Published in final edited form as:

Expert Rev Cardiovasc Ther. 2015 ; 13(9): 975–987. doi:10.1586/14779072.2015.1074861.

Understanding the pathogenesis of abdominal aortic aneurysms

Helena Kuivaniemi[*,1,2,3], **Evan J. Ryer**[4], **James R. Elmore**[4], and **Gerard Tromp**[1,3]

Helena Kuivaniemi: hkuivaniemi@sun.ac.za; Evan J. Ryer: ejryer@geisinger.edu; James R. Elmore: jelmore@geisinger.edu; Gerard Tromp: gctromp@sun.ac.za

[1]Sigfried and Janet Weis Center for Research, Geisinger Health System, Danville, PA 17822, USA

[2]Department of Surgery, Temple University School of Medicine, Philadelphia, PA 19140, USA

[3]Division of Molecular Biology and Human Genetics, Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, 7505, South Africa

[4]Department of Vascular and Endovascular Surgery, Geisinger Health System, Danville, PA 17822, USA

Summary

An aortic aneurysm is a dilatation in which the aortic diameter is ≥ 3.0 cm. If left untreated, the aortic wall continues to weaken and becomes unable to withstand the forces of the luminal blood pressure resulting in progressive dilatation and rupture, a catastrophic event associated with a mortality of 50 – 80%. Smoking and positive family history are important risk factors for the development of abdominal aortic aneurysms (AAA). Several genetic risk factors have also been identified. On the histological level, visible hallmarks of AAA pathogenesis include inflammation, smooth muscle cell apoptosis, extracellular matrix degradation, and oxidative stress. We expect that large genetic, genomic, epigenetic, proteomic and metabolomic studies will be undertaken by international consortia to identify additional risk factors and biomarkers, and to enhance our understanding of the pathobiology of AAA. Collaboration between different research groups will be important in overcoming the challenges to develop pharmacological treatments for AAA.

Keywords

embryologic origin; extracellular matrix; genetic susceptibility; risk factors; smoking; epigenetics; animal models; inflammation; doxycycline; matrix metalloproteinases

[*]Author for correspondence: Helena Kuivaniemi, MD, PhD, FAHA, Division of Molecular Biology and Human Genetics, Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, 7505, South Africa; Tel: +27 (21) 938-9251; Fax: +27 (21) 938-9863, hkuivaniemi@sun.ac.za.

Financial and competing interests disclosure

H. Kuivaniemi has received research funding from the National lnstitutes of Health, Pennsylvania Universal Research Enhancement Program, and Penn Franklin Technology Development Fund of Pennsylvania. E.J. Ryer has received research funding from the Geisinger Clinical Research Fund. J.R. Elmore has received research funding from the Geisinger Clinical Research Fund, American Heart Association, Pennsylvania Universal Research Enhancement Program, and Penn Franklin Technology Development Fund of Pennsylvania. G. Tromp has received research funding from. the National lnstitutes of Health, Pennsylvania Universal Research Enhancement Program and the Geisinger Clinical Research Fund. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The aorta is generally subdivided into its thoracic and abdominal components (Figure 1). The thoracic aorta is further classified into the ascending aorta, aortic arch, and descending thoracic aorta, while the abdominal aorta spans the distance between the diaphragm and the aortic bifurcation. An aortic aneurysm is a permanent localized dilatation associated with a diameter ≥ 3.0 cm. If left untreated, the aortic wall continues to weaken and becomes unable to withstand the forces of the luminal blood pressure resulting in progressive dilatation and rupture. Rupture risk increases with increasing aortic diameter and this catastrophic event is associated with a mortality of 50 – 80% [1].

Aortic aneurysms can develop in both the thoracic and abdominal aorta (Figure 1), albeit more patients suffer from and undergo surgery for aneurysms of the abdominal aorta [2,3]. Abdominal aortic aneurysms (AAAs) can be further categorized into supra-renal or para-visceral aneurysms if they involve the visceral arteries, para-renal if they involve the origins of the renal arteries or infra-renal if they begin lower than the renal arteries [4]. The majority of AAAs are infra-renal in extent [5]. Historically, thoracic aortic aneurysms (TAAs) and AAAs were thought to both arise from atherosclerotic degeneration of the aortic wall. More recent research, however, has demonstrated that these diseases are distinct disease entities [6].

Differences in the thoracic and abdominal regions of the human aorta

To better understand how the pathophysiology of TAAs and AAAs differs, it is helpful to begin by examining the embryology of the aorta. Different segments of the aorta are comprised of cells originating from the neural crest, mesenchyme and splanchnic mesoderm with a clear difference depending upon the segment (Figure 1). The early embryo develops a common set of precursor vessels that differentiate into arteries, veins and lymphatic vessels. Primitive arteries are surrounded by smooth muscle cells (SMCs) of mesodermal origin. Following extensive remodeling, the original primitive SMCs of the aortic arch and the thoracic aorta are replaced by a second wave of SMCs that migrate from the neural crest [7]. These neural crest–derived SMCs are likely better suited to adaptively remodel the thoracic aorta to withstand the higher pulse pressure and ejection volume by laying down more elastic lamellae during development and growth. In contrast, the epigenetic programming of the SMCs in the abdominal aorta remains more similar to that of the original primitive arterial SMCs [6]. Moreover, the neural crest cell precursors of the thoracic aorta respond differently to various cytokines and growth factors than the mesodermal precursors of the abdominal aorta [8]. One well known example is homocysteine, a sulfur containing amino acid involved in atherosclerosis, elastolysis, collagen deposition and aortic compliance [9,10]. Homocysteine has been found to stimulate the proliferation and synthetic activity of neural crest vascular smooth muscle cells while those of mesodermal origin are unaffected [11]. Another example is angiotensin II, a vasoactive peptide associated with vascular remodeling and atherosclerosis [12], which when continuously infused led to aneurysms of the suprarenal abdominal aorta in mice deficient in the gene for apolipoprotein E (*Apoe*$^{-/-}$) without effect on the thoracic aorta [13]. This study, too, highlights the differential response of the cells comprising the thoracic aorta as compared to the abdominal aorta. A final example is transforming growth factor-beta (TGF-β), which is an established contributor to vascular development and regulator of cell growth and differentiation. When treated with

TGF-β, neural crest vascular SMCs demonstrated increased DNA synthesis and collagen production, while mesodermal vascular SMCs did not respond [14]. This may explain why mutations in the TGF-β receptor may lead to TAA but have little effect on the abdominal aorta.

Corresponding to their differing embryology, the thoracic aorta and abdominal aorta are also structurally very different from one another. Both the thoracic aorta and the abdominal aorta are elastic arteries that consist of an intimal, medial and adventitial layer. The intima is a single layer of endothelial cells upon connective tissue, the media consists of SMCs embedded in structural proteins (elastin and collagen) while the adventitia is composed of fibroblasts and collagen fibers [15]. The aorta, regardless of the location, is dependent upon distinct fibromuscular layers (so called lamellar units) to distribute stress and provide elasticity. The media of the thoracic aorta is comprised of ~60 units divided into avascular and vascular regions. On the other hand, the abdominal aorta consists of ~30 units and is entirely avascular. In addition to being less substantial with regards to the number of fibromuscular layers, the media of the abdominal aorta is completely dependent on trans-intimal diffusion of nutrients for SMC survival [16]. It is likely that the fewer lamellar units and avascular nature make the abdominal aorta more prone to aneurysmal degeneration.

Lastly, the genetic differences underlying aneurysms of the thoracic and abdominal aorta differ (Figure 2; Supplementary Table). While there is a 10–15% chance of an individual with a AAA having a metachronous or synchronic TAA [17], most family–based studies have demonstrated a predisposition for either aneurysmal involvement of the thoracic or abdominal aorta, but not both [18]. Indeed, most recent genetic studies show no genetic overlap between AAA and TAA.

Clinical features of abdominal aortic aneurysms

Clinical picture and risk factors for AAA

The main risk of an untreated AAA is progressive expansion, rupture, hemorrhage and death. Despite advances in screening and treatment, AAA rupture remains a major cause of death in the elderly. A recent review of 3 million patients undergoing a medical and lifestyle questionnaire prior to ultrasound screening found that smoking is by far the strongest modifiable risk factor for AAA [19]. Additionally, other important risk factors including age, male gender, and family history was confirmed [19]. In this study, Kent et al. [19] went on to construct a predictive scoring system to identify AAA. Applying this model to US population statistics, these investigators estimated that there are ~ 1 million AAAs in the United States, of which half were women, nonsmokers and those less than 65 years of age. This translated to an overall prevalence of AAA of 2.8% for men aged 65 to 79 years of age. These numbers advocate for a broader application of AAA screening to reduce mortality from ruptured AAA. In contrast, an AAA screening program in Sweden found a lower prevalence of AAA suggesting that there has been a change in AAA epidemiology [20]. In this study, Svensjo et al. [20] examined all 65 year old males, identified through a National Population Registry, who underwent ultrasound screening for AAA. In total 22,187 patients were screened and 373 AAAs (1.7%) were identified. When accounting for 127 known AAAs undergoing surveillance, the investigators calculated a AAA prevalence of 2.2%.

Similar to the study by Kent et al. [19], smoking was again the most important risk factor for AAA. In contrast to the study by Kent et al [19], the Swedish investigators [20] found only a 1.7% prevalence of AAA in the screened population (65 year old males), which is the lowest AAA prevalence reported to date. This low prevalence, combined with the small size of AAAs identified (70% were < 4.0 cm) and decreasing tobacco use among the current population, has led these researchers to question the need for expansion of current AAA screening guidelines.

