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Genes and Abdominal Aortic Aneurysm

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Abstract

Abdominal aortic aneurysm (AAA) is a multifactorial disease with a strong genetic component. Since first candidate gene studies were published 20 years ago, nearly 100 genetic association studies using single nucleotide polymorphisms (SNPs) in biologically relevant genes have been reported on AAA. The studies investigated SNPs in genes of the extracellular matrix, the cardiovascular system, the immune system, and signaling pathways. Very few studies were large enough to draw firm conclusions and very few results could be replicated in another sample set. The more recent unbiased approaches are family-based DNA linkage studies and genome-wide genetic association studies, which have the potential of identifying the genetic basis for AAA, if appropriately powered and well-characterized large AAA cohorts are used. SNPs associated with AAA have already been identified in these large multicenter studies. One significant association was of a variant in a gene called *CNTN3* which is located on chromosome 3p12.3. Two follow-up studies, however, could not replicate the association. Two other SNPs, which are located on chromosome 9p21 and 9q33 were replicated in other samples. The two genes with the strongest supporting evidence of contribution to the genetic risk for AAA are the *CDKN2BAS* gene, also known as *ANRIL*, which encodes an antisense RNA that regulates expression of the cyclin-dependent kinase inhibitors CDKN2A and CDKN2B, and *DAB2IP*, which encodes an inhibitor of cell growth and survival. Functional studies are now needed to establish the mechanisms by which these genes contribute to AAA pathogenesis.

INTRODUCTION

Abdominal aortic aneurysm (AAA) is a life threatening disease that affects 10% of Caucasian males over 65 years of age.[1] It is the 17th leading cause of death in the United States with about 15,000 deaths per year (WISQARS Leading Causes of Death Reports, 1999–2004.2007). Thanks to improved diagnostic efforts using ultrasonography imaging of the abdominal aorta to detect a dilatation, AAAs are identified earlier and only about 15% of AAA present as ruptured AAA in hospitals of industrialized nations.[2]

AAA is a complex disease with several recognized risk factors such as smoking, male sex, age over 65 years, and positive family history.[1, 3, 4] Protective factors are type 2 diabetes mellitus, African-American ethnicity and female sex.[5–9] The familial nature of AAA was first reported in a study published in 1977 where three brothers were all described to have AAA.[10] Subsequent studies on families in which at least two relatives had AAA, demonstrated that the risk for developing an AAA is eight-fold higher for a first-degree

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relative than in the general population.[11] It is, therefore, common practise for every vascular surgeon to include questions about family history of AAA when examining a patient.

The first studies on the genetic basis of AAA were reported more than 25 years ago and compared the frequencies of blood groups or HLA-A and HLA-B in AAA patients and controls.[12] Subsequent candidate gene studies in single AAA families with several affected individuals identified mutations in connective tissue genes.[13–16] These mutations, however, were not seen in sporadic AAA patients. More recently genome-wide approaches were used to provide unbiased ways of identifying genetic risk factors for AAA. These included DNA linkage studies in affected relative pairs from AAA families[17, 18] and genome-wide association studies (GWAS)[19, 20] with AAA cases and controls.

Another approach to study disease pathogenesis at the molecular level is to carry out a genome-wide expression analysis to identify genes actively transcribed in AAA and non-aneurysmal aortic tissue. Only one such large-scale microarray-based study has been reported for AAA tissue[21] and it identified over 3,000 genes with significantly elevated or decreased expression levels in AAA aortic wall tissue compared to control aortic tissue. A follow-up study analyzed the promoter regions of the up- and downregulated genes with an *in silico* approach and determined the transcription factor (TF) binding sites which were overrepresented in the 5-kb promoter regions of the 3,274 genes. [22] There were only 13 distinct overrepresented transcription factor binding sites on the upregulated genes and eight of them belong to the ETS family. Additionally, NFκB and its subunits p50 and p65 also showed enrichment.[22] Another microarray-based expression study investigated the differences between ruptured and unruptured AAA samples.[23] A severe limitation of these studies is the fact that tissue specimens can be obtained only from the end-stage disease, when the patient undergoes repair operation. In most cases the architecture of the aortic wall has changed considerably. Expression profiles of peripheral blood have also been generated for AAA patients[24] with the hope of being able to study different stages of the AAA development, and identify biomarkers for AAA.

Studies on early stages of AAA development are currently feasible only in animal models. Three mouse models have been established but none of them simulate all the features of human AAAs.[4] For example, the widely-used model in which aneurysms are induced with angiotensin II-treatment in mice lacking the apolipoprotein E gene (*APOE)* produces suprarenal AAAs with dissection, which is only in rare cases a feature of the human infrarenal AAAs.

In this review we summarize the results of nearly 100 genetic studies on AAA. The individual studies and their results are summarized in Tables I-VI. To help the reader evaluate these studies we have separated the studies showing genetic association from those with no association. Furthermore, we provide an indicator of the robustness of the result based on the number of AAA patients and controls studied. Finally, for those readers of *the Annals* who just want a quick summary, Figure 1 provides the genes studied with associations indicated in green type. Most of these findings still need to be replicated in additional sample sets. In addition, the biological mechanisms need to be elucidated as to how the variation in each of the replicated genes contribute to increased risk for AAA. The ultimate goals of genetic research on AAA are to 1) predict who is at increased risk for developing AAA, and 2) identify the biological pathways involved in AAA pathogenesis and subsequently design ways to interfere their function to slow growth or prevent rupture of AAAs. To date these goals have not yet been attained, but some progress has been made.

CANDIDATE GENE STUDIES (Tables I–V)

Candidate gene study-approach has been used widely and has been the most common form of study design for the genetics of AAA. It requires selection of candidate genes based on their biological function and plausibility as genes with potential role in disease pathogenesis. One approach is to sequence the complete coding region, adjacent parts of the introns and the promoter of a biologically relevant candidate gene in the patient's DNA to find new sequence variants. Follow-up studies determine the variant's frequency in the general population and in larger patient groups. Most sequencing studies analysed only a small number of individuals (Table I). The other approach is to use known genetic markers called polymorphisms and carry out a genetic association study with cases and controls (Tables II–V). Most studies use SNPs as markers since they are easy to detect with high-throughput techniques. Blood samples are collected from cases and controls and DNA isolated from the blood. Only small quantities of genomic DNA are needed from the study subjects to perform these studies using PCR-based genotyping assays.

