.

Other sources of funding include foundations such as the American Heart Association, the John Ritter Foundation, the Marfan Foundation, and the Genetic Aortic Disorders Association Canada. We have received funding from all of these foundations for our studies, and we're very grateful for their support of our research.

What other genes or variants have been identified, if any, that are linked to an increased risk for thoracic aortic disease?

We're up to 18 genes now. We recently did an overview of those genes using an international working group that included experts in genetically triggered thoracic aortic disease.[1] Of those 18 genes, 11 were determined to have sufficient evidence that they cause disease and could be used in clinical testing; those genes are currently being used worldwide to identify individuals at risk for aortic dissection.

If a patient presents with thoracic aortic disease, such as an ascending or root aneurysm or a type A or B dissection, we recommend genetic testing for the 11 genes that have been validated as a trigger for this disease. We also recommend this testing in patients with features of Marfan syndrome or other conditions that we know predispose to dissection, such as Loeys-Dietz syndrome, and those with a family history of dissection. For patients younger than 55 years who present with acute aortic dissections but with no family history, we can find disease-causing changes in one of the 11 genes in 10% of cases, so we also recommend genetic testing in these patients.

In what ways do genetically caused aortic pathologies differ from those resulting from other factors that would cause the same conditions?

If a patient learns that they have inherited a mutation in one of the genes known to confer a high risk for thoracic aortic disease, it means that they are highly likely to get the disease even if they avoid environmental risk factors for the disease, such as high blood pressure and lifting heavy weights. In cases like Marfan syndrome, that risk approaches 100% for thoracic aortic disease. It doesn't matter if blood pressure is controlled, sooner or later the patient will develop the disease.

For patients who haven't inherited one of these high-risk gene alterations, we may be able to modify risk factors to prevent the disease. For example, hypertension is often the trigger for someone who doesn't have one of these high-risk genes. We're working on a hypothesis that patients with thoracic aortic disease without a family history have low-risk genetic variants for the disease and that a secondary factor, such as hypertension or pregnancy, is needed to trigger the thoracic aortic disease. If we can find those low-risk variants, then we can tell those people what they need to prevent thoracic aortic disease in their lifetime.

It is notable that there are people with hypertension who don't take their medications and never have an aortic dissection, and these individuals may not have any risk variants for thoracic aortic disease. However, they may have other problems such as a stroke, heart attack, or heart failure. We hypothesize that we can use genetic variation to identify who in the general population is at an increased risk for aortic dissection based on underlying genetic variation.

How has the discovery of these genetics helped shape treatment decisions related to these patients?

First, identification of an altered gene that confers a high risk for thoracic aortic disease allows us to identify who else in a family is also at risk for thoracic aortic disease. Surveillance and clinical management are then initiated to prevent acute aortic dissections in the family members.

Second, it informs us when a patient needs to undergo aneurysm repair. With Marfan syndrome, we're pretty safe watching the aortic root grow to 5 cm. With some other altered genes associated with thoracic aortic disease, a significant number of patients will have dissections when their aortic aneurysms are smaller than 5 cm. For many of the genes, we're recommending repair at 4.5 cm.

Third, some genes confer a risk for additional vascular diseases. For example, mutations in the *TGFBR1* gene increase the risk for aortic root aneurysms that can progress to an acute aortic dissection, as well as the risk for intracranial aneurysms, iliac aneurysms, and basically aneurysms of any artery that branches off the aorta. So, if this genetic mutation is identified, we not only have to watch for aortic root aneurysms, we also have to perform imaging for aneurysms elsewhere.

In contrast, patients with mutations in the *ACTA2* gene are at risk for aortic aneurysms that can progress to dissection, but in addition, a subset of patients with *ACTA2* mutation are also at risk for blockages in other arteries, leading to early onset coronary artery disease and strokes. Thus, the underlying gene tells us if there is a risk for additional vascular diseases beyond thoracic aortic disease and what type of vascular diseases will occur.

Once we know the underlying gene and the specific change in the gene, it tells us a lot about the management. These data indicate that the field needs to move toward gene-based management for thoracic aortic disease in individuals where the gene mutation triggering the disease is identified. We're pushing the American Heart Association, American College of Cardiology, and European Society of Cardiology to allow us to write gene-based treatment guidelines for thoracic aortic disease.

How does a patient's sex and age impact the diagnosis and treatment of heritable thoracic aortic disease?

For most of these genes that confer a high risk for thoracic aortic disease, sex does not matter much. There are a few genes where women have later-onset disease than men. *TGFBR1* is the gene where this is most dramatic; we have seen women in their 60s or 70s with small aneurysms whose sons have died of aortic dissections in their late teens or early 20s. The women will still develop aortic disease, just much later. For the other genes, there is minimal or no difference between the age of onset based on sex.

All of these genes have an age-related component, and the gene and the actual genetic variant help determine the age of aortic disease onset. For genes such as *SMAD3* and *MYLK*, those affected develop aortic disease later in life. Additionally, within some genes, we can pull out specific variants in the genes that predict childhood-onset disease, such as with *TGFBR2*, *ACTA2*, and *TGFBR1*. In this case, where disease onset is in childhood, it's important that we identify those variants so that patients can be aggressively managed during childhood.

Are protocols currently available to aid physicians in identifying the known genes in patients?