In addition to smoking, family history is another major risk factor for the development of AAA. Indeed, a recent investigation has confirmed this documenting that ~10% of AAA are familial in nature with a prevalence of 13% among affected families and a staggering 25% prevalence among brothers [21]. This substantial prevalence among brothers was confirmed in a Danish population based cross section study [22]. In this cross sectional study, Joergensen et al. examined 560 participants of a population based screening program with at least one first degree relative diagnosed with AAA. In addition to an increased prevalence of AAA in those with a family history, patients with a positive family history had a significantly larger mean aortic diameter (20.5 mm) compared to those without a family history ($p<0.001$). A unique finding of this family history study was that a positive family history with female relatives with a AAA had a more than a two fold increase in the prevalence of AAA when compared with those who had a positive family history with male relatives with AAA (OR = 2.65, 95% CI: 1.37 – 5.13). In addition to an increased AAA prevalence in those with a positive family history, a positive family history may also be responsible for accelerated growth, and possibly rupture, of small (< 5.0 cm) AAAs. Recently, a Japanese investigation by Akai et al. [23] found that the growth rate of small AAAs in patients with a positive family history of an AAA was twice that of those without a family history (4.2 mm/y vs 2.0 mm/y, respectively; $P < 0.009$). This finding, albeit from a small patient cohort, may have impact on the future recommendations regarding AAA surveillance.

Treatment of AAA

The main aim of treating large AAAs is to prevent rupture and its associated high mortality rate. Prior to proceeding with repair, it is imperative to understand the risk:benefit ratio of elective asymptomatic AAA repair and weigh this against the annual risk of rupture prior to proceeding. The perioperative mortality of traditional open AAA repair varies greatly in the surgical literature. Single institution studies from centers of excellence report a perioperative mortality that ranges from 1 to 4% [24,25]. Other investigators using state-wide or national data sets report a significantly higher mortality rate that ranges from 4 to 8% [26]. While these numbers seem substantial, the risk of developing a major adverse event following open AAA repair is even greater and ranges from 15 to 30%. These major adverse events include myocardial infarction (15%), pneumonia (5%), renal insufficiency (5–12%), limb ischemia (1–4%), deep venous thrombosis (5–8%), colonic ischemia (1–2%), stroke (1–2%), and many others [26]. Since its approval by the Food and Drug Administration in 1999, endovascular AAA repair (EVAR) has been increasingly used in an effort to reduce the perioperative mortality, hospital stay, and blood loss associated with traditional open repair. While providing some short term benefit, it is important to realize that EVAR does not

provide a quality of life benefit, does not improve long term mortality, is associated with the need for continued surveillance and re-interventions, and carries a substantially increased cost and its own unique set of complications [27]. Furthermore, the perioperative morbidity and mortality of EVAR is not different when compared to appropriately selected patients who undergo traditional AAA repair. In addition, the freedom from graft-related re-intervention after open AAA repair is far superior to that of patients treated with EVAR [24].

Due to the risks associated with aortic surgery and AAA repair, several recent investigations have focused on using pharmacologic means to slow aneurysmal growth and postpone or lessen the need for surgical repair of large AAAs. The most well-known drug candidate for pharmacologic stabilization of AAA is doxycycline. Doxycycline, a member of the tetracycline antibiotic family, has been shown in inhibit matrix-metallopeptidase 9 (MMP9) expression and activity as well as AAA growth in several studies utilizing AAA animal models [28]. Despite its promise in animal models, a recent randomized, placebo controlled double blind trial by Meijer et al. [29] found that 18 months of doxycycline treatment did not attenuate aneurysm progression nor did it influence the need for or time to AAA repair. Furthermore, doxycycline not only failed to slow AAA growth but its administration was associated with a small increase in AAA growth (4.1 mm vs. 3.3 mm at 18 months, P=0.016). Based on this surprising finding, the authors suggested we re-evaluate all existing models of AAA. Another potential medical therapy is the angiotensin converting enzyme (ACE) inhibitors, a commonly used anti-hypertension agent. Interest in the use of ACE inhibitors to prevent expansion and rupture of AAA peaked in 2006 with a publication by Hacham et al. [30]. This study utilized an administrative database in Ontario, Canada to perform a population based case control study involving over 15,000 patients. This analysis found that patients receiving ACE inhibitors were significantly less likely to present with a ruptured AAA (OR = 0.82, 95% CI: 0.74 – 0.90). This finding remained significant even after adjustment for demographic characteristics, risk factors for rupture, and comorbidities. As a result of these findings, Sweeting et al. [31] examined a prospective cohort of 1,701 patients enrolled in the UK Small Aneurysm trial. Unfortunately, this investigation found that the mean aneurysm growth rate in 169 patients taking ACE inhibitors at baseline was significantly greater than the 1,532 patients who were not on an ACE inhibitor (ACEi: 3.33 mm/y vs None: 2.77 mm/y, $P=0.009$.). The contrasting results highlight a need for a randomized controlled trial to determine the beneficial or potentially harmful effects of this medication class in AAA patients. Another potential medication class with pleiotropic effects which may benefit AAA patients are statins. Some investigators have hypothesized that statins may reduce AAA growth, and hence rupture risk, by attenuating aortic wall inflammation [32,33]. Indeed, two large meta-analyses have demonstrated decreased aneurysm growth rates in AAA patients on statin therapy [34,35]. Furthermore, investigators recently performed a nationwide analysis of patients presenting with ruptured AAA in Denmark from 1996 to 2008. Using 3584 cases and 3584 matched controls, these researcher found that statin use was associated with a decreased risk of a ruptured AAA (OR 0.7, 95%CI: 0.60–0.81) and lower case fatality following rupture (OR 0.80, 95%CI: 0.78–1.22) [36]. Undoubtedly, the future will involve multiple other studies before a pharmacologic agent without significant side effects is found suitable to attenuate AAA growth.

Pathophysiology of AAA

Several biological processes and risk factors have been identified that contribute to AAA pathogenesis. On the histological level, visible hallmarks of AAA pathogenesis include inflammation, VSMC apoptosis, extracellular matrix (ECM) degradation, and oxidative stress (Figure 3) [37–39]. Autoimmunity may also play a role in AAA development and progression [18,35,36]. Although the mechanism of autoimmunity is not precisely known, we hypothesize and others hypothesize that there must be a breakdown of the immunoregulatory mechanisms or some type of a molecular mimicry following a bacterial or viral infection. As previously mentioned, the exact [18,40,41]. The order of the pathological events and their direct contribution to AAA, are not yet understood.

An unbiased approach to study AAA pathogenesis at the molecular level is to carry out a genome-wide microarray-based mRNA or microRNA (miRNA) analysis to identify changes in mRNA and miRNA levels associated with AAA [6,42–44]. The results are then analyzed using computational tools to classify the genes into functional groups and pathways. Additional computational approaches aim to find transcription factor binding sites in the genes with altered expression [45] and network analyses to obtain a more comprehensive picture of the various biological pathways and their interactions through shared molecules [46].

Microarray-based mRNA expression data exist for both aortic tissue [46–51] and whole blood [52] collected from AAA patients and controls. The most recent analyses compared expression in aortic tissue samples between AAA patients and aortic occlusive disease [47]. Interestingly, the expression patterns were quite different, supporting the hypothesis that AAAs are not simply a manifestation of atherosclerosis, but a separate, although related disease entity.

The genome-wide expression analyses have demonstrated a large number of genes with altered mRNA levels in the AAA tissue. A large fraction of these genes belong to immunological pathways such as the Natural Killer Cell Cytotoxicity pathway [48,53]. Follow-up studies on aortic tissue samples using immunohistochemical staining with specific antibodies showed that the corresponding proteins are expressed in the aortic tissue and suggest that the Natural Killer Cell Cytotoxicity pathway is activated during AAA development [53]. Another follow-up study used chromatin immunoprecipitation and antibodies against the transcription factors predicted to bind to the differentially expressed genes [54]. Bioinformatic analyses were used to find the transcription factor binding sites in the chromatin enriched regions and categorize the target genes into biologically functional groups. Again, genes with immune function were highly enriched among the genes with transcription factor binding in the AAA tissue. Interestingly, the biological categories of the genes with decreased mRNA levels in AAA tissue compared to control aorta included cytoskeleton organization, muscle cell development, and organ morphogenesis and thus differed from pathways among the genes with increased expression in AAA [54].

miRNAs are small, well-conserved, non-coding molecules which can inhibit gene expression at the posttranscriptional level. Each miRNA is predicted to regulate a large

number of target genes (mRNAs). One recently published microarray-based genome-wide analysis of miRNA patterns in human AAA [55] identified five miRNAs (miR-133b, miR-133a, miR-331-3p, miR-30c-2 and miR-204) which were downregulated in AAA when compared to age- and sex-matched control samples also taken from the infrarenal regions of the human aorta. The results were validated with real-time quantitative RT-PCR in an independent set of samples. Extensive bioinformatic analyses were carried out to identify the mRNA targets of these miRNAs. A total of 1,836 potential target genes were found, 222 of which were significantly upregulated in a previously published mRNA expression study [48]. One of these targets was *MMP9* which has a well-established role in AAA pathogenesis [38].

Several studies have investigated the role of miRNAs in AAA using mouse models and cell culture systems [56–58]. These studies revealed that overexpression of miR-24 [57] and inhibition of miR-29b [56] slowed down AAA progression in mouse models, whereas inhibition of miR-195 [58] had no effect on aortic dilatation. The action of miR-24 appeared to be via inhibiting vascular inflammation Maegdefessel 2014}. Furthermore, miR-24 [57] and miR-195 [58] levels were reduced in plasma samples of AAA patients. The levels of miR-29b, however, were decreased in human and mouse AAA tissue samples suggesting a more complex regulatory network [56].

Recent advances in techniques to analyze proteins have made quantitative proteomic analyses of aortic tissues, red blood cells and plasma samples from AAA patients feasible [59–62]. A proteomic analysis of blood polymorphonuclear neutrophils showed that catalase levels were elevated in AAA patients [62] and a similar analysis of organ cultures of aortic tissues identified peroxiredoxin-1 in AAA patients [61]. A preliminary study found 39 different proteins in the red cell membrane whose levels varied between AAA patients and controls based on mass spectrometry analyses [59]. Another intriguing approach is to study plasma-derived microvesicles, including microparticles and exosomes, as a source for biomarker discovery in proteomic analyses [60].