Analysis of Candidate Genes by DNA Sequencing (Table I)

In only a few studies the entire candidate gene was sequenced in a family or a group of AAA patients (Table I). Since mutations in fibrillin I (*FBN1)* gene were found to cause the Marfan syndrome,[25] it was plausible to consider a role for the extracellular matrix (ECM) genes also in AAA, since these molecules are the main structural components of the aortic wall. Thus the genes for the *α1 chain of type III collagen (COL3A1)*, elastin (*ELN*), fibulin 2 (*FBLN2)*, *FBN1* and the genes of matrix degrading proteases and their inhibitors were of great interest in AAA research.

The α1 chain of type III collagen (*COL3A1*)—Collagens are major components of the ECM, and provide support and tensile strength to the aorta.[26] The loss of collagen plays a role in aneurysm rupture.[26] Mutations in this gene are responsible for the rare genetic disorder Ehlers-Danlos syndrome type IV, also known as the vascular type of the Ehlers-Danlos syndrome.[27] *COL3A1* was the first candidate gene to be investigated by DNA sequencing in patients with aortic aneurysms. Sequencing revealed a G619R mutation in a family with three generations of individuals with aortic aneurysms[15] and an RNA splicing mutation G+1 IVS20 in another family.[14] Detailed clinical evaluation showed, however, that both of these families likely had the Ehlers-Danlos syndrome type IV even though diagnosis had not been made before the sequencing results were revealed.

In subsequent studies the *COL3A1* gene was sequenced in 50 different families with at least one additional blood relative with AAA.[16] Two mutations were detected (G136R and T501P), but they were present in only 2% of AAA patients.[16] Another study examined the *COL3A1* sequences in 40 AAA patients with 22.5% having positive family history and 29 patients with aortic occlusive disease.[13] Only one patient among the 40 AAA patients was found with a mutation (607C>T, which replaces a leucine with phenylalanine) in the coding region of *COL3A1*.[13] In conclusion, mutations in the *COL3A1* can be found in only a small fraction of AAA patients, most likely in patients who have an undiagnosed Ehlers-Danlos syndrome type IV.

Fibulin 2 (*FBLN2*)—FBLN2 is also a protein of the ECM. A candidate gene study in which the cDNA of *FBLN2* was sequenced in eleven AAA patients and two controls found no mutations. A total of 14 SNPs were detected, but these variants did not segregate with AAA in families.[28]

Matrix metallopeptidase 2 (*MMP2*)—Matrix metallopeptidase 2 (MMP2) is one of the most abundant collagen-degrading proteinases in the ECM. Increased mRNA and protein levels in the wall of AAA have been shown in several studies.[29–31] The coding region (13 exons with adjacent parts of the introns), 5′-untranslated region (UTR) and selected parts of the promoter region of the *MMP2* gene were analyzed from genomic DNA in 51 AAA patients and 48 controls. No mutations were found. Eighteen SNPs were described, ten of which were located in the coding region, three SNPs in the promoter region and 5′-UTR, but none of the SNPs showed an association with the AAA phenotype.[32]

Tissue inhibitor of metallopeptidase 1 and 2 (*TIMP1 and 2*)—Metallopeptidases and their inhibitors, the TIMPs have a dynamic balance in the ECM. Imbalance of their activity or expression levels can cause degradation of the ECM. Decreased mRNA levels of TIMPs have been reported in the aneurysmal aortic wall.[33, 34] In a mouse model, elastase perfusion led to a development of larger aneurysms in *Timp1*-deficient mice than wild-type mice.[35] In humans, *TIMP1* is localized on the X chromosome and is, therefore, of special interest in AAA, which is a disease with male predominance.

The first DNA sequencing analysis of *TIMP1* was carried out in six AAA patients and revealed a silent polymorphism in two of the six patients.[36] A subsequent sequencing study found a SNP (C>T) at nucleotide (nt) position 434.[37] The investigators showed a significant association with the C-allele in female AAA patients.[37] Due to the small number (n = 20) of patients analyzed, the results should be interpreted with caution. Another sequence analysis of the coding region of *TIMP1* gene (six exons) in 50 patients did not detect any mutations and the three SNPs that were found were not associated with AAA.[38]

Serum levels of TIMP2 are decreased in AAA patients.[39] Additionally the ratio of MMP2/TIMP2 mRNA levels is elevated in AAA tissue compared to control aortic tissue[40] suggesting a role for TIMP2 in AAA development. One DNA sequencing study of the *TIMP2* gene revealed a SNP at nt 573G>A. The G allele was significantly more frequent in males with AAA (n = 64) than in male controls (n = 29).[37] Another complete sequence analysis of the *TIMP2* gene (50 AAA patients and 41 controls) identified six polymorphisms, but no mutations and did not find an association between the SNP nt 573G>A with AAA phenotype.[41]

Cholesteryl ester transfer protein (CETP)—After a promising, although small (44 AAA cases and 32 controls), genetic association study published in 1990 in which a polymorphism at the *CETP* locus was associated with AAA,[42] a candidate gene study of the 16 exons in the *CETP* gene was performed by single stranded conformation polymorphism analysis, followed by a restriction enzyme analysis and DNA sequencing in 85 AAA patients and 34 controls. The study revealed four polymorphisms (two in exons 9 and 14, and two in introns 12 and 15). The polymorphism in exon 9 was an A>T transversion which produced a stop codon in the CETP protein and could potentially result in an inactive protein. The polymorphism in exon 14 was a G>A transition which resulted in a substitution of isoleucine for valine. The surprising finding was that none of the polymorphisms differed in frequency between the cases and the controls.[43]

Genetic Association Studies Using Known Polymorphisms in Candidate Genes (Tables II–V)

Most genetic studies on AAA have been genetic association studies which focused on specific known SNPs or other genetic variants (see below) in biologically plausible candidate genes. Taken together the results from these various genetic studies on AAA suggest that mutations in one single gene cannot account for the liability to AAA. Altogether

83 candidate genes with more than 1,000 SNPs or other gene alterations have been studied. Most of the early genetic association studies were substantially underpowered with fewer than 150 cases and 150 controls. The number of samples required for a genetic association study is dependent on allele frequency, genotypic relative risk (penetrance), linkage disequilibrium (marker to effective variant) and can be much larger than 150.

The candidate genes can be divided into four different groups[4] according to their potential role in the AAA pathophysiology (Fig. 1; Tables II through VI). We discuss these categories separately in this review. All studies published by July 2010 and identified in a PubMed search were included in this review.

Group I: Genes of the extracellular matrix (ECM) – Structure and Remodelling of the Aorta (Table II)

Type III Collagen (*COL3A1*)—As mentioned above *COL3A1* gene was the first ECM gene analyzed by DNA sequencing (Table I). Using genetic association study approach, five reports have been published investigating the potential role of *COL3A1* polymorphisms in AAA pathogenesis,[44–48] but no evidence of association was shown in any of these studies.

