

Expanding Horizons for Abdominal Aortic Aneurysms

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Abstract

Recent technological advances have allowed researchers to interrogate the genetic basis of abdominal aortic aneurysms in great detail. The results from these studies are expected to transform our understanding of this complex disease with both multiple genetic and environmental risk factors. Clinicians need to keep abreast of these genetic findings and understand the implications for their practice. Patients will become increasingly informed on genetic risk, and a new era of individualized risk assessment for AAA is just beginning. This brief update aims to provide the clinician with a succinct précis of the recent progress in this area.

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Key Words

Genetic • Association Studies • Risk score • Aneurysm • DNA Sequencing

Introduction

Abdominal aortic aneurysms (AAAs) are a common condition that affects approximately 4-8% of individuals greater than 65 years of age [1]. AAAs are a multifactorial disease, and we know that there is a significant genetic contribution to their formation [2]. Since the 1970s, clinicians have observed that an important risk factor for AAA formation is a positive family history for the disease with an estimated increased indi-

vidual risk between two and eleven fold [3-7]. Several studies have described familial aggregation of AAA [7-10], the largest one of these studies with 233 multiplex families [11]. The AAA families displayed multiple forms of inheritance patterns suggesting that AAA is a complex, multifactorial disease.

Based on a recent twin study in Sweden, the estimated genetic contribution to overall susceptibility for AAA formation is approximately 70% [6]. In this study, 265 twins with AAA, including seven monozygotic and five concordant pairs with the disease, were identified in a Swedish population and disease registries. The odds ratio (OR) of the disease in monozygotic twins was 71 [95% confidence interval (CI): 27-183] and for dizygotic twins 7.6 (95% CI: 3.0-19).

Genetic Studies: Have We Made Any Progress?

The evidence supporting a strong genetic component to AAA formation has encouraged a number of research groups to perform hypothesis-driven candidate gene association studies for AAA; some of these studies have yielded highly significant findings, which we summarize in Table 1. With unbiased genome-wide association studies (GWAS), researchers have been able to interrogate the entire genomes of AAA patients, resulting in the dis-



Table 1. Summary of Genetic Variants Significantly Associated with AAA Risk from Candidate Gene Association Studies.

Study with Literature Citation	Type of Study	Gene and Variant(s)	Potential Functional Role	Odds Ratio [95% Confidence Interval]	P-value
Morris et al. 2014 [35]	Meta-analysis	MMP3: rs3025058 (5A/6A)	Altered remodeling of extracellular matrix	1.48 [1.23 – 1.78]	4.0 x 10 ⁻⁵
Galora et al. 2013 [36]	Association study	LRP5: rs3781590* and rs4988300*	Lipoprotein metabolism	2.16 [1.41 – 3.29]	< 0.0001
Jones et al., 2013 [37]	Association study	SORT1: rs599839	Lipid metabolism	0.81 [0.76 – 0.85]	7.2 x 10 ⁻¹⁴
Helgadottir et al., 2012 [38]	Association study	LPA: rs10455872a and rs3798220a	Increased atherosclerotic burden	1.23 [1.11 – 1.36]	6.0 x 10 ⁻⁵
Harrison et al., 2012 [39]	Meta-analysis	IL6R: rs7529229 (Asp358A-la)	Reduction in downstream targets in response to IL6 signaling	0.85 [0.80 – 0.89]	2.7x10 ⁻¹¹
Saracini et al., 2012 [40]	Meta-analysis	MMP13: rs2252070 (-77A/G)	Altered remodeling of extracellular matrix	1.37 [1.04 – 1.82]	
Biros et al., 2011 [41]	Meta-analysis	TGFBR2: rs764522	Altered regulation of vascular remodeling	1.69 [1.28 – 2.25]	2.7 x 10 ⁻⁴
		TGFBR2: rs1036095		1.59 [1.23 – 2.07]	4.8 x 10 ⁻⁴
McColgan et al., 2009 [42]	Meta-analysis	IL10: rs1800896 (nt -1082)	Interleukin signaling	1.51 [1.13 – 2.02]	0.006
		ACE: rs4646994 (I/D)	50% increased ACE activity	1.35 [1.17 – 1.56]	< 0.0001
		MTHFR: rs8003379 (C677T)	70% reduction in activity; increased homocysteine levels	1.34 [1.08 – 1.65]	0.007
Jones et al. 2008 [43]	Association study	AGTR1: rs5186	Renin-angiotensin system	1.60 [1.32 – 1.93]	1.1 x 10 ⁻⁶
Giusti et al. 2008 [44]	Association study	MTHFD1: rs8003379	Methionine metabolism	0.41 [0.26 – 0.65]	< 0.0001
		MTRR: rs326118		0.47 [0.29 – 0.77]	0.003

Studies are listed in chronological order with the most recent one first. Only studies with a minimum of 400 AAA cases and 400 controls and highly significant ($p < 0.01$) results were included. Gene symbols: ACE, angiotensin converting enzyme; AGTR1, angiotensin II type 1 receptor; IL10, interleukin 10; IL6R, interleukin 6 receptor; LRP5, low density lipoprotein receptor-related protein 5; LPA, apolipoprotein a; MMP3, matrix metalloproteinase 3; MMP13, matrix metalloproteinase 13; MTHFD1, methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1; MTHFR, 5,10-methyltetrahydrofolate reductase; MTRR, 5-methyltetrahydrofolate-homocysteine methyltransferase reductase; SORT1, sortilin 1; TGFBR1, transforming growth factor beta receptor 1; and TGFBR2, transforming growth factor beta receptor 2.