One of the striking differences in aneurysmal aortic wall compared to non-aneurysmal one is the reduced number of VSMCs. Another difference is the increased number of inflammatory cells in the aneurysmal aorta [18,41]. To elucidate the role of the different cell types in the pathogenesis of AAA, investigators have isolated the various cell types using laser-capture-microdissection and then studied the specific cell populations using e.g. microarray-based expression or proteomic analyses [63,64]. In one of these studies, Airhart and co-workers [63] found that the SMCs isolated from AAA tissue could be distinguished from those isolated from non-aneurysmal aorta based on their gene expression and enhanced MMP activity. In another study, Boytard and co-workers [64] microdissected mannose receptor (MR)-positive and negative macrophages from AAA tissue and control aorta and showed that peroxiredoxin-1 mRNA and protein levels were higher in MR-negative cells [64].

A recent study found that the number of stem cells was significantly elevated in human AAA tissue compared with matched control aortic tissue [65]. The AAA stem cells expressed macrophage surface antigens (CD68), but not VSMC (SM22) or fibroblast (FSP1) markers, and co localized in the aortic wall with the cellular marker of proliferation Ki67. In

another study adipose-tissue-derived mesenchymal stem cells were delivered to the aortae of mice induced to have AAA with an elastase treatment [66]. The mice receiving stem cells had smaller AAAs and the elastin fragmentation was less pronounced. In another mouse study mesenchymal stem cells from a female donor were more effective in attenuating the growth of AAA than cells from male donors [67]. These three studies raised the possibility of localized replenishment therapy in the aneurysm wall, in which the stem cells could promote aortic ECM stability by secreting growth factors and cytokines necessary for healing. Adipose-tissue-derived mesenchymal stem cells for this potential treatment should be easily available from liposuctions.

Smoking is a well-established and the most important risk factor for AAA, playing even greater role in AAA than atherosclerosis [68]. In clinical studies, it has also been shown to increase the growth rates and the risk of rupture of AAA [34]. Even though in many populations smoking rates have declined in recent years, the effect of smoking on AAA risk is likely to continue for a long time. The mechanism by which smoking exerts the increased risk for AAA, is not fully understood. In cultured aortic endothelial cells, components of cigarette smoke induced MMP1 through inhibition of mTOR signaling [69], whereas in cultured VSMCs they promoted proliferation and survival [70]. Nicotine alone has been shown to enhance AAA formation in mouse models [71,72]. The more elegant studies have exposed experimental animals to inhaled cigarette smoke to fully mimic the human exposure [73]. In these studies, tobacco smoke alone did not lead to AAA formation, but it exaggerated aneurysm formation in response to elastase-treatment. When leukocytes isolated from mice exposed to tobacco smoke were transferred to mice that were not exposed to tobacco smoke, the cells could be found in the AAA tissue and the size of AAA increased in the smoke-free mice [73].

Several studies have suggested that microorganisms, including *Chlamydia*, *Mycoplasma pneumoniae*, *Helicobacter pylori*, *human cytomegalovirus*, *herpes simplex virus*, *Borrelia burgdorferi sensu lato (sl)* and different oral bacteria may serve as possible triggers for the development of AAAs [40]. Based on these studies it is plausible to hypothesize that AAAs could develop due to induced autoimmunity via molecular mimicry due on similarities between the proteins of the microorganism and those of the aortic wall [40].

Animal models of aortic aneurysms

Aortic aneurysms in mice can be induced by three experimental techniques: elastase perfusion, $CaCl_2$ application, and angiotensin II (AngII) infusion [43,74]. In the elastase model the abdominal aorta is isolated and the lumen of the vessel is perfused for a short period with crude elastase, leading to a local dilatation of the aorta after about 14 days. Similar to the human AAA histology, a chronic inflammatory response is seen in the aortic wall. In the second model $CaCl_2$ is applied periarterially, making it less invasive and technically less demanding than the elastase model [74]. Like the elastase model, the mice used in these experiments develop aneurysms gradually, with an increase of 100% in the diameter, seen at the end of the third week, characterized by a chronic inflammatory response. In the third model biologically active Ang II is infused into hyperlipidemic mice deficient in the gene for *Apoe* or the low density lipoprotein receptor ($Ldlr^{-/-}$) using a

subcutaneous, osmotic mini-pump for approximately four weeks. This model mimics the actions of the renin-angiotensin system, in which renin cleaves angiotensin I to form Ang II. In these mice the aneurysms develop in the suprarenal region of the aorta, often preceded by an aortic dissection. The histology of these aneurysms is somewhat different from that seen in human AAA with more intact elastin. Even with the differences between classical human AAA and the AngII model, this method has become the most widely used AAA model since it does not require abdominal surgery on the experimental animals and it is, therefore, technically less demanding than the elastase and calcium-chloride models.

In this review we have room to highlight only a small number of recent mouse studies. Many recently published studies have carried out experiments using at least two of the models to provide increased validity for the findings. Liu et al. [75] used all three AAA models to demonstrate that trombospondin-1 regulated the migration and adhesion of mononuclear cells implying a role for it in vascular inflammation. Another recent study used the Ang II model in mice deficient in the *LRP1* gene only in their VSMCs [76]. Since *LRP1* is one of the genes associated with human AAA (see below), the results were somewhat surprising with no AAAs in the mice, although they had dilatated superior mesenteric arteries and ascending aortae. The study by Sawada et al. [77] examined the outcome of iron overload in both the Ang II and $CaCl_2$ model and showed that dietary iron restriction inhibited the development of AAAs by reducing oxidative stress and inflammation. Using the elastase AAA model Raaz et al. [78] came up with a new hypothesis in which segmental aortic stiffening is considered a critical early phenomenon towards AAA development. According to their hypothesis degenerative stiffening of the aneurysm-prone regions of the aortic wall increases axial stress, generated by cyclic tethering of adjacent, more compliant wall segments. Axial stress induces inflammation and vascular wall remodeling, which are known hallmarks of AAA pathogenesis. They found that stiffening the aortic segment with surgical glue near the area used for elastase perfusion and where aneurysm was expected to form reduced the cyclic axial stress and led to fewer mice developing AAAs in the elastase mouse model.

AAA as a complex genetic disease

AAA is a complex, multifactorial disease with a strong genetic component [19,39,79–82]. About 10–20% of AAA patients have at least one relative with this condition and formal segregation analyses have favored genetic models in explaining this familial aggregation [21,38,39,83]. The Swedish Twin registry, which contains data on all 172,890 twins born in Sweden since 1886, has 265 twins with an AAA [80]. A monozygotic (identical) twin has a 24% probability of having an aneurysm given an aneurysm in the other twin, whereas the probability is only 4.8% in dizygotic twins. Based on the Swedish Twin Study phenotypic variance determined by genetics was estimated to be 70% and non-shared environmental effects (such as smoking, infections, or occupational exposure) 30% [80].

Since the first candidate gene studies were published more than 20 years ago, over 100 genetic association studies using single nucleotide polymorphisms (SNPs) in biologically relevant genes have been reported on AAA [83]. More recently, unbiased genome-wide approaches such as family-based DNA linkage studies and genome-wide association studies

(GWAS) have been carried out to identify susceptibility loci for AAA. DNA linkage studies with the affected relative-pair approach identified two genetic loci, containing several plausible candidate genes located on chromosomes 4q31 and 19q13, for AAA [84,85].

AAA is a late-age-at-onset and deadly disease, making it difficult to collect samples for family-based studies. Case-control approaches have, therefore, gained more interest in deciphering the genetic risk factors for AAA. GWAS carried out by international consortia on large sample sets of AAA cases and controls identified several susceptibility loci for AAA [86–89] and include 1) *CDKN2BAS* gene (located on chromosome 9p21), also known as *ANRIL*, which encodes an antisense RNA that regulates expression of the cyclin-dependent kinase inhibitors *CDKN2A* and *CDKN2B* [89]; 2) DAB2 interacting protein (*DAB2IP*; located on chromosome 9q33), which encodes an inhibitor of cell growth and survival [88]; 3) low density lipoprotein receptor-related protein 1 (*LRP1*; located on chromosome 12q13.3), a plasma membrane receptor involved in vascular smooth muscle and macrophage endocytosis [87], and 4) low density lipoprotein receptor (*LRPR*; located on chromosome 19p13.2) [86]. We have summarized the findings of the most significant associations based on GWAS and candidate gene studies in Table 1. Figure 2 shows all the known genetic loci for both AAA and TAAD to provide a quick comparison between these two aneurysmal diseases. Details on these loci can be found in the Supplementary Table. We concentrated on the non-syndromic forms of TAAD and AAA and omitted studies on rare genetic diseases with aortic aneurysms. As can been seen from the ideograms in Figure 2, the genetic loci associated with AAA differ from those linked to TAAD.

Another promising approach used recently in human genetic studies is the so called Mendelian randomization, also known as a “natural” randomized controlled trial. This approach relies on the fact that genotypes are assigned randomly when passed from parents to offspring. The genotype distribution in the population is, therefore, unrelated to the confounders present in observational epidemiological studies. Two highly significant associations for AAA were found with this approach: one was between a SNP in the *IL6R* [90] and another in the *IL1RN* gene [91] (Table 1, Figure 2), both of which are members of the interleukin gene family. In the IL1 study two genetic variants known to contribute to inhibition of IL1, were analyzed and were found to be associated with increased risk for AAA, whereas the same variants conferred decreased risk for rheumatoid arthritis.. Interestingly, the results suggested that while pharmacological inhibition (e.g. anakinda, rilonacept) of the IL1A/B is beneficial for patients with rheumatoid arthritis, another inflammatory disease, such an inhibition would increase the patient’s risk for AAA. Additionally, these results on humans differed from those obtained with AAA mouse models where the inhibition of IL1A/B pathway was found to slow down the growth of AAAs [92] indicating that differences in the human and mouse immune systems make interpretation of results from experimental models difficult [93].