Fibrillin I (*FBN1*)—A large number of different mutations have been identified in *FBN1* in patients with the Marfan syndrome.[49–51] Concerning AAA, one study, which compared patients with AAA to those with AAA and popliteal artery aneurysms (PAA), showed a significant difference in the frequency of a repeat polymorphism in the *FBN1* gene between the two study groups, but the number of samples investigated was too small to draw any conclusions about the findings.[47]

Elastin (*ELN*)—Elastin is also a component of the aortic ECM, accounting for 30% of the aorta by weight.[52] Its function is to maintain the shape of the vessel,[26] and loss of elastin in the aortic wall causes dilatation without rupture.[26] Elastin deposition in the vessel wall does not continue in adulthood. Mutations in the *ELN* gene cause supravalvular aortic stenosis and Williams-Beuren syndrome (different cardiac valve pathologies with neurobehavioral features and mental retardation).[53, 54] Mutations in the *ELN* gene are also found in patients with another connective tissue disease, cutis laxa.[55] Two association studies investigated a SNP located in the *ELN* gene (nt 422 G>A) in AAA patients and controls.[48, 56] No association was shown in sporadic AAA cases,[48, 56] but a nominally significant association was shown in a subgroup of patients with a positive family history.[48]

ATP-binding cassette transporter, subfamily C (CFTR/MRP), member 6 (*ABCC6*)—Mutations in the *ABCC6* gene are known to cause pseudoxanthoma elasticum (PXE), a hereditary connective tissue disorder characterized by fragmentation of elastic fibers. It is, therefore, plausible that this gene might play a role also in AAA.[57] One study investigated *ABCC6* polymorphisms in 133 AAA patients and 910 controls, detected only five genetic variants (missense or silent amino acid variants) in the 133 AAA cases, and no significant associations.[57]

Fibulin 5 (*FBLN5*)—Fibulin 5 is expressed in the great vessels during embryogenesis and in many adult tissues including the aorta.[58–60] It is an elastin-binding protein which localizes to the surface of elastic fibers in vivo.[58] Mice lacking *Fbln5* gene have fragmented elastin.[61] The protein acts as a bridging peptide between blood vessel wall cell surface integrins and elastin fibers.[62] Mutations in *FBLN5* gene cause cutis laxa and might contribute to age-related macular degeneration.[63, 64] Thus *FBLN5* is of interest also in the AAA pathogenesis. One recent genetic association study on AAA used three SNPs in the

FBLN5 gene in a total of 230 AAA cases and 278 controls and showed no association with AAA.[65]

Family of Matrix Metallopeptidases (*MMPs*)—Several studies have focussed on the MMP genes as candidate genes since elevated levels of MMPs, especially MMP9 and MMP2 have been measured in the serum and aortic wall of AAA patients.[29–31, 40, 66] The list of MMP genes investigated for their role in AAA includes *MMP1*, *MMP2*, *MMP3*, *MMP9*, *MMP10*, *MMP12* and *MMP13*. SNPs in genes of *MMP1*, MMP2, *MMP10*, *MMP12*, and *MMP13* showed no associations with AAA.[48] One of the *MMP2* SNPs (rs243865) was also investigated with regard to rate of AAA growth, but no association was shown.[67, 68]

MMP3 is a known activator of MMP9 and its mRNA levels are significantly increased in AAA tissue.[69] The promoter region of *MMP3* which has a SNP (5A/6A) at nt –1621 has gained special interest. One study with 405 AAA patients and controls showed a significant association with the 5A allele.[70] Other studies, including AAA growth studies, could not detect this association.[48, 67, 68, 71] A meta analysis of this *MMP3* polymorphism found 5A allele associated with a dominant model giving the best fit (OR, 1.4; 95% CI, 1.12 to 1.76; p = 0.003).[72]

The T allele of C>T SNP (rs3918242) in the promoter region of *MMP9* results in increased transcriptional activity compared to the C-allele.[73] The frequency distribution of the genotypes for this SNP in 414 AAA cases was significantly different from 172 cases with peripheral vascular disease (PVD) ($p = 0.0013$), but not if compared to 203 healthy controls ($p = 0.334$).[74] Subsequent studies with larger sample sizes showed no association.[48, 75] The results were also negative when using aneurysm growth rate as the phenotype.[67, 68] Two smaller studies showed no association with AAA when studying a CA-repeat in the *MMP9* promoter region.[76, 77] Two meta analyses found contradictory results in that, one meta analysis published in 2008 demonstrated a significant allelic dose effect for rs3918242,[78] whereas a more recent meta analysis which included an additional non-significant association study from Smallwood and co-workers[75] with 678 AAA patients and 659 controls, found no association.[72]

Tissue Inhibitor of Metallopeptidase 1, 2 and 3 (*TIMP1, -2 and -3*)—DNA sequence analysis detected a SNP in the *TIMP1* gene (nt 434 C>T) which was associated ($p = 0.0047$) with AAA in 235 male AAA patients without family history and 425 controls.[48] A meta analysis of this *TIMP1* SNP, however, found no association.[78] Another SNP (rs2070584) in the same gene was also associated with AAA in male patients without family history.[48] In the same study SNPs in *TIMP2* and *TIMP3* genes showed no association to AAA phenotype.[48]

Serine peptidase inhibitor, clade A, member 1 (*SERPINA1*)—This peptidase inhibitor is better known under the name of α1-antitrypsin (α1-AT), the deficiency of which leads to a severe hereditary disease, characterized by lung emphysema, which is aggravated by smoking. α1-AT levels are influenced by variation at the protease inhibitor (PI) locus. The SERPINA1 locus was previously known as the PI locus and was studied by isoelectric focusing, which identified over 50 different alleles. [79, 80] The so called PI*S- and PI*Z alleles lead to lower serum levels of α1-AT than the more frequent PI*M1, PI*M2, PI*M3 and PI*M4 alleles. Two studies measured the PI*S and PI*Z α1-AT-deficiency alleles in aneurysm patients by isoelectric focusing in the plasma, and both observed no excess in the PI deficiency alleles compared to controls.[81, 82] Another study detected fewer PI*MM phenotypes ($p = 0.0003$) and significantly more PI*MV phenotypes ($p = 0.0001$) in AAA patients.[82] The functional role of the PI*MV allele was not investigated.