Yes. Worldwide, DNA genetic testing is available for the genes that predispose to thoracic aortic disease. In other words, all of the genes that my lab and others have identified are tested on diagnostic panels worldwide. Therefore, if patients see their physician and they have thoracic aortic disease and a family history, the physician can order genetic testing. There is a movement now where patients can order their own genetic testing; one company recently started direct-to-consumer testing, and other companies are following suit this year. I think we're going to see more patients directly ordering their genetic testing over time. In the meantime, most physicians will refer to a geneticist or genetic counselor for DNA diagnostic testing for thoracic aortic disease.

In recent years, public sector genetic testing services (eg, 23andMe) have exploded in use. As a genetics researcher, is there potential for those data sets to make new discoveries and improve medical diagnosis?

At this point, no, because companies like 23andMe are primarily testing for common variants in the human genome, and these variants are not responsible for triggering conditions like Marfan syndrome and familial thoracic aortic disease. The genetic triggers for Marfan syndrome and heritable thoracic aortic disease are rare variants in the genome and are not picked up on public sector genetic tests.

As the Executive Chair of the Montalcino Aortic Consortium, can you provide insight into how and why it was formed?

It goes back to establishing gene-based management for thoracic aortic disease. We now have all these genes for heritable thoracic aortic disease. We've known how to manage Marfan syndrome to prevent aortic dissections for many years, but we don't have decades' worth of clinical studies for all of these new genes to tell us how to manage these patients. So, the question becomes, how do we get to gene-based management as rapidly and efficiently as possible? My hypothesis is that we will get there the fastest if we can work with aortic centers worldwide and collect all the clinical data that we can in patients who have established mutations in all the new genes.

The Montalcino Aortic Consortium was launched with the mission of collecting high-quality clinical data worldwide in patients with mutations in heritable thoracic aortic disease genes so that we can rapidly reach gene-based management. It doesn't help us to find the genes if we don't have a complete understanding of the vascular complications associated with that gene, especially if complications are life-threatening.

The consortium's growth has been amazing to me. We are up to about 50 participating centers worldwide throughout the United States, Europe, Canada, Japan, China, Australia, and New Zealand. The Montalcino Aortic Consortium has been publishing about two to three papers per year for the past 2 to 3 years, so research is moving along very rapidly.

We're at the point now where we can write treatment guidelines based on seven of the known genes. The idea is to take all of the cross-sectional data we've compiled to help us define the phenotype associated with each gene and use this information to propose treatment guidelines. Next, we need longitudinal data to make sure that the way we're treating and managing these patients is preventing the complications that we've defined. The Montalcino Aortic Consortium can also be used to further understand the disease through additional molecular, imaging, and similar studies and aid in the identification of patients for future clinical and device trials. For example, the Montalcino Aortic Consortium registry can help answer questions such as whether losartan works as well in a patient with an *ACTA2* mutation as it does in a patient with Marfan syndrome. Many questions may be answered with the information gained from the Montalcino Aortic Consortium.

In an article in *Arteriosclerosis, Thrombosis, and Vascular Biology,*[2] you and Dr. Francesco Ramirez addressed controversies in genetic aortic disease and related therapy. Can you summarize that concern, the discrepancies observed between experimental findings and clinical trials, and the impact on future aortic disease treatment?

This article was focused on what we know about the molecular pathways driving aortic disease in the Marfan mouse models. The initial studies coming out of the Marfan mouse models indicated that blocking transformation growth factor-β (TGFβ) signaling was good and prevented the disease. We now know that that's a very simplistic model of the pathways driving aortic disease and that blocking TGFβ signaling has the potential to make the disease much worse. The point of this article is to say that we should not be trying to develop therapeutics that block TGFβ signaling, and instead, we should focus on other novel molecular pathways that participate in driving aortic disease.

How do you envision the potential for genetics-based screening and treatment over the next few years?

Gene-based screening is already being done in patients and their family members in whom the defective gene triggering the disease has been identified. We need to pursue research to find all of the genes responsible for thoracic aortic disease running in families, so that we can explain the cause of the disease in every family with an inherited predisposition.

The next step is to find all of the low-risk genetic variants that are triggering dissection in the general population. I think that in the next 5 to 10 years, we will have a more comprehensive understanding of these low-risk genetic triggers of disease. We're moving toward genome sequencing in the general population. I'm hoping by the time we are sequencing everyone's genome for medical care, we will know the majority of high- and low-risk variants that confer a risk for aortic dissection so that we can inform patients about their risk for disease; initiate surveillance, appropriate medications, and timely surgical repair; and minimize the environmental triggers for dissection in that individual so that aortic dissections are prevented. For women who may become pregnant, we can also ensure that imaging is performed before pregnancy and they are carefully evaluated during pregnancy and for a few months after.

With these genetic advancements, we can hopefully reach a goal of preventing aortic dissections in the general population within the next 10 to 15 years. ■

1. Renard M, Francis C, Ghosh R, et al. Clinical validity of genes for heritable thoracic aortic aneurysm and dissection. J Am Coll Cardiol. 2018;72:605-615.
2. Milewicz DM, Ramirez F. Therapies for thoracic aortic aneurysms and acute aortic dissections. Arterioscler Thromb Vasc Biol. 2019;39:126-136.

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