Do familial AAA cases differ clinically from the sporadic ones? A recent Belgian study compared the clinical characteristics of familial (n = 79) and sporadic (n = 539) AAA and found that: 1) the familial AAA cases were more likely to have a ruptured AAA than the sporadic ones; and 2) familial AAA cases were less likely to have heart disease [21]. Another study on 361 Dutch AAA patients found that familial AAA cases were less likely to

have increased common carotid intima-media thickness (a widely used marker for generalized atherosclerosis), hypertension, or diabetes mellitus, and were less likely to smoke than sporadic AAA cases [94]. Findings with major clinical implications include poorer outcomes in familial AAA patients after endovascular aneurysm repair [95,96], and the fact that familial AAA cases are more likely to have aneurysms in other arteries of their body than sporadic AAA patients [97].

Role for epigenetics in AAA pathogenesis

AAA is a complex disease that develops due to the interaction of environmental risk factors and genetics [19,39,79–82]. In addition to an individual's DNA base pair sequence, other mechanisms are at work to influence gene expression. The process of controlling gene expression through these alternative methods is known as epigenetics and includes RNA associated silencing, histone modifications and DNA methylation [98]. DNA methylation, the most well studied epigenetic modification, is a process in which a methyl group is added to a region where a cytosine nucleotide that is located next to a guanine nucleotide that is linked by a phosphate (CpG). A cluster of CpGs is called a CpG island (CpGI) [98]. CpGIs are methylated by a group of enzymes called DNA methyltransferases. Classically, insertion of methyl groups at CpGIs was thought to block the binding of transcription factors to promoters and therefore result in repressed gene expression. More recent investigations have demonstrated that DNA methylation has a varied influence on gene expression [98]. Despite uncertainty with regard to its effect on gene expression, there is accumulating evidence implicating DNA methylation in several common chronic human disease states including atherosclerosis [99]. Furthermore, cigarette smoking has proven to be a powerful environmental modifier of DNA methylation and is a potential mechanism by which tobacco can affect gene expression [100]. In the face of the potential relationship between cigarette smoking, AAA formation and DNA methylation [101], it is surprising that only one study has been published about the direct role of DNA methylation in AAA [102]. This study analyzed genome-wide DNA methylation profiles of patients with AAA using peripheral blood mononuclear cells, which have been used for methylation studies in other inflammatory disorders [103]. Using isolated human mononuclear blood cells and controlling for smoking status, significant differences in DNA methylation at specific CpG islands that mapped to two genes were identified: *CNN2* and *SERPINB9* [102]. The first gene, *CNN2*, which is also known as h2-calponin or calponin 2, is an actin-binding protein implicated in cytoskeletal organization and vascular development. Furthermore, calponin has been found to be upregulated in stretched vascular walls and may be an important regulator of VSMC phenotype. Additionally, circulating levels of calponin are found in patients with acute aortic dissection and may be a potential biomarker for this aortic pathology [104]. The second gene, *SERPINB9*, which is also known as PI9, belongs to a family of serine protease inhibitors present in the cytoplasm of cytoxic lymphocytes and protects these cells from granzyme B induced apoptosis. Moreover, SERPINB9 has been shown to inhibit apoptosis of human VSMCs, again a key process in AAA pathogenesis. These findings, while novel, come from a small patient cohort [102]. Hopefully, future research efforts will help to clarify the role of DNA methylation and epigenetic modification in the development of AAA.

Expert commentary

Due to the space limitations we were able to cite only a small fraction of all the studies published on AAA pathogenesis in the past five years. As the title of this review implies "Understanding the pathogenesis of AAA" is important for making progress in the clinic. We need to critically evaluate the progress made in the AAA field. What have we learned about the disease process from the research studies summarized above and can this information be translated to clinical practice to help the patients?

When evaluating the progress made on the field, the key questions are:

1. Can this information help us in identifying individuals at risk for developing AAAs?
2. Is there anything we can do to prevent the AAAs from forming in at-risk individuals?
3. How do we slow down the growth of AAAs?
4. Can we provide other treatment options to patients with small AAAs besides the "watchful waiting"?
5. How can we prevent the rupture of AAA, a catastrophic event leading to sudden death in over 60% of the cases?

Despite the large number of published studies and the huge amount of new data available on AAA pathogenesis, the honest answer to all of the questions listed above is humble "no, we have no concreate data to help translate the findings to the clinic and patient care". We have identified several clinical, environmental and genetic risk factors on the population level, but these are not yet sufficiently predictive when applied to individual patients. The only finding that is starting to change the trends of AAA prevalence, is the fact that smoking has such an important role in AAA pathogenesis. Inflammation has been found in a number of studies, both on human and animal studies, as a key pathological feature in AAA. Yet, a female patient on immunosuppressive drugs developed an AAA, which grew rapidly and ruptured [105], challenging the idea of treating AAAs by anti-inflammatory drugs. We have no methods to prevent AAAs from forming or growing in human patients. And most disappointing of all is the fact that we have no alternative treatment options and patients, therefore, have to wait until their AAA has grown to 5 to 5.5 cm before surgical intervention is carried out. The situation is, however, not that different for most complex, adult-onset diseases in that implementing risk scores has been found to be challenging [106].

Five-year view

We expect that large genetic, genomic, epigenetic, proteomic and metabolomic studies will be undertaken by international consortia to identify additional risk factors and biomarkers, and to enhance our understanding of the pathobiology of AAA. Collaboration between different research groups will be important in overcoming the challenges the field has met in the past five years. The genetic studies will include whole genome and whole exome sequencing of AAA patients and their family members requiring use of robust computational

tool for analyzing large amounts of sequence data [107]. The studies to be employed will include integrative analyses incorporating results from multiple techniques leading to a comprehensive picture of the disease stage. It will also be important to include multiple clinical and environmental (such as smoking) variables into the models and to study different stages of the AAA development.

Studies on AAA animal models will continue to play a key role in elucidating the pathobiology of AAA [108]. These studies are critical especially in studying the early stages of AAA, since it is nearly impossible to obtain tissue samples from small human AAA. It is, however, important to realize that some of the findings from mouse studies are hard to translate to humans due to differences in the immune system between the two species and the fact that the AAAs develop quickly over a short time period in the mouse models, whereas the human AAA is a chronic condition which develops over a long time period.

Next steps will require translating the basic science findings into diagnostic tests and medical treatment of AAA. It will be important to develop biomarkers detectable in serum samples which could be used for monitoring the progress of the AAA. The primary goal remains to prevent rupture by finding AAAs early to allow safe surgical repair. It is likely that one day AAAs will be treated medically to slow their growth, helping to transform a surgical disease into a medical disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

Reference annotations

* Of interest

** Of considerable interest

1. Filardo G, Powell JT, Martinez MA, Ballard DJ. Surgery for small asymptomatic abdominal aortic aneurysms. Cochrane Database Syst Rev. 2015; 2:CD001835. [PubMed: 25927098]
2. Larsson E, Granath F, Swedenborg J, Hultgren R. More patients are treated for nonruptured abdominal aortic aneurysms, but the proportion of women remains unchanged. J Vasc Surg. 2008; 48(4):802–807. [PubMed: 18639419]
3. Olsson C, Thelin S, Stahle E, Ekbom A, Granath F. Thoracic aortic aneurysm and dissection: increasing prevalence and improved outcomes reported in a nationwide population-based study of more than 14,000 cases from 1987 to 2002. Circulation. 2006; 114(24):2611–2618. [PubMed: 17145990]
4. Kent KC. Clinical practice. Abdominal aortic aneurysms. N Engl J Med. 2014; 371(22):2101–2108. [PubMed: 25427112]
5. Jongkind V, Yeung KK, Akkersdijk GJ, et al. Juxtarenal aortic aneurysm repair. J Vasc Surg. 2010; 52(3):760–767. [PubMed: 20382492]
6. Tromp G, Kuivaniemi H, Hinterseher I, Carey DJ. Novel genetic mechanisms for aortic aneurysms. Curr Atheroscler Rep. 2010; 12(4):259–266. [PubMed: 20446064]
7. Wiegreffe C, Christ B, Huang R, Scaal M. Remodeling of aortic smooth muscle during avian embryonic development. Dev Dyn. 2009; 238(3):624–631. [PubMed: 19235723]

8. Ruddy JM, Jones JA, Ikonomidis JS. Pathophysiology of thoracic aortic aneurysm (TAA): is it not one uniform aorta? Role of embryologic origin. Progress in cardiovascular diseases. 2013; 56(1): 68–73. [PubMed: 23993239]

9. Steed MM, Tyagi SC. Mechanisms of cardiovascular remodeling in hyperhomocysteinemia. Antioxidants & redox signaling. 2011; 15(7):1927–1943. [PubMed: 21126196]

10. Zhou J, Austin RC. Contributions of hyperhomocysteinemia to atherosclerosis: Causal relationship and potential mechanisms. BioFactors. 2009; 35(2):120–129. [PubMed: 19449439]

11. Dalton ML, Gadson PF Jr, Wrenn RW, Rosenquist TH. Homocysteine signal cascade: production of phospholipids, activation of protein kinase C, and the induction of c-fos and c-myb in smooth muscle cells. FASEB J. 1997; 11(8):703–711. [PubMed: 9240971]

12. Bruemmer D, Daugherty A, Lu H, Rateri DL. Relevance of angiotensin II-induced aortic pathologies in mice to human aortic aneurysms. Ann N Y Acad Sci. 2011; 1245:7–10. [PubMed: 22211965]