Serine peptidase inhibitor, clade E, member 1 (*SERPINE1*)—Plasminogen activator inhibitor-1 (PAI-1), now formally known as *SERPINE1*, can inhibit MMPs and also fibrin degradation by repressing plasmin.[83] The amount of SERPINE1 is decreased in cultured smooth vessel cells isolated from the aortic wall of AAAs compared to those from non-aneurysmal aorta.[84] Most studies have focused on a functional repeat variant (4G/5G) located at nt –675 in the promoter region. Individuals who are homozygous for the 4G allele (4G/4G genotype) have increased SERPINE1 expression.[85] A study with 39 AAA cases with strong family history and 163 controls showed a significantly higher frequency of the 5G allele in the AAA group,[85] but a previous study could not detect an association when analyzing 47 AAA patients without family history and 173 controls.[71] Other studies investigated the AAA expansion rate related to the 4G/5G allele distribution with no association.[67, 68, 86] A meta analysis of this *SERPINE1* variant concluded that there is no association with AAA.[72]

Secreted phosphoprotein 1 (*SPP1*)—Experimental studies support a role for *SPP1*, also known as osteopontin (*OPN*), in promoting inflammation, proteolysis, and atherosclerosis.[87–89] SPP1 has been linked to development of AAA in an animal model, in which double knockout ($Apoe^{-/-}Opn^{-/-}$) mice developed smaller aneurysms after angiotensin II-infusion with decreased MMP2 and MMP9 activity compared to $Apoe^{-/-}Opn^{+/+}$ mice ($p < 0.005$).[90] In human AAA patients, SPP1 concentrations in the serum and aortic tissue are significantly increased particularly in aortic wall specimens of small AAA with a diameter from 3.0 to 5.0 cm, but no genetic association has been shown between five polymorphisms in the *SPP1* gene and AAA.[91]

Xylosyltransferase 1 (*XYLT1*)—XYLT1 is the first enzyme in the biosynthesis of the proteoglycan-linked glycosaminoglycan chains. Proteoglycan content and biosynthesis are altered in AAA and thus make *XYLT1* a plausible candidate gene to study in AAA.[92] A genetic association study using 129 AAA cases and 129 controls demonstrated that individuals with the T-allele of SNP G>T at nt 343 had a 5-fold risk of developing AAA ($p = 0.011$).[92] These intriguing preliminary findings need replication in larger samples.

Cystatin C (*CST3*)—Cystatin C is a natural inhibitor of elastolytic cysteine peptidase such as the cathepsin family of peptidases. Cathepsin inhibitors are potentially relevant since cathepsins S and K are overexpressed at sites of arterial elastin damage and in vascular smooth muscle cells.[93] Decreased cystatin C levels measured from serum have been correlated with the presence of AAA and with the growth rate of aneurysms.[94, 95] A British-Swedish study examined 424 AAA patients with two SNPs located in the *CST3* gene. The number of homozygote individuals with the C-allele (CC genotype) for one of the SNPs (nt -82G>C) was low, and individuals who were homozygous for the A-allele (AA genotype) for another SNP (nt 148G>A) had a slower growth rate of AAA.[96]

Group II: Genes of the Cardiovascular System (Table III)

Genes of the cardiovascular system constitute another group of genes investigated for their role in AAA. Proteins regulating blood pressure, and factors involved in blood cell development and coagulation or genes known to be associated with other cardiovascular diseases serve as candidate genes (Table III).

Genes involved in the renin-angiotensin-aldosterone system—The renin-angiotensin-aldosterone system plays a critical role in blood pressure regulation and angiotensin converting enzyme inhibitors are one of the most frequently prescribed antihypertensive medications. Clinical studies on AAA patients have demonstrated that ACE-inhibitors augment collagen synthesis, reduce stiffness of the aortic wall,[97] and reduce

the risk of rupture of AAA.[98] Thus, different genes of the renin-angiotensin-aldosterone system have been investigated for their role in AAA pathogenesis.

Angiotensin I converting enzyme (peptidyl-dipeptidase A) 1 (ACE): *ACE* itself has been investigated for its role in AAA pathogenesis. An insertion(I)/deletion(D) polymorphism in an Alu repeat in intron 16 (rs4646994) correlates with plasma levels of ACE, and homozygotes with the deletion allele have higher ACE levels.[99, 100] A small study (125 AAA cases and 153 controls) showed no association with aneurysm.[101] Another study investigated the polymorphism in AAA growth in 58 AAA patients, detected 14 patients with D/D, 29 with D/I and 15 with I/I genotype, but no association to aneurysm growth rate (median AAA growth rate was 0.28 cm/year) was shown.[102] The small numbers in the subgroups, however, make conclusions difficult.

Another small study (133 AAA cases and 152 controls) showed an association only when comparing subgroups of hypertensive AAA patients (n = 81) with normotensive AAA patients (n = 43).[103] In another study Pola and co-workers showed an association with the deletion allele and AAA in 56 normotensive AAA when compared to 122 controls.[104] Since all of the studies were small, the results should be interpreted with caution. Three other larger studies detected an association with the deletion allele.[105–107] Two meta analyses observed an association between AAA and this *ACE* polymorphism with the best fit in a dominant model,[72, 78] but significant inter-study heterogeneity.[72] Recently, another study tried to replicate the association in a large British case-control set of 1,155 AAA patients and 996 controls with an estimated power of 90%. No association was shown.[108]

Angiotensinogen (AGT): In a large genetic association study the T-allele of rs699 in exon 2 of *AGT* was associated with AAA in a patient cohort (576 AAA cases and 472 controls) from New Zealand. The association, however, could not be replicated in cohorts from the United Kingdom (298 AAA cases and 912 controls) and Australia (352 AAA cases and 339 controls).[107]

Angiotensinogen II receptor, type 1 (AGTR1): The most significant genetic association in the angiotensin-renin-system was shown for a SNP (1166A>C; rs5186) in *AGTR1*.[107] The odds ratio (OR) was 1.60 (95% CI: 1.32–1.93; $p = 1.1\times10^{-6}$).[107] Two other large studies, however, were not able to replicate this association,[105, 109] but a meta analysis for the same SNP found an association in a dominant genetic model.[72]

Bradykinin receptor 2 (BDKRB2): Bradykinin is a vaso-depressor which works in the renin-angiotensin-system as a functional antagonist of angiotensin II, and it can be inactivated by ACE. No association between a polymorphism (rs5223; I/D of 9 bp, in exon 1 and the 5′-UTR) in *BDKRB2* and the presence of AAA, or AAA growth rate, was shown.[107]

Genes involved in lipid metabolism—Because of the crucial role of lipid metabolism in atherosclerosis, the genes involved in this pathway are also of interest in AAA pathogenesis.