*Analyses were performed by combining the risk alleles of both variants in the same gene.

covery of four reproducible chromosomal regions that confer susceptibility to AAA formation:

- i. The G-allele of a single nucleotide polymorphism (SNP), rs10757278, located on chromosome 9p21.3 in the noncoding RNA CDKN2B-AS was first discovered in an analysis of patients with coronary artery disease (CAD) [12] and then found to be associated with multiple vascular phenotypes including AAA with an OR of 1.31 (95% CI: 1.22–1.41) and a highly significant $p = 1.2 \times 10^{-12}$ [13,14]. The potential role of this SNP in AAA formation is discussed below.
- ii. The A-allele of SNP rs7025486 located near a gene called DAB2-interacting protein (DAB2IP) on chromosome 9q33.2 was associated with AAA with an OR of 1.21 (95% CI: 1.14–1.28) and a highly significant $p = 4.6 \times 10^{-10}$ [15]. DAB2IP encodes a potent inhibitor of cell growth and survival, which results in increased smooth muscle cell susceptibility to apoptosis via the ras GTPase [16].
- iii. The C-allele of SNP rs1466535 located on chromosome 12q13.3 within intron 1 of the gene for low-density-lipoprotein receptor-related protein 1 (LRP1) had a significant association with AAA

with an OR of 1.15 (95% CI: 1.10–1.21) and a highly significant $p = 4.52 \times 10^{-10}$ [17]. The LRP1 protein is involved in the regulation of extracellular matrix remodeling as well as vascular smooth muscle cell migration and proliferation, all of which are plausible mechanisms in AAA pathogenesis [18].

- iv. The A-allele of SNP rs6511720 located on chromosome 19p13.2 in the gene for low-density-lipoprotein receptor (LDLR) had a significant association with AAA with an OR of 0.76 (95% CI: 0.70–0.83) and a highly significant $p = 2.08 \times 10^{-10}$ [19]. This same variant has also been associated with lipid levels and CAD [19]. In each of these three traits, it is the A-allele that is associated with a protective effect (OR <1) [19]. These findings suggest that AAA and CAD have at least some shared biological pathways that contribute to disease initiation or progression.

These studies have begun to unravel the genetic variants contributing to the heritability of AAA. Little, however, is known about the biological mechanisms and how they may contribute to the complex disease process. AAA is a difficult phenotype to study due to a number of aspects. It is a late-age-at-onset disease that is often fatal, which can hinder extended family analysis. Similarly, “unaffected” family members may not have manifested the disease at the time of the study but may develop AAA in due course. Overall, GWAS studies have identified loci that collectively account for a very small fraction of the observed heritability of AAA. This raises the questions: Where are the missing genetic variants contributing to AAA heritability, how to find them, and what do these variants do?

Emerging Fields in Genetic Research

With the advent of increasing technological advances in the field of DNA sequencing, the capacity for in-depth sequencing within laboratories has risen exponentially, called Next Generation Sequencing (NGS). A task that used to take months to perform is now possible in a matter of days at a vastly reduced cost, which will drive the search for AAA genes into new and exciting frontiers. Considerable success has

been made using these techniques to discover novel DNA variants that underpin the heritability of rare clinical phenotypes, such as Miller syndrome [20]. The next challenge for geneticists is to begin to sequence the whole exomes and genomes of AAA patients for missing variants predisposing to AAA formation.

Using exome sequencing, a novel frame-shift mutation in the SMAD3 gene was identified in a family with autosomal dominant inheritance of thoracic aortic aneurysms with intracranial aneurysms and AAA [21]. This study illustrated the effectiveness of NGS in discovering variants if extended families are available for analysis. Researchers are, however, faced with a number of challenges when applying NGS analysis to AAA to identify causal mutations. Currently, exome coverage is not 100%, some exons are poorly sequenced, and methods for calling small insertion/deletions (so called INDELS) and copy number variants (CNVs) are in further development [22]. Additional challenges related to NGS are low reproducibility of detection of variants and uncertainty about which variants are truly clinically important [23]. Another difficulty for AAA is that, when sequencing families, the segregation of the phenotype in the family may be due to nongenetic, lifestyle factors rather than a genetic sequence variant.

Beyond the SNPs: Where Do We Go from Here?