13. Rateri DL, Howatt DA, Moorleghen JJ, Charnigo R, Cassis LA, Daugherty A. Prolonged infusion of angiotensin II in apoE(−/−) mice promotes macrophage recruitment with continued expansion of abdominal aortic aneurysm. The American journal of pathology. 2011; 179(3):1542–1548. [PubMed: 21763672]

14. Gadson PF Jr, Dalton ML, Patterson E, et al. Differential response of mesoderm- and neural crest-derived smooth muscle to TGF-beta1: regulation of c-myb and alpha1 (I) procollagen genes. Experimental cell research. 1997; 230(2):169–180. [PubMed: 9024776]

15. Ruddy JM, Jones JA, Spinale FG, Ikonomidis JS. Regional heterogeneity within the aorta: relevance to aneurysm disease. J Thorac Cardiovasc Surg. 2008; 136(5):1123–1130. [PubMed: 19026791]

16. Wolinsky H, Glagov S. Comparison of abdominal and thoracic aortic medial structure in mammals. Deviation of man from the usual pattern. Circulation research. 1969; 25(6):677–686. [PubMed: 5364644]

17. Chaer RA, Vasoncelos R, Marone LK, et al. Synchronous and metachronous thoracic aneurysms in patients with abdominal aortic aneurysms. J Vasc Surg. 2012; 56(5):1261–1265. [PubMed: 22727846]

18. Kuivaniemi H, Platsoucas CD, Tilson MD 3rd. Aortic aneurysms: an immune disease with a strong genetic component. Circulation. 2008; 117(2):242–252. [PubMed: 18195185]

19**. Kent KC, Zwolak RM, Egorova NN, et al. Analysis of risk factors for abdominal aortic aneurysm in a cohort of more than 3 million individuals. J Vasc Surg. 2010; 52(3):539–548. Large study on risk factors found in individuals screened for AAA. [PubMed: 20630687]

20. Svensjö S, Björck M, Gurtelschmid M, Djavani Gidlund K, Hellberg A, Wanhainen A. Low prevalence of abdominal aortic aneurysm among 65-year-old Swedish men indicates a change in the epidemiology of the disease. Circulation. 2011; 124(10):1118–1123. [PubMed: 21844079]

21. Sakalihasan N, Defraigne JO, Kerstenne MA, et al. Family Members of Patients with Abdominal Aortic Aneurysms Are at Increased Risk for Aneurysms: Analysis of 618 Probands and Their Families from the Liege AAA Family Study. Ann Vasc Surg. 2014; 28(4):787–797. [PubMed: 24365082]

22. Joergensen TM, Houlind K, Green A, Lindholt JS. Abdominal aortic diameter is increased in males with a family history of abdominal aortic aneurysms: results from the Danish VIVA-trial. Eur J Vasc Endovasc Surg. 2014; 48(6):669–675. [PubMed: 25443525]

23. Akai A, Watanabe Y, Hoshina K, et al. Family history of aortic aneurysm is an independent risk factor for more rapid growth of small abdominal aortic aneurysms in Japan. J Vasc Surg. 2015; 61(2):287–290. [PubMed: 25175636]

24. Conrad MF, Crawford RS, Pedraza JD, et al. Long-term durability of open abdominal aortic aneurysm repair. J Vasc Surg. 2007; 46(4):669–675. [PubMed: 17903647]

25. Hertzer NR, Mascha EJ, Karafa MT, O'Hara PJ, Krajewski LP, Beven EG. Open infrarenal abdominal aortic aneurysm repair: the Cleveland Clinic experience from 1989 to 1998. J Vasc Surg. 2002; 35(6):1145–1154. [PubMed: 12042724]

26. Chaikof EL, Brewster DC, Dalman RL, et al. The care of patients with an abdominal aortic aneurysm: the Society for Vascular Surgery practice guidelines. J Vasc Surg. 2009; 50(4 Suppl):S2–49. [PubMed: 19786250]
27. Brown LC, Powell JT, Thompson SG, Epstein DM, Sculpher MJ, Greenhalgh RM. The UK EndoVascular Aneurysm Repair (EVAR) trials: randomised trials of EVAR versus standard therapy. Health technology assessment. 2012; 16(9):1–218. [PubMed: 22381040]
28. Kurosawa K, Matsumura JS, Yamanouchi D. Current status of medical treatment for abdominal aortic aneurysm. Circulation journal: official journal of the Japanese Circulation Society. 2013; 77(12):2860–2866. [PubMed: 24161907]
29**. Meijer CA, Stijnen T, Wasser MN, et al. Doxycycline for stabilization of abdominal aortic aneurysms: a randomized trial. Annals of internal medicine. 2013; 159(12):815–823. First larger randomized clinical trial for the use of doxycycline in the treatment of small AAA. [PubMed: 24490266]
30. Hackam DG, Thiruchelvam D, Redelmeier DA. Angiotensin-converting enzyme inhibitors and aortic rupture: a population-based case-control study. Lancet. 2006; 368(9536):659–665. [PubMed: 16920471]
31. Sweeting MJ, Thompson SG, Brown LC, Greenhalgh RM, Powell JT. Use of angiotensin converting enzyme inhibitors is associated with increased growth rate of abdominal aortic aneurysms. J Vasc Surg. 2010; 52(1):1–4. [PubMed: 20494541]
32. Liao JK. Effects of statins on 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibition beyond low-density lipoprotein cholesterol. Am J Cardiol. 2005; 96(5A):24F–33F.
33. Liao JK, Laufs U. Pleiotropic effects of statins. Annu Rev Pharmacol Toxicol. 2005; 45:89–118. [PubMed: 15822172]
34. Sweeting MJ, Thompson SG, Brown LC, Powell JT. collaborators R. Meta-analysis of individual patient data to examine factors affecting growth and rupture of small abdominal aortic aneurysms. The British journal of surgery. 2012; 99(5):655–665. [PubMed: 22389113]
35. Takagi H, Yamamoto H, Iwata K, Goto S, Umemoto T, Group A. Effects of statin therapy on abdominal aortic aneurysm growth: a meta-analysis and meta-regression of observational comparative studies. Eur J Vasc Endovasc Surg. 2012; 44(3):287–292. [PubMed: 22824348]
36. Wemmelund H, Hogh A, Hundborg HH, Thomsen RW, Johnsen SP, Lindholt JS. Statin use and rupture of abdominal aortic aneurysm. Br J Surg. 2014; 101(8):966–975. [PubMed: 24849021]
37. Boddy AM, Lenk GM, Lillvis JH, Nischan J, Kyo Y, Kuivaniemi H. Basic research studies to understand aneurysm disease. Drug News Perspect. 2008; 21(3):142–148. [PubMed: 18560612]
38. Kuivaniemi, H.; Tromp, G.; Carey, DJ.; Elmore, JR. The Molecular Biology and Genetics of Aneurysms. In: Homeister, JW.; Willis, MS., editors. Molecular and Translational Vascular Medicine. Springer Science+Business Media; New York: 2012. p. 3-33.
39. Kuivaniemi, H.; Ryer, EJ.; Yoon, HR.; Elmore, JR.; Tromp, G. Genetic risk factors for abdominal aortic aneurysms (AAA). In: Bennington, EH., editor. Horizons in World Cardiovascular Research. Nova Science Publishers; Hauppauge, NY: 2015.
40. Hinterseher I, Gabel G, Corvinus F, et al. Presence of Borrelia burgdorferi sensu lato antibodies in the serum of patients with abdominal aortic aneurysms. Eur J Clin Microbiol & Infec Dis. 2011
41. Dale MA, Ruhlman MK, Baxter BT. Inflammatory Cell Phenotypes in AAAs: Their Role and Potential as Targets for Therapy. Arterioscler,Thromb, Vasc Biol. 2015
42. Estrelinha M, Hinterseher I, Kuivaniemi H. Gene expression studies in human abdominal aortic aneurysm. Rev Vasc Med. 2014; 2(3):77–82.
43. Nischan, J.; Lenk, GM.; Boddy, AM.; Lillvis, JH.; Tromp, G.; Kuivaniemi, H. Abdominal aortic aneurysms- a complex genetic disease. In: Laurent, A.; Morel, E., editors. Aneurysms: Types, Risks, Formation and Treatment. Nova Science Publishers, Inc; Hauppage, NY: 2010. p. 35-93.
44. Tromp G, Kuivaniemi H. Developments in genomics to improve understanding, diagnosis and management of aneurysms and peripheral artery disease. Eur J Vasc Endovasc Surg. 2009; 38(6): 676–682. [PubMed: 19783185]
45. Nischan J, Gatalica Z, Curtis M, Lenk GM, Tromp G, Kuivaniemi H. Binding sites for ETS family of transcription factors dominate the promoter regions of differentially expressed genes in abdominal aortic aneurysms. Circ Cardiovasc Genet. 2009; 2(6):565–572. [PubMed: 20031636]

46. Hinterseher I, Erdman R, Elmore JR, et al. Novel pathways in the pathobiology of human abdominal aortic aneurysms. Pathobiology. 2013; 80(1):1–10. [PubMed: 22797469]

47*. Biros E, Gabel G, Moran CS, et al. Differential gene expression in human abdominal aortic aneurysm and aortic occlusive disease. Oncotarget. 2015 Largest genome-wide mRNA expression study comparing AAA and atherosclerosis.