Apolipoprotein B (including Ag(x) antigen) (APOB): APOB is a marker for triglyceride-rich lipoproteins and the *Xbal* polymorphism in this gene is correlated with plasma levels of triglycerides.[110] One small study investigated the *Xbal* polymorphism in AAA patients without (n = 124) and with (n = 24) additional PAA and no differences in allele frequencies were seen.[47]

Apolipoprotein E (APOE): *APOE* polymorphism has long been known to be associated with risk for atherosclerosis.[111] In mice *Apoe* deficiency predisposes to AAA formation and

atherosclerotic changes after angiotensin II-infusion.[112] The *APOE*2*, *-*3*, and *4* alleles were investigated in patients with small AAAs (n = 57), and the AAA expansion rates were followed over 2 to 4.5 years.[113] Compared with the E3/E3 genotype, individuals with the E3/E4 genotype had a significantly lower AAA expansion rate ($p = 0.001$).[113] These findings, however, were not replicated in another larger study (640 men with small AAA).[114]

Cholesteryl ester transfer protein, plasma (*CETP*)—The first small study on *CETP* and AAA was published in 1990 and it investigated the *TaqIA* polymorphism at the *CETP* locus in AAA patients (n = 44) and controls (n = 32).[42] The frequency of the rare 9.0 kb allele was significantly increased in AAA patients ($p < 0.01$).[42] Another later study in which the entire gene was sequenced revealed no mutations or associations with AAA.[43] In both studies the sample numbers were too small to draw conclusions.

Coagulation factor II (thrombin; *F2*) and coagulation factor V (proaccelerin, labile factor; *F5*)—Since the aneurysm sac is nearly always filled with mural thrombus, a role for thrombophilic risk factors in AAA pathogenesis has been suggested.[115] Two genetic variants predisposing to thrombosis, the so called Leiden mutation of *F5* and the G20210A variant of *F2* were investigated in 438 AAA cases and 438 controls, but no associations were shown.[115]

Genes involved in the methionine metabolism—Hyperhomocysteinemia is a risk factor for thrombosis and atherosclerosis and in animal models hyperhomocysteinemia induced an ECM remodelling of the arterial wall.[116, 117] Two studies demonstrated a correlation between AAA and mild hyperhomocysteinemia.[115, 118] Homocysteine is an intermediate of the methionine metabolism. Several polymorphisms in 17 genes coding for enzymes involved in the methionine metabolism have been tested for association with hyperhomocysteinemia, which might play a role in the development of AAA.

5,10-Methylenetetrahydrofolate reductase (MTHFR): *MTHFR* is a cardiovascular candidate gene, located on chromosome 1p36.3 and is involved in homocysteine metabolism. Studies have focused on the SNP (rs1801133; nt 677 C>T), which results in an alanine to valine substitution and in 70% reduction in enzymatic activity *in vitro*.[119] Three small studies showed that the T-allele was associated with AAA.[120–122] Another small study restricted the analysis to normotensive AAA patients and showed an association with AAA.[123] Recent, larger studies, however, were not able to confirm these associations.[115, 118, 124, 125] When combining all the studies published to date, two meta analyses revealed an association between the T allele and AAA[72, 78] in a dominant model. Analysis of three additional polymorphisms, two exonic SNPs with amino acid substitutions (rs1801131: A1298C and rs2274976: C1793T) and one in the 3′-UTR region (rs48846049) showed no association with AAA.[125] A small subgroup analysis in male, non-smoking AAA patients (20 vs 33) showed an association with the A1298C SNP.[126]

Methylenetetrahydrofolate dehydrogenase 1 (MTHFD1): One large study (423 AAA cases and 423 controls) which evaluated 56 polymorphisms in 17 genes coding for enzymes in the methionine metabolism demonstrated an association between one SNP (rs8003379) in *MTHFD1* and AAA, whereas six additional SNPs in the same gene were not associated.[125] Of interest is that smaller aortic diameter in AAA patients was associated with SNP rs8003379, which is located in an intron and no functional information is known about it.[125]

5-Methyltetrahydrofolate-homocysteine methyltransferase (MTR): The MTR enzyme catalyses the final step in methionine biosynthesis.[125] Five polymorphisms were

investigated in the *MTR* gene, and one of them (rs2853523) showed an association with AAA for the C-allele, with individuals having the A-allele showing smaller aortic diameter.[125] This SNP is localized in the 3′-UTR which can have a role in the control of gene expression.[125]

5-Methyltetrahydrofolate-homocysteine methyltransferase reductase (MTRR): In the methionine metabolism MTR enzyme eventually becomes inactive due to the oxidation of its cob(I)alamin cofactor. The protein encoded by *MTRR* gene regenerates a functional MTR enzyme via reductive methylation. A study investigating the *MTRR* gene showed that one SNP (rs326118) out of seven polymorphisms, was associated with AAA (A-allele).[125] This variant is located in the 5′-UTR of the gene.[125]

Thymidylate synthetase (TYMS): There is a SNP (rs16430) in the 3′-UTR of the *TYMS* gene which influences the expression and stability of TYMS mRNA,[127] and is associated with higher red blood cell folate and homocysteine concentrations.[128] The C-allele of this variant was associated with AAA in one study, while another SNP (rs502396) in the same gene was not associated.[125] The naturally occurring antisense transcript to the human thymidylate synthase (*TYMS*) gene is *enolase superfamily member 1 (ENOSF1)*. One SNP (rs8423) in the *ENOSF1* gene has been investigated in one study, and no association was shown with AAA.[125]

Adenosylhomocysteinase (AHCY): *AHCY* regulates the intracellular S-adenosylhomocysteine concentration and is important in transmethylation reactions.[125] Deficiency in the protein is one of the causes of hypermethioninemia. The promoter region of *AHCY* contains a SNP (rs819146) near the start codon which might have regulatory role on gene expression.[125] Interestingly, this SNP was associated with AAA in one study.[125]

Folate hydrolase 1 (FOLH1): Folic acid play a role in intestinal absorption of dietary folates, and therefore, a genetic variation could lead to an altered absorption followed by low blood folate levels and hyperhomocysteinemia. A SNP (rs202676; Q75X), which results in a stop codon was studied, but no association with AAA was shown.[125] Another SNP (rs202680) was associated with larger aortic diameter in AAAs, but increased levels of homocysteine were not detected.[125]