Identifying the risk conferring DNA variants is the first step in a long process to understanding the underlying disease mechanism; the next step is the challenging task of deciphering how the variant is predisposing to disease. For example, GWAS established that the sequence variant rs10757278-G on 9p21.3 confers an increased risk for CAD and AAAs [13]. The loss of the INK4a/ARF/INK4b region on chromosome 9p21 was first identified in 2006 as a key process in the cytogenetic events resulting in tumorigenesis, with further characterization since then [24, 25]. Mouse models were used to discover the mechanism by which sequence polymorphisms on chromosome 9p21 confer an increased risk of arterial disease. In culture, aortic smooth muscle cells obtained from mice with a 70-kb deletion encompassing rs10757278 showed excessive proliferation and altered regula-

tion of the neighboring genes [26]. CDKN2B, a tumor suppressor gene, lies within the risk locus on 9p21. An elegant study by Leeper et al. [27] demonstrated an increased aortic diameter in *Cdkn2b* knockout mice using the elastase AAA model. Furthermore, in vitro studies using cultured human cells showed marked apoptosis of smooth muscle cells related to increased p53 signaling pathways. Pharmacological inhibition of p53 signaling in the *Cdkn2b* knockout mice reversed the vascular phenotype in the elastase model. The authors concluded that reduced CDKN2B expression and increased smooth muscle cell apoptosis may underlie the 9p21.3 association with AAA. In depth sequencing of the 9p21.3 region within the Framingham cohort identified additional sequence variants [28]. Harismendy et al. [29] interrogated the 9p21 risk alleles (rs10811656 and rs10757278) further and demonstrated their location within enhancer intervals that interact physically with an interval downstream of IFNA21 (interferon, alpha 21). Their work established a connection between the 9p21 risk variants and aberrant vascular cell responses to inflammatory signaling, leading to CAD susceptibility. These promising advances demonstrate that we are only starting to embark on a new era in understanding aneurysm formation directed by genetic discoveries.

Moving Towards an Era of Individualized Risk Assessment: The Future of AAA Diagnoses

Until recently, classical risk factors for AAA have been used to identify patients in the general population for aneurysm screening. These risk factors have formed the basis of the national AAA screening program in the UK: for example, age over 65 years, male sex, and positive family history for the disease (<http://aaa.screening.nhs.uk/>). Large-scale epidemiological studies have enabled more complex scoring algorithms for AAA risk to be constructed. Greco et al. [30] evaluated 3.1 million individuals screened for AAA and recorded their demographics and environmental risk factors. Using multivariable logistic regression analysis, they developed a novel scoring system for AAA risk that included several clinical variables and achieved a predictive accuracy C statistic of 0.82. The benefits of a healthy lifestyle including exercise,

maintaining normal weight, and dietary habits were reinforced in this study, which showed that these factors do contribute to lowering risk and were included in the algorithm [30,31].

As we continue to identify additional genetic variants associated with AAA, individual genetic profiling in addition to environmental risk assessment will become possible. Recent studies on other complex diseases have shown that screening the population for only a single genetic variant for each disease has a poor predictive value; however, a profile of 50 variants, each with odds ratios of 1.02–1.15, may improve the accuracy of disease prediction [32]. Using simulated genetic models, some studies have concluded that substantial predictive power is only achieved when a large number of genetic variants ($n = 100\text{--}160$) with greater effect sizes is employed [33, 34].

The future challenge is to use the variants identified in genetic studies to produce integrated genetic and environmental predictive models to more accurately identify at risk individuals in the population that, in turn, will allow alignment of individuals to different types and intensities of screening.

Conclusions

The field of AAA genetics is rapidly progressing with new high-throughput genotyping and DNA sequencing technologies, identifying increasing numbers of genetic variants associated with the disease. With an emerging number of international collaborative projects generating GWAS data, meta-analysis of GWAS data will be required. Once a larger number of variants are identified, the possibility of integrated genetic and environmental predictive models may become a reality for personalized risk assessment and screening.

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Conflict of Interest

The authors have no conflict of interest relevant to this publication.

Comment on this Article or Ask a Question

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EDITOR'S QUESTIONS

1. **What do you recommend in terms of genetic testing for AAA patients we are currently seeing in the office? Should we be testing everyone clinically (i.e., outside of investigational protocols)? What specific tests should we order? Where do we send samples?**

We currently do not recommend genetic testing for AAA patients outside of investigational protocols. Unfortunately, current genetic variants related to abdominal aneurysm formation have a poor pre-

dictive value when tested in isolation. An increased number of variants with greater effects are required to create integrative predictive models for future testing by clinicians.

If a patient wishes to investigate their genetic risk further, a number of private genetics services are available; these, however, are not in the patients' best interests due to a lack of supporting evidence for this practice and uncertainty with the interpretation of results.

2. Are there specific genetic variants in AAA that predict a more malignant clinical behavior? If so, which?

Current research is beginning to characterize genetic subtypes of AAA. A preliminary report with a small sample size was recently published [1] that used logistic regression studies to identify genetic variants in LRP1 associated with an aggressive AAA phenotype. In the future, the results of these studies may enable us to categorize patients into indolent and aggressive phenotypes, and tailor monitoring and treatment to the individual.

References

1. Duellman T, Warren CL, Matsumura J, Yang J. Analysis of multiple genetic polymorphisms in aggressive-growing and slow-growing abdominal aortic aneurysms. *J Vasc Surg.* 2014;60:613-621. [10.1016/j.jvs.2014.03.274](https://doi.org/10.1016/j.jvs.2014.03.274)