48. Lenk GM, Tromp G, Weinsheimer S, Gatalica Z, Berguer R, Kuivaniemi H. Whole genome expression profiling reveals a significant role for immune function in human abdominal aortic aneurysms. BMC Genomics. 2007; 8(1):237. [PubMed: 17634102]

49. Biros E, Moran CS, Rush CM, et al. Differential gene expression in the proximal neck of human abdominal aortic aneurysm. Atherosclerosis. 2014; 233(1):211–218. [PubMed: 24529146]

50. Choke E, Cockerill GW, Laing K, et al. Whole genome-expression profiling reveals a role for immune and inflammatory response in abdominal aortic aneurysm rupture. Eur J Vasc Endovasc Surg. 2009; 37(3):305–310. [PubMed: 19111481]

51. Courtois A, Nusgens BV, Hustinx R, et al. Gene expression study in positron emission tomography-positive abdominal aortic aneurysms identifies CCL18 as a potential biomarker for rupture risk. Mol Med. 2015; 20(1):697–706. [PubMed: 25517227]

52. Giusti B, Rossi L, Lapini I, et al. Gene expression profiling of peripheral blood in patients with abdominal aortic aneurysm. Eur J Vasc Endovasc Surg. 2009; 38(1):104–112. [PubMed: 19233690]

53. Hinterseher I, Schworer CM, Lillvis JH, et al. Immunohistochemical analysis of the natural killer cell cytotoxicity pathway in human abdominal aortic aneurysms. Int J Mol Sci. 2015; 16:11196–11212. [PubMed: 25993291]

54*. Pahl MC, Erdman R, Kuivaniemi H, Lillvis JH, Elmore JR, Tromp G. Transcriptional (ChIP-Chip) analysis of ELF1, ETS2, RUNX1 and STAT5 in human abdominal aortic aneurysm. Int J Mol Sci. 2015; 16:11229–11258. First genome-wide chromatin-immunoprecipitation study with human AAA tissue to elucidate transcriptional regulation of differentially expressed genes. [PubMed: 25993293]

55*. Pahl MC, Derr K, Gabel G, et al. MicroRNA expression signature in human abdominal aortic aneurysms. BMC Med Genomics. 2012; 5(1):25. Comprehensive analysis of microRNAs in human AAA tissue with replication and extensive bioinformatics. [PubMed: 22704053]

56. Maegdefessel L, Azuma J, Toh R, et al. Inhibition of microRNA-29b reduces murine abdominal aortic aneurysm development. J Clin Invest. 2012; 122(2):497–506. [PubMed: 22269326]

57. Maegdefessel L, Spin JM, Raaz U, et al. miR-24 limits aortic vascular inflammation and murine abdominal aneurysm development. Nat Commun. 2014; 5:5214. [PubMed: 25358394]

58. Zampetaki A, Attia R, Mayr U, et al. Role of miR-195 in aortic aneurysmal disease. Circ Res. 2014; 115(10):857–866. [PubMed: 25201911]

59. Martinez-Pinna R, Burillo E, Madrigal-Matute J, et al. Label-free proteomic analysis of red blood cell membrane fractions from abdominal aortic aneurysm patients. Proteomics Clin Appl. 2014; 8(7–8):626–630. [PubMed: 24976601]

60. Martinez-Pinna R, Gonzalez de Peredo A, Monsarrat B, Burlet-Schiltz O, Martin-Ventura JL. Label-free quantitative proteomic analysis of human plasma-derived microvesicles to find protein signatures of abdominal aortic aneurysms. Proteomics Clin Appl. 2014; 8(7–8):620–625. [PubMed: 24888668]

61. Martinez-Pinna R, Ramos-Mozo P, Madrigal-Matute J, et al. Identification of peroxiredoxin-1 as a novel biomarker of abdominal aortic aneurysm. Arterioscler Thromb Vasc Biol. 2011; 31(4):935–943. [PubMed: 21273562]

62. Ramos-Mozo P, Madrigal-Matute J, Martinez-Pinna R, et al. Proteomic analysis of polymorphonuclear neutrophils identifies catalase as a novel biomarker of abdominal aortic aneurysm: potential implication of oxidative stress in abdominal aortic aneurysm progression. Arterioscler Thromb Vasc Biol. 2011; 31(12):3011–3019. [PubMed: 21940941]

63. Airhart N, Brownstein BH, Cobb JP, et al. Smooth muscle cells from abdominal aortic aneurysms are unique and can independently and synergistically degrade insoluble elastin. J Vasc Surg. 2014; 60(4):1033–1041. [PubMed: 24080131]

64. Boytard L, Spear R, Chinetti-Gbaguidi G, et al. Role of proinflammatory CD68(+) mannose receptor(−) macrophages in peroxiredoxin-1 expression and in abdominal aortic aneurysms in humans. Arterioscler Thromb Vasc Biol. 2013; 33(2):431–438. [PubMed: 23241402]

65. Ryer EJ, Garvin RP, Schworer CM, et al. Proinflammatory role of stem cells in abdominal aortic aneurysms. J Vasc Surg. 2014 S0741-5214(0714)00934-00933.

66. Blose KJ, Ennis TL, Arif B, Weinbaum JS, Curci JA, Vorp DA. Periadventitial adipose-derived stem cell treatment halts elastase-induced abdominal aortic aneurysm progression. Regen Med. 2014; 9(6):733–741. [PubMed: 25431910]

67. Davis JP, Salmon M, Pope NH, et al. Attenuation of aortic aneurysms with stem cells from different genders. J Surg Res. 2015

68**. Norman PE, Curci JA. Understanding the effects of tobacco smoke on the pathogenesis of aortic aneurysm. Arterioscler Thromb Vasc Biol. 2013; 33(7):1473–1477. Comprehensive and critical review on the role of smoking in AAA including human and mouse studies. [PubMed: 23685557]

69. Lemaitre V, Dabo AJ, D'Armiento J. Cigarette smoke components induce matrix metalloproteinase-1 in aortic endothelial cells through inhibition of mTOR signaling. Toxicol Sci. 2011; 123(2):542–549. [PubMed: 21742783]

70. Chen QW, Edvinsson L, Xu CB. Cigarette smoke extract promotes human vascular smooth muscle cell proliferation and survival through ERK1/2- and NF-kappaB-dependent pathways. Sci World J. 2010; 10:2139–2156.

71. Maegdefessel L, Azuma J, Toh R, et al. MicroRNA-21 blocks abdominal aortic aneurysm development and nicotine-augmented expansion. Sci Transl Med. 2012; 4(122):122ra122.

72. Wang S, Zhang C, Zhang M, et al. Activation of AMP-activated protein kinase alpha2 by nicotine instigates formation of abdominal aortic aneurysms in mice in vivo. Nat Med. 2012; 18(6):902–910. [PubMed: 22561688]

73. Jin J, Arif B, Garcia-Fernandez F, et al. Novel mechanism of aortic aneurysm development in mice associated with smoking and leukocytes. Arterioscler Thromb Vasc Biol. 2012; 32(12):2901–2909. [PubMed: 23042818]

74. Wang Y, Krishna S, Golledge J. The calcium chloride-induced rodent model of abdominal aortic aneurysm. Atherosclerosis. 2013; 226(1):29–39. [PubMed: 23044097]

75. Liu Z, Morgan S, Ren J, et al. Thrombospondin-1 (TSP1) contributes to the development of vascular inflammation by regulating monocytic cell motility in mouse models of abdominal aortic aneurysm. Circ Res. 2015

76. Davis FM, Rateri DL, Balakrishnan A, et al. Smooth muscle cell deletion of low-density lipoprotein receptor–related protein 1 augments angiotensin II–induced superior mesenteric arterial and ascending aortic aneurysms. Arterioscler Thromb Vasc Biol. 2015; 35(1):155–162. [PubMed: 25395615]

77. Sawada H, Hao H, Naito Y, et al. Aortic iron overload with oxidative stress and inflammation in human and murine abdominal aortic aneurysm. Arterioscler Thromb Vasc Biol. 2015

78. Raaz U, Zöllner AM, Schellinger IN, et al. Segmental aortic stiffening contributes to experimental abdominal aortic aneurysm development. Circulation. 2015

79. Tromp, G.; Kuivaniemi, H. How does one study genetic risk factors in a complex disease such as aneurysms?. In: Sakalihasan, N.; Kuivaniemi, H.; Michel, J-B., editors. Aortic aneurysms: new insights into an old problem. Les Editions de l'Universite de Liège; Liège, Belgium: 2008. p. 115-144.

80. Wahlgren CM, Larsson E, Magnusson PK, Hultgren R, Swedenborg J. Genetic and environmental contributions to abdominal aortic aneurysm development in a twin population. J Vasc Surg. 2010; 51(1):3–7. [PubMed: 19939604]

81. Greco G, Egorova NN, Gelijns AC, et al. Development of a novel scoring tool for the identification of large >/=5 cm abdominal aortic aneurysms. Ann Surg. 2010; 252(4):675–682. [PubMed: 20881774]

82. Smelser DT, Tromp G, Elmore JR, et al. Population risk factor estimates for abdominal aortic aneurysm from electronic medical records: a case control study. BMC Cardiovasc Disord. 2014; 14:174. [PubMed: 25475588]

83. Hinterseher I, Tromp G, Kuivaniemi H. Genes and abdominal aortic aneurysm. Ann Vasc Surg. 2011; 25(3):388–412. [PubMed: 21146954]

84. Shibamura H, Olson JM, van Vlijmen-Van Keulen C, et al. Genome scan for familial abdominal aortic aneurysm using sex and family history as covariates suggests genetic heterogeneity and identifies linkage to chromosome 19q13. Circulation. 2004; 109(17):2103–2108. [PubMed: 15096456]

85. Van Vlijmen-Van Keulen CJ, Rauwerda JA, Pals G. Genome-wide linkage in three Dutch families maps a locus for abdominal aortic aneurysms to chromosome 19q13.3. Eur J Vasc Endovasc Surg. 2005; 30(1):29–35. [PubMed: 15933979]

86. Bradley DT, Hughes AE, Badger SA, et al. A Variant in LDLR Is Associated With Abdominal Aortic Aneurysm. Circ Cardiovasc Genet. 2013; 6(5):498–504. [PubMed: 24046328]

87**. Bown MJ, Jones GT, Harrison SC, et al. Abdominal aortic aneurysm is associated with a variant in low-density lipoprotein receptor-related protein 1. Am J Hum Genet. 2011; 89(5):619–627. The largest genome-wide genetic association study for AAA, which was carried out by an international consortium. [PubMed: 22055160]

88. Gretarsdottir S, Baas AF, Thorleifsson G, et al. Genome-wide association study identifies a sequence variant within the DAB2IP gene conferring susceptibility to abdominal aortic aneurysm. Nat Genet. 2010; 42(8):692–697. [PubMed: 20622881]

89. Helgadottir A, Thorleifsson G, Magnusson KP, et al. The same sequence variant on 9p21 associates with myocardial infarction, abdominal aortic aneurysm and intracranial aneurysm. Nat Genet. 2008; 40(2):217–224. [PubMed: 18176561]

90*. Harrison SC, Smith AJ, Jones GT, et al. Interleukin-6 receptor pathways in abdominal aortic aneurysm. Eur Heart J. 2013; 34(48):3707–3716. This study used Mendelian randomization as a novel approach to identify genetic risk factors for AAA. [PubMed: 23111417]

91. Consortium IG. Cardiometabolic effects of genetic upregulation of the interleukin 1 receptor antagonist: a Mendelian randomisation analysis. Lancet Diabetes & Endocrin. 2015; 3(4):243–253.