Several other SNPs in genes involved in the methionine metabolism have been investigated in AAA, mostly in only one study and all results were negative for an association with AAA: Four polymorphisms in the *betaine-homocysteine methyltransferase (BHMT)* gene have been investigated for their role in AAA pathogenesis with no associations identified.[125] In *betaine-homocysteine methyltransferase 2 (BHMT2*) two *SNPs* have been studied, but no associations were shown with AAA.[125] Five SNPs in the *cystathione-beta-synthase (homocysteine; CBS)*, three of them leading to amino acid substitutions, and one located in the 3′-UTR were tested without evidence for association with AAA.[125] *Nicotinamide-N-methyltransferase (NNMT)* is another important enzyme in homocysteine metabolism.[129] Four SNPs have been investigated, two in the 5′ region, one in 5′-UTR and one intronic, but no associations were shown with AAA.[125] The enzyme activity of *paraoxonase 1 (PON1)* is predictive of vascular disease,[125] but polymorphisms found in this gene (rs8545560, rs662 and rs3917594) cannot explain this variation in activity.[125] One small study detected an association between a SNP (nt –108 C>T) in the *PON1* gene and AAA in a subgroup analysis of a small number of AAA patients who were more than 65 years of age and smokers.[126] In *paraoxonase 2 (PON2)* one amino acid changing SNP (rs12026; A148G) has been investigated, but no association with AAA was shown.[125] Three SNPs have been analyzed in the gene called *solute carrier family 19 (folate transporter), member 1 (SLC19A1)*, all located in the 5′ end of the gene or 5′-UTR, but they were not associated

with AAA.[125] *Serine hydroxymethyl-transferase, cytosolic (SHMT1)* has two SNPs, one in 5′-UTR, the other in the exon with amino acid change L474F. Both of these SNPs were analysed in one study, but no evidence for association with AAA was detected.[125] And three SNPs (rs1801198: P259R; rs5749131 and rs10418) in *transcobalamin II (TCN2)* were studied, but no association with AAA was shown.[125]

Endothelial constitutive nitric oxide synthase (*NOS3*)—NOS3 is a modulator of vascular disease and maintains endothelial function and antithrombotic intravascular environment. A SNP (G894T in exon 7) is associated with reduced basal nitric oxide production.[130] The minor, less common T-allele leads to an amino acid substitution Q298N. This SNP is associated with coronary artery disease[131] and carotid atherosclerosis.[132] Studies on mice lacking this gene gave evidence for the role of nitric oxide in controlling vessel wall geometry.[133] Thus *NOS3* is a plausible candidate gene also for AAA.[134] A study published in 2005, analyzed 250 AAA patients and 250 controls and showed an association between the G894T SNP and AAA.[135] The association remained significant in multivariate analysis adjusted for other vascular risk factors and other atherosclerotic localizations.[135] An association was also shown in a smaller study (62 AAA cases and 62 controls).[136]

A SNP located in the promoter region (nt –786T>C) of *NOS3* gene influences promoter activity with the T-allele showing 50% more transcriptional activity than the C-allele.[137] No association, however, has been detected between this SNP and AAA.[135] Another study focused on a variable number tandem repeat (VNTR), called 4a/4b polymorphism, located in intron 4, which is correlated with altered nitric oxide plasma levels.[138] The 4a/4b polymorphism is associated with hypertension[139] and coronary lesions in smokers.[140] In 58 AAA patients and 410 controls no association was shown with this VNTR, although a subgroup analysis showed an association with the need of surgery in AAA patients, but the sample numbers were small (34 surgical and 24 non-surgical AAA patients).[141] A second study with more samples did not observe any association between the VNTR and AAA.[135] A meta analysis of these two studies concluded that there was no association.[78]

Prostaglandin-endoperoxide synthase 2 (*PTGS2*)—The biological activity of PTGS2 (known also as cyclooxygenase 2) is critical in the inflammatory response, modulates cardiovascular diseases and promotes atherosclerotic plaque progression and instability.[142, 143] A SNP located in the promoter region (nt –756G>C; rs20417) is functionally important, and the C-allele produces less *PTGS2* mRNA than the G-allele, and correlates with significantly reduced serum levels of C-reactive protein in myocardial infarction or stroke patients.[144] This SNP may act as a protective factor against myocardial infarction and stroke.[144] It has been speculated that a reduced *PTGS2* expression and the consequent suppression of local and systemic inflammation may also be protective in AAA development and rupture.[145] One study investigated *PTGS2* in AAA and showed no association with the SNPs in this gene with AAA.[146]

Haptoglobin (*HP*)—*HP* was one of the first genes investigated in AAA patients. In a small sample group the α1 chain was seen more frequently than the α2 chain,[42] but in a follow-up study of 28 AAA-families the *HP* variants were equally distributed.[44] Another study investigated the HP phenotypes by starch gel electrophoresis in 52 AAA, 37 PVD patients, and a control group of 37 without atherosclerosis. The 3 different HP phenotypes were equally distributed in the 3 study groups.[147] Recently a study assessed the relationship between AAA expansion and HP phenotypes. They determined three major HP phenotypes (1-1, 2-1, and 2-2) in 83 AAA patients. Rescanning at 6- to 12-month intervals up to a period of 2 to 7 years, the mean yearly rate of growth of the AAA was calculated from the largest transverse diameter for each group of HP patients and HP 2-1 patients had a significantly higher growth rate (3.69 [2.40] mm/y) compared with patients with HP 2-2

(1.24 [0.79], p < 0.00001) and HP 1-1 (1.45 [0.68], p = 0.00004). This association remained significant in the multivariate analysis. Elastase serum activity and CRP serum levels were also higher in AAA patients with HP 2-1. Larger follow-up studies are needed to confirm if the HP 2-1 phenotype is useful as independent predictor of AAA expansion rate.[148]

Blood groups—A Swedish study investigated the ABO blood groups and Rh-system in 117 AAA patients and 59,862 controls.[149] Blood group A of the ABO-system was relatively common in AAA patients but the difference between AAA patients and controls did not reach statistical significance.[149] A statistically lower frequency of the Rh-negative blood group of the Rh-system was observed in the AAA group.[149] The MNS blood group was studied in 54 AAA cases and 2,164 controls, and the frequencies of the MNss type and the number of MN heterozygotes were significantly increased in AAA patients.[149] The KELL blood group was investigated in 54 AAA cases and 287 controls, and the AAA group had significantly more KELL positive individuals than the control group.[149]

Group III: Genes of the Immune System (Table IV)

AAA disease typically involves inflammation with leukocyte infiltrates and increased amounts of various cytokines.[150–153,152–154] A large number of different immune-related genes, especially the human leukocyte antigen (HLA) class II genes, interleukins and the tumor necrosis factor (*TNF*) gene, have been investigated for their potential role in AAA pathogenesis (Table IV).

