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# Unraveling the Genetic and Epigenetic Complexities of Hereditary Aortic Diseases and the Breakthroughs of Precision Medicine: An Editorial

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## 1. Introduction

The field of genetics in cardiovascular disease has introduced new possibilities for understanding the fundamental causes of aortic diseases. Aortic aneurysms, dissections, and ruptures pose a significant health risk, with disproportionately high mortality rates and limited treatment options. On the other hand, only one-third of patients undergoing surgical intervention for thoracic or abdominal aneurysms in the US survive; hence, it ranks seventeenth on the list of the leading causes of death among individuals who are older than 65 years [1–3]. However, over 20% of patients with non-syndromic thoracic aortic disease will report a positive family history, prompting research into predictive genetic and epigenetic markers [4,5]. People with known genetic variants affiliated with this disease experience dissections and rupture espoused by smaller aortic diameters among young people, which increases the need for better research aimed towards identifying these genes earlier so that they can be monitored before they become potentially fatal. Therefore, comprehensive yet targeted genetic screening should be encouraged for individuals with a family history of aortic diseases, as the early detection of pathogenic variants can enable both proactive monitoring and preventive interventions.

In this Editorial, we explore the intricate genetic landscape of aortic diseases, summarizing some of the latest research breakthroughs and emerging advancements that are reforming our understanding of aortic diseases while highlighting the potential for precision medicine to revolutionize diagnostic and therapeutic strategies.

## 2. Editor's Perspective

Extensive research has shed light on the genetic factors associated with aortic diseases. Genome-wide association studies (GWAS) have identified several genetic variants associated with an increased risk of hereditary thoracic aortic aneurysm and dissection (HTAAD). HTAAD frequently involves mutations in key genes which play vital roles in extracellular matrix protein manufacturing, TGF-β signaling, and connective tissue structure. Mutations in these genes often exhibit an increased risk of dissection and rupture. Recent studies have discovered novel gene variants that have emerged as potential drivers. Large-scale meta-analyses and familial studies have expanded the list of implicated loci to over 50, underlining the intricate genetic landscape. Despite progress in identifying genetic drivers, many challenges with the interpretation of the gene VUS still persist, as only a minority of these interpretations have established clinical significance [6]. Precision medicine approaches such as next-generation sequencing and whole-exome sequencing are promising in overcoming these challenges. Increasing the accessibility and cost-effectives of these technologies will enable us to unlock the potential for personalized medicine in aortic disease management. One of the most controversial findings in this field is the possible

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role of common genetic variants in the development of aortic diseases. While rare genetic variants are known to play a major role in certain forms of aortic disease (i.e., Marfan syndrome and Loeys-Dietz syndrome), the contribution of other common genetic variants to disease risk remains questionable. Some studies have suggested that common genetic variants near genes involved in aortic tissue homeostasis, such as the ACTA2 and FBN1 genes mentioned earlier, may also contribute to aortic disease risk [7,8]. Conversely, other studies reported conflicting results, therefore highlighting the need for further research.

## 3. Review of Current Contemporary Genetic Research

New exciting avenues have emerged in aortic disease genetics through the utilization of RT-PCR. This has allowed for the identification of differentially expressed genes in HTAAD, implicating two genes involved in immune-inflammatory responses post-dissection, *SLC11A1* and *FGL2*, which may serve as targets to alleviate damage post-injury [9]. As the list of novel cell death pathways continues to grow, it is imperative that we also identify which of these pathways is involved in aortic injury. Ferroptosis has recently been implicated as a major mode of cell death in HTAAD with several ferroptosis suppressive proteins and genes being downregulated in HTAAD patients, namely *FSP1*, *GPX4*, and liproxstatin-1, thus presenting new possibilities for targeted therapies [10].

Recent work with *ANGLPT8* knockout mice suggests that its expression may contribute to aortic dissection development, with knockout mice having a significantly reduced rupture rate of 0% [11]. Similarly, phospholipase Cε (PLCε) knockout mice were shown to have a markedly increased rate of death as a result of TAAD (43% mortality in knockouts vs. 5% in wildtype) [12]. Follow-up studies using whole exome sequencing of 258 patients with Type A aortic dissections showed that 5 patients had mutations in *PLCE1*, the gene encoding PLCε, suggesting that *PLCE1* may be a key target in the treatment of HTAAD [12].

Some examples of recent publications on genetic research in aortic diseases, as well as potential future directions for research in this field, include recent studies investigating the genetic basis of aortic aneurysms and dissections in individuals with a bicuspid aortic valve (BAV). Several genetic variants were associated with BAV-associated aortic disease, including variants in the *GATA4*, *GATA5*, *GATA6*, *MUC4* and *NOTCH1* genes, which were found to alter the expression of aortic tissue homeostasis [13–15]. Future studies may investigate the functional effects of these genetic variants and their potential as targets for therapeutic intervention. Another recent study explored the genetic basis of aortic dilation in patients with Turner syndrome. This study noted the association of *TIMP1* and *TIMP3* with BAV and aortopathies in patients with Turner syndrome. Further studies may investigate the role of these genetic variants in aortic tissue homeostasis and their potential as therapeutic targets in Turner syndrome. In addition to these specific examples, future research in the field of aortic disease genetics may also explore the use of genome editing technologies, such as CRISPR/Cas9, to modify genetic variants associated with disease risk.

## 4. Emerging Epigenetic and Non-Coding RNA Insights

Beyond the genetic causes of HTAAD, recent research has shown that over a dozen micro-RNA (miRNA) and long non-coding RNA have been associated with aortic disease [16]. Many of these miRNAs have inhibitory effects on collagen, extracellular matrix composition, or vascular smooth muscle differentiation. Research exploring the DNA methylation and histone acetylation patterns at key smooth muscle loci is still in its initial stages, but provides an additional explanatory mechanism regarding the complex etiology of HTAAD [1]. There are also therapeutic opportunities, with miRNAs with miR-126 showing the ability to suppress inflammation in aneurysm development in pre-clinical trials [16]. These discoveries offer promising opportunities as potential targets for pharmacological modulation.

## 5. Advancements in Precision Medicine

Recent breakthroughs in genetic sequencing technologies have revolutionized the field of aortic disease genetics. Next-generation sequencing (NGS) and whole-exome sequencing (WES) have become more accessible and affordable, enabling the comprehensive profiling of individuals' genetic makeup. These advancements offer unparalleled opportunities for personalized risk assessment, early detection, and tailored treatment strategies. By integrating genetic information with clinical data, clinicians can make informed decisions, implement proactive surveillance, and provide timely interventions, thereby optimizing patient outcomes. Furthermore, studies may explore the interactions between genetic and environmental factors in the development of aortic disease, for example, the impact of diet and smoking on aortic tissue homeostasis.

## 6. Conclusions

The genetic landscape of aortic diseases is complex and multifaceted. By embracing advancements in genetic research, we can unlock a deeper understanding of the underlying mechanisms and risk factors involved. The path to precision medicine in aortic disease management lies in identifying key genetic drivers, elucidating novel pathways of cell death, and leveraging epigenetic mechanisms. As we look to the future, it is crucial to continue exploring these avenues to pave the way for improved diagnosis, risk stratification, and targeted therapeutic interventions. Ultimately, by unraveling the genetics of aortic diseases, we can optimize patient care and outcomes in this demanding medical domain.

**Conflicts of Interest:** The authors declare no conflict of interest.

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