92. Johnston WF, Salmon M, Su G, et al. Genetic and pharmacologic disruption of interleukin-1beta signaling inhibits experimental aortic aneurysm formation. Arterioscler Thromb Vasc Biol. 2013; 33(2):294–304. [PubMed: 23288154]

93. Seok J, Warren HS, Cuenca AG, et al. Genomic responses in mouse models poorly mimic human inflammatory diseases. Proc Natl Acad Sci USA. 2013; 110(9):3507–3512. [PubMed: 23401516]

94. van de Luijtgaarden KM, Bastos Goncalves F, Hoeks SE, et al. Lower atherosclerotic burden in familial abdominal aortic aneurysm. J Vasc Surg. 2014; 59(3):589–593. [PubMed: 24239112]

95. van de Luijtgaarden KM, Bastos Goncalves F, Hoeks SE, et al. Familial abdominal aortic aneurysm is associated with more complications after endovascular aneurysm repair. J Vasc Surg. 2014; 59(2):275–282. [PubMed: 24139982]

96. Ryer EJ, Garvin RP, Thomas B, Kuivaniemi H, Franklin DP, Elmore JR. Patients with familial abdominal aortic aneurysms are at increased risk for endoleak and secondary intervention following elective endovascular aneurysm repair. J Vasc Surg. 2015 in press.

97. Brown CR, Greenberg RK, Wong S, et al. Family history of aortic disease predicts disease patterns and progression and is a significant influence on management strategies for patients and their relatives. J Vasc Surg. 2013; 58(3):573–581. [PubMed: 23809203]

98. Jones PA. Functions of DNA methylation: islands, start sites, gene bodies and beyond. Nat Rev Genet. 2012; 13(7):484–492. [PubMed: 22641018]

99. Napoli C, Crudele V, Soricelli A, et al. Primary prevention of atherosclerosis: a clinical challenge for the reversal of epigenetic mechanisms? Circulation. 2012; 125(19):2363–2373. [PubMed: 22586291]

100. Breitling LP. Current genetics and epigenetics of smoking/tobacco-related cardiovascular disease. Arterioscler Thromb Vasc Biol. 2013; 33(7):1468–1472. [PubMed: 23640490]

101. Toghill BJ, Saratzis A, Harrison SC, Verissimo AR, Mallon EB, Bown MJ. The potential role of DNA methylation in the pathogenesis of abdominal aortic aneurysm. Atherosclerosis. 2015; 241(1):121–129. [PubMed: 25974102]

102. Ryer EJ, Ronning KE, Erdman R, et al. The potential role of DNA methylation in abdominal aortic aneurysms. Int J Mol Sci. 2015; 16:11259–11275. [PubMed: 25993294]
103. Obata Y, Furusawa Y, Hase K. Epigenetic modifications of the immune system in health and disease. Immunol Cell Biol. 2015; 93(3):226–232. [PubMed: 25666097]
104. Suzuki T, Distante A, Zizza A, et al. Preliminary experience with the smooth muscle troponin-like protein, calponin, as a novel biomarker for diagnosing acute aortic dissection. Eur Heart J. 2008; 29(11):1439–1445. [PubMed: 18436559]
105. Lindeman JH, Rabelink TJ, van Bockel JH. Immunosuppression and the abdominal aortic aneurysm: doctor jekyll or mister hyde? Circulation. 2011; 124(18):e463–465. [PubMed: 22042930]
106. Schrodi SJ, Mukherjee S, Shan Y, et al. Genetic-based prediction of disease traits: prediction is very difficult, especially about the future. Front Genet. 2014; 5:162. [PubMed: 24917882]
107. Ritchie MD, de Andrade M, Kuivaniemi H. The foundation of precision medicine: integration of electronic health records with genomics through basic, clinical, and translational research. Front Genet. 2015; 6:104. [PubMed: 25852745]
108. Trollope A, Moxon JV, Moran CS, Golledge J. Animal models of abdominal aortic aneurysm and their role in furthering management of human disease. Cardiovasc Pathol. 2011; 20(2):114–123. [PubMed: 20133168]
109. Jones GT, Bown MJ, Gretarsdottir S, et al. A sequence variant associated with sortilin-1 (SORT1) on 1p13.3 is independently associated with abdominal aortic aneurysm. Hum Mol Genet. 2013; 22(14):2941–2947. [PubMed: 23535823]
110. Helgadottir A, Gretarsdottir S, Thorleifsson G, et al. Apolipoprotein(a) genetic sequence variants associated with systemic atherosclerosis and coronary atherosclerotic burden but not with venous thromboembolism. J Am Coll Cardiol. 2012; 60(8):722–729. [PubMed: 22898070]
111. Jones GT, Thompson AR, van Bockxmeer FM, et al. Angiotensin II type 1 receptor 1166C polymorphism is associated with abdominal aortic aneurysm in three independent cohorts. Arterioscler Thromb Vasc Biol. 2008; 28(4):764–770. [PubMed: 18239157]
112. Biros E, Norman PE, Jones GT, et al. Meta-analysis of the association between single nucleotide polymorphisms in TGF-beta receptor genes and abdominal aortic aneurysm. Atherosclerosis. 2011; 219(1):218–223. [PubMed: 21855067]
113. McColgan P, Peck GE, Greenhalgh RM, Sharma P. The genetics of abdominal aortic aneurysms: a comprehensive meta-analysis involving eight candidate genes in over 16,700 patients. Int Surg. 2009; 94(4):350–358. [PubMed: 20302034]

Key issues

- AAA is a permanent localized dilatation with an anteroposterior diameter ≥ 3.0 cm.
- Rupture risk of AAA increases with increasing aortic diameter and this catastrophic event is associated with a mortality of 50 – 80%.
- Perioperative mortality of traditional open AAA repair ranges from 1 to 4%.
- Thoracic and abdominal aortic aneurysms differ in many aspects.
- AAA is a complex, multifactorial disease with a strong genetic component.
- Smoking is the most important risk factor for AAA development, growth and rupture.
- Positive family history of AAA is an important risk factor for developing an AAA.
- Several genetic regions are associated with human AAA, but the full picture of the genetic make-up in individuals at-risk for AAA development is far from complete.
- Hallmarks of AAA pathogenesis include inflammation, vascular smooth muscle cell apoptosis, extracellular matrix degradation, and oxidative stress.

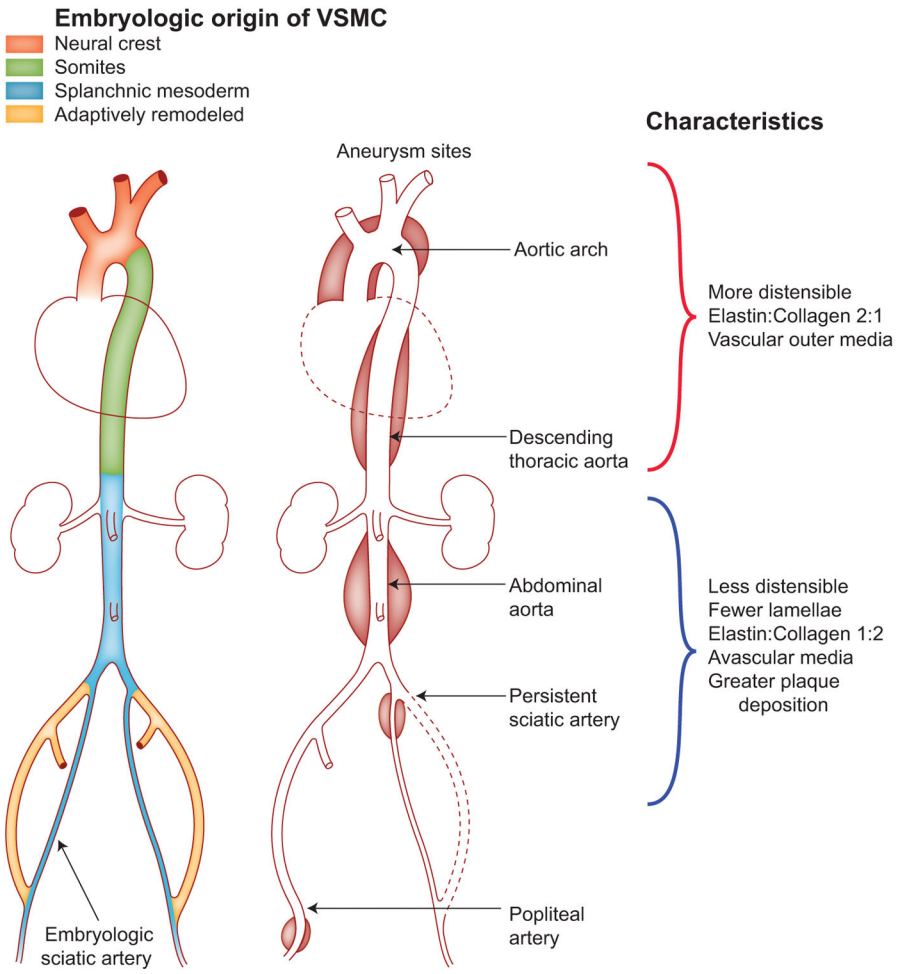

Figure 1. Regional variation in the aorta of embryologic origin, structure and disease susceptibility

Different parts of the aorta are from different embryologic origin. Disease susceptibility also varies, with the infrarenal abdominal aorta being more prone to atherosclerosis and aneurysm formation than the thoracic aorta. VSMC—vascular smooth muscle cell. Modified and reproduced with kind permission from Springer Science+Business Media:Tromp et al. [6].