Human leukocyte antigen locus (HLA)—The first study concerning the role of HLA-A and –B in AAA was performed 26 years ago in Sweden. Serotyping of patients for 18 HLA-A and –B antigens detected no significant differences between the AAA group (n = 48) and the control group (n = 368). More than ten years later studies using genetic approaches found that HLA-DRB1*15, HLA-DR B1*04 and –B1*02 were associated with AAA but the sample size was rather small.[155–157] Several follow-up studies concerning HLA-DR and HLA-B subgroups were also small and their findings should be interpreted with caution.[158–161] A larger study showed an association with HLA-DQA1*0102,[162] but yet another study showed no evidence of an association between HLA-A*11, HLA-B*08 or HLA-B1*11 and AAA.[163]

Chemokine (C-C motif) receptor 5 (*CCR5*)—Chemokines are cytokines that promote migration of leukocytes into inflammatory sites.[164] CCR5 is expressed in macrophages, T-cells, aortic smooth muscle cells and coronary artery endothelial cells[165, 166] and CCR5 ligands have been detected in atherosclerotic plaques.[167] Genetic screening studies showed that CCR5 deficiency protects from severe coronary artery disease.[168] A loss of CCR5 receptors on lymphoid cell surfaces is caused by a 32-bp deletion, called delta 32, in the *CCR5* gene.[169] Investigation of 70 AAA patients, 76 patients with PVD and 62 carotid artery stenosis patients showed that AAA patients had a higher frequency of the deletion allele. Comparing to 172 controls it was not an independent risk factor. The study concluded that the presence of at least one deletion allele provided a 4-fold higher risk for AAA rupture.[170] A follow-up study with larger sample sizes (285 AAA cases and 273 controls) showed the same frequency of the deletion allele in both groups.[171] To interpret the role of the delta 32 deletion in the development and rupture of AAA, larger sample sizes are necessary.

Interleukin 1α (*IL1A*), interleukin 1β (*IL1B*) and interleukin 1 receptor antagonist (*IL1RN*)—IL1 is an important regulator of the inflammatory cascade and it is present in aneurysmal tissue. AAA patients have significantly higher plasma levels of IL1B than patients with coronary artery disease without AAA.[150, 172, 173] IL1 induces MMPs and

promotes vascular smooth muscle cell apoptosis.[174, 175] Some polymorphisms in the *IL1* gene cluster modulate cytokine expression and contribute to a wide range of inflammatory conditions.[176] Six SNPs in *IL1A*, *IL1B* and *IL1RN* were investigated in 135 AAA cases and 270 controls, but no associations between the SNPs and AAA were detected.[176] One SNP in the *IL1B* gene (nt 3953 C>T) was investigated in two different small case-control studies and no association was shown.[176, 177] A meta analysis of the two studies found no association with AAA.[78]

Interleukin 6 (interferon β2; *IL6*)—IL6 is a pro-inflammatory cytokine, and elevated levels of circulating IL6 have been measured in AAA patients[178] and IL6 has increased expressed in the wall of AAA and popliteal aneurysms[153]. In a large well-designed case-control study (677 AAA and 656 controls) three SNPs in the *IL6* gene promoter were examined. One SNP (rs1800796; –572 G>C), which was present in only 1.5% of cases, was identified as an independent risk factor for AAA in an analysis using a recessive model, and no association was seen in an additive or dominant model.[179] Two other SNPs (rs1800795 and rs1800796) showed no association.[177, 178] A meta analysis of one SNP (rs1800795; *IL6* G174C) found no evidence of association.[72]

Interleukin 10 (*IL10*)—IL10 is a predominantly anti-inflammatory cytokine. In a small study increased levels of IL10 were measured in the aortic wall of patients with AAA,[180] but in another study mRNA levels did not differ between AAA tissue and control tissue.[153] The presence of an A-allele at nt -1082 instead of a G-allele resulted in 25% reduction in IL10 production by lymphocytes.[181] This SNP has been associated with chronic inflammatory diseases.[182] The same SNP was first tested in a small study on AAA and an association with AAA was seen,[177] but a confirmation study with larger sample groups (389 AAA cases and 404 controls) showed that after a multivariate regression analysis the association was not independent from age, smoking, hypertension or history of PVD.[182] A meta analysis of the two studies, however, found that the best fit for an association with AAA was the dominant genetic model.[72]

Phospholipase A2, group VII (*PLA2G7*)—PLA2G7 catalyzes platelet activating factor (PAF) and inactivates its inflammatory function. Deficiency of the *PLA2G7* gene is caused by a missense mutation G994T, which has been described only in the Japanese population. The T-allele had a significantly higher frequency (independent from other risk factors) in the AAA group (n = 131) than in the controls (n = 106) in a Japanese study.[183]

Tumor necrosis factor (TNF superfamily, member 2; *TNF*)—TNFα is a pro-inflammatory cytokine produced by macrophages. The A-allele of a SNP located at nt –308 produces six to nine times more *TNFα* mRNA in human B-cells than the G-allele.[184]. A small association study in AAA patients and controls could not show any association between the A-allele and AAA patients.[177]

Peroxisome proliferator-activated receptor gamma (*PPARG*)—PPARG is a target receptor for TNFRSF11B (tumor necrosis factor receptor superfamily, member 11 B), which is also called osteoprotegerin. High concentrations of TNFRSF11B were detected in human AAA tissue and serum levels of TNFRSF11B were elevated in AAA patients.[185] Based on the known influence of PPARG on TNFRSF11B,[186] two SNPs were examined in 689 AAA patients and 3,538 controls.[187] For one SNP (rs1801282; c.34 G>C), which causes an amino acid substitution P12A, a weak association with AAA was shown in a dominant model, and for another SNP (rs3856806; c.1347 C>T), which is a silent SNP, only the subgroup with faster AAA progression had significantly higher frequency of the TT genotype.[187]

C-reactive protein (*CRP*)—CRP is an acute phase protein produced mainly in hepatocytes and lymphocytes and its production is stimulated by cytokines.[188, 189] Higher than control serum levels of CRP have been detected in AAA patients.[190, 191] One study tested a SNP (rs3091244)[192] for an association with AAA and if the serum concentrations of CRP were influenced by this SNP.[193] Serum levels of CRP were significantly higher in the AAA group than in the control group and especially in patients with large AAAs, but the SNP was not associated with AAA nor with elevated CRP serum levels.[193]

Heme oxygenase (decycling) 1 (*HMOX1*)—HMOX1 is a vascular anti-inflammatory factor with antioxidant capacity and is produced by vascular smooth muscle cells.[194] HMOX1 is one of the stress proteins expressed in atherosclerotic plaque lesions in the aorta.[195] A dinucleotide repeat present in the promoter region of this gene modulates the level of transcription and shorter repeats correlate with increased HMOX1 levels.[196] A small case-control study (70 AAA cases and 61 controls) showed that fewer AAA patients than controls had the shorter repeats.[197]

Group IV: Genes of Signaling Pathways (Table V)

Transforming growth factor β (TGFB) plays a role in growth and ECM protein expression in vascular smooth muscle cells, and TGFB can be induced by angiotensin II.[105] Variants in the *TGFB1, −2, and −3* genes can inhibit development of vascular smooth muscle cells, and mutations in the TGFB-receptor genes cause syndromic forms of thoracic aortic aneurysms.[198] It is, therefore, plausible that the TGFB-pathway with its receptors and binding proteins is involved in AAA development (Table V). Other candidate genes belonging to this group are the estrogen and progesterone receptors.