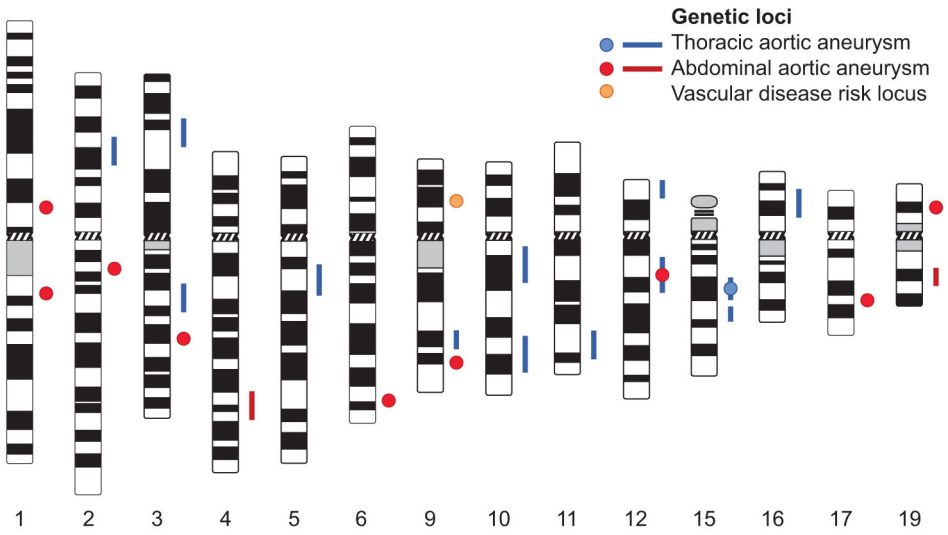

Figure 2. Genetic map of non-syndromic thoracic and abdominal aortic aneurysms

Underlying genetic factors contributing to the aneurysmal diseases differ based on the site of the clinical manifestation. Vertical lines adjacent to the chromosome ideograms indicate regions identified by DNA linkage studies, and round symbols indicate locations of SNPs found in genome-wide (GWAS) or candidate gene association studies. See Supplementary Table for details on the studies. The ideograms can be obtained from "Idiogram Album: Human" (copyright© 1994 David Adler, University of Washington, Department of Pathology) at http://www.pathology.washington.edu/research/cytopages/idiograms/human/.

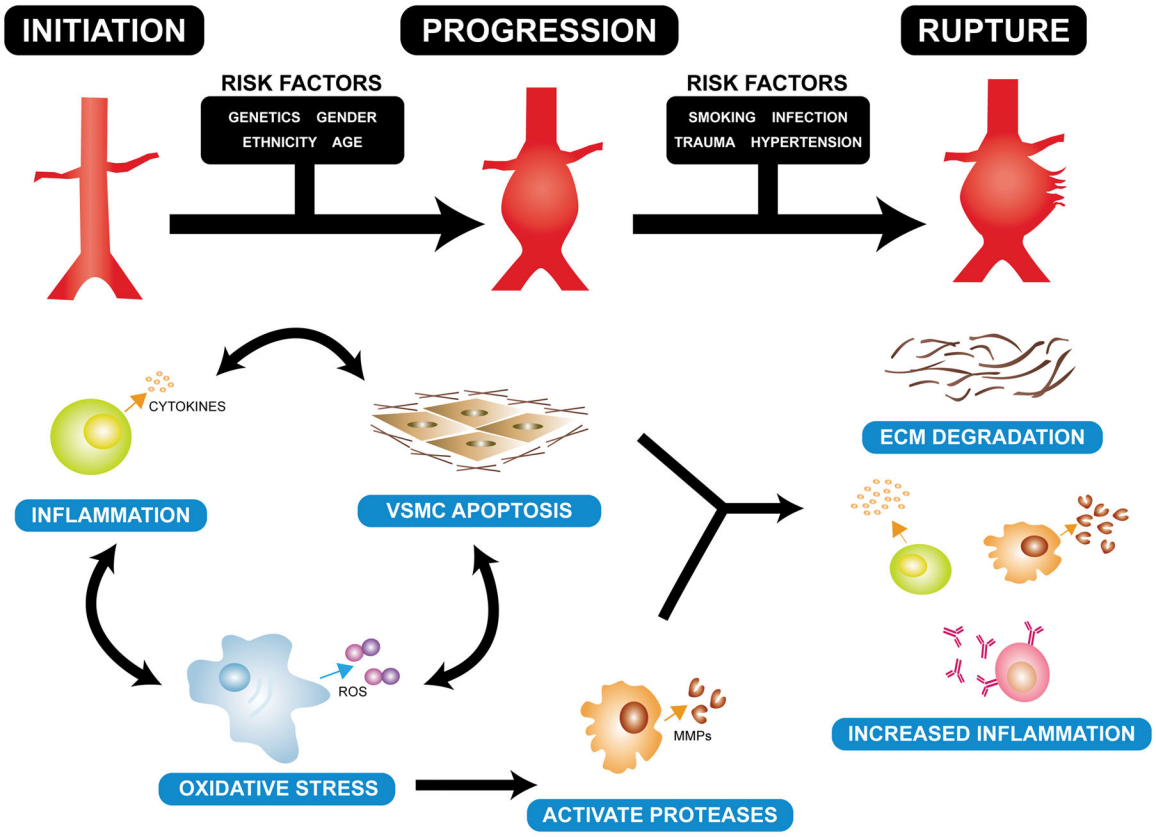

Figure 3. Summary of the pathogenesis of AAA

Several biological processes and risk factors have been identified that contribute to AAA pathogenesis. Genes in the biological pathways have been used in candidate gene studies. VSMC, vascular smooth muscle cell; ECM, extracellular matrix; ROS, reactive oxygen species; MMPs, matrix metalloproteinases. Reproduced with permission from Boddy et al. Drug News Perspect 2008, 21(3): 142–148 [37]. Copyright © 2008–2015 Prous Science, S.A.U. or its licensors. All rights reserved. DOI: 10.1358/dnp.2008.21.3.1203410.

Table 1

Most Significant Genetic Associations for AAA from GWAS and Candidate Gene Studies

Gene Symbol	Literature Citation	Study Design	Functional Class	Polymorphism	AAA Cases N	Controls N	OR [95% CI]	Association P-value[a]
SORT1	[109][b]	Candidate gene study	Lipid metabolism	rs599839	7,048	75,976	0.81 [0.76 – 0.85]	7.2×10^{-14}
CDKN2BAS1	[89]	GWAS	Cell cycle	rs10757278	2,836	16,732	1.31 [1.22 – 1.42]	1.2×10^{-12}
IL6R	[90]	Candidate gene study; Mendelian randomization	Inflammation	rs7529229	4,524	15,710	0.84 [0.80 – 0.89]	2.7×10^{-11}
LDLR	[86]	GWAS	Lipid metabolism	rs6511720	5,138	39,273	0.76 [0.70 – 0.83]	2.1×10^{-10}
LRP1	[87]	GWAS	Lipid metabolism	rs1466535	6,228	49,182	1.15 [1.10 – 1.21]	4.5×10^{-10}
DAB2IP	[88]	GWAS	Cell growth	rs7025486	4,559	37,954	1.21 [1.14 – 1.28]	4.6×10^{-10}
IL1RN	[91]	Candidate gene study: Mendelian randomization	Inflammation	rs6743376 with rs1542176	4,682	38,739	1.08 [1.04 – 1.12]	1.8×10^{-5}
LPA	[110]	Candidate gene study	Lipid metabolism	rs10455872 with rs3798220	4,572	33,520	1.23 [1.11 – 1.36]	6.0×10^{-5}
AGTR1	[111][b]	Candidate gene study	Renin-angiotensin system	rs5186	1,226	1,723	1.60 [1.32 – 1.93]	1.1×10^{-6}
TGFBR2	[112][b]	Candidate gene study	TGFB signaling	rs1036095	1,904	2,616	1.59 [1.23 – 2.07]	4.8×10^{-4}
TGFBR2	[112][b]	Candidate gene study	TGFB signaling	rs764522	1,904	2,616	1.69 [1.28 – 2.25]	2.7×10^{-4}
ACE	[113][b]	Candidate gene study	Renin-angiotensin system	rs4646994	1,415	1,677	1.35 [1.17 – 1.56]	<0.0001

Results were included only from studies in which a minimum of 1,000 cases and 1,000 controls were analyzed and the $P < 0.0005$ (5×10^{-4}).

AAA, abdominal aortic aneurysm; GWAS, genome-wide association study; N, number of subjects in the study; OR, odds ratio; 95% CI, 95% confidence interval; TGFB, transforming growth factor beta. Gene symbols are available from http://www.ncbi.nlm.nih.gov/gene/

[a] P-values were taken from either a meta-analysis or the largest report demonstrating association with AAA and cited in the first column.

[b] Meta-analysis.

Expert Rev Cardiovasc Ther. Author manuscript; available in PMC 2016 April 13.