Transforming growth factor β1 (*TGFB1*) and Transforming growth factor β1-receptor (*TGFBR1*)—Two studies have investigated the role of SNPs in the *TGFB1* gene,[48, 199] but no associations with AAA were seen. One study analyzed a repeat variant in the *TGFBR1* gene in 201 AAA cases and 252 controls, and showed no association.[105] A Dutch group examined three SNPs in the *TGFBR1* gene with two independent large case-control sets, but showed no associations.[200]

Transforming growth factor β2-receptor (*TGFBR2*)—SNPs located in the *TGFBR2* gene have also been investigated for their potential role in AAA. Study populations from Australia (640 AAA cases and 1071 controls) and New Zealand (654 AAA cases and 389 controls) were examined for 49 SNPs in the *TGFBR2* gene, only one of which (rs1078985) showed a weak association with AAA, which did not withstand correction for multiple testing.[201] A Dutch study investigated nine different SNPs with two large case-control sets, and two of the SNPs (rs1036095 and rs4522809) showed an association with AAA in both case-control sets.[200]

Transforming growth factor β3 (*TGFB3*)—A SNP located in the *TGFB3* gene (rs11466414) was examined for its role in the growth of AAAs, but no association was shown.[199]

Latent TGF-β binding protein 1, 3 and 4 (*LTBP1, LTBP3* and *LTBP4*)—Selected SNPs in the *LTBP1* and *LTBP3* genes were investigated in four geographically different case-control sets (altogether 1,890 AAA cases and 3,785 controls) but no association with the presence of AAA nor growth rate of AAA was detected.[199] *LTBP4* gene is located on chromosome 19q13, in the candidate interval identified in a DNA linkage study.[17] Several SNPs (nt –4234A>G, 10384 G>A, 21011A>T, 25859C>T and 32603C>G) in the *LTBP4* gene showed an association with AAA growth rates.[199]

Estrogen receptors 1 (*ESR1*), and 2 (*ESR2*), and Progesterone receptor (*PGR*)—Based on the fact that AAAs are more common in males and that the prevalence of AAA increases by age in women, it is plausible to hypothesize that female sex hormones play a role in AAA development. Most biological effects of steroids are mediated by their nuclear receptors and genetic variants in these receptor genes might contribute to the disease.[56] Two SNPs in the *ESR1* gene, one in the *ESR2* gene, and one in the *PGR* gene were investigated in one study with 99 AAA patients and 225 controls. Only the SNP located in the *ESR2* gene (nt 1730A>G) showed an association with AAA.[56]

DNA LINKAGE STUDIES IN AAA FAMILIES

DNA linkage studies are used to find regions on the human chromosomes that harbor sequence changes contributing to the disease. They require samples from several family members. The identified regions are called susceptibility loci. The first DNA linkage analysis for AAA was performed in 48 AAA families with DNA markers located in only three candidate genes: 1) *BHMT* (betaine-homocysteine methyltransferase), 2) *COL1A2* (the α2 chain of type I collagen) and 3) *CTSH* (cathepsin H) gene. None of the selected candidate genes showed linkage to AAA.[202] The first genome-wide DNA linkage study on AAA used an affected-relative-pair design because it is difficult to find large families for AAA which is a late-age-at-onset and deadly disease.[17] A set of 235 affected relative-pairs from 119 families showed a strong linkage to chromosomes 19q13 and 4q31. These genomic regions have now been designated as the AAA1 and AAA2 susceptibility loci for AAA.[17] Another DNA linkage study carried out on Dutch AAA families also found evidence for linkage on chromosome 19q13.[18]

A recent genetic association study followed-up on the linkage findings by using 1,615 sequence variants on chromosome 19q13 in two independent case control sets.[203] Altogether eight SNPs (rs16968029, rs281407, rs1075453, rs6509496, rs1530878, rs285676, rs576556, rs4802552) had a significant association ($p = 0.015$) in the first case-control-set, but the association could not be confirmed in the second case-control set (Table VI).[203] These results suggest that the genetic basis of familial and sporadic AAA might be different.

GENOME-WIDE ASSOCIATION STUDIES

Another unbiased genetic approach to study complex diseases without prior hypotheses on candidate genes is a GWAS.[204] Two GWASs on AAA have so far been reported.[19, 20] It is expected that more such studies are in progress from at least one large consortium.[205]

The first GWAS for AAA was carried out using pooled DNA samples from 123 AAA cases and 112 controls on a SNP array (Affymetrix 500K) which can measure half a million SNPs simultaneously. A SNP (rs763518) located on chromosome 3p12.3, a region near contactin-3 (*CNTN3*) gene, was associated with AAA.[19] The association was confirmed by individual genotype assays on 502 AAA cases and 736 controls, and by a replication on a second independent set (448 cases and 410 controls). By analysing subgroups the association with rs763518 was even stronger in the subset of smokers. The function of this SNP is unclear and it is considered a marker for a functional genetic variant most likely located upstream in the regulatory region of *CNTC3* gene.[19] The CNTC3 protein is a lipid-anchored cell adhesion molecule known to be expressed in nervous tissue[206] and aortic wall.[19] A group from New Zealand followed-up these findings by genotyping rs763518 in 567 cases and 552 controls but could not confirm the association. The group also tested three SNPs in intron 2 of *CNTC3* and found a weak association with AAA.[207]

The second GWAS on AAA was carried out with 1,292 AAA patients and 30,503 controls from Iceland and the Netherlands, with a follow-up of most significant findings in up to

3,267 AAA patients and 7,451 controls. The A allele of a SNP (rs7025486) on 9q33 was found to associate with AAA, with an OR of 1.21 and $p = 4.6 \times 10^{-10}$. The same SNP was also found to be associated with early onset myocardial infarction (OR = 1.18, $p = 3.1 \times 10^{-5}$), peripheral artery disease (OR = 1.14, $p = 3.9 \times 10^{-5}$) and pulmonary embolism (OR = 1.20, p = 0.00030), but not with intracranial aneurysm or ischemic stroke. No association was observed between this SNP and common risk factors for arterial and venous diseases such as smoking, lipid levels, obesity, type 2 diabetes or hypertension. This SNP is located within *DAB2IP*, which encodes an inhibitor of cell growth and survival.[20]

Altogether 24 additional SNPs with $p < 5.5 \times 10^{-5}$ on 13 chromosomes were detected in the combined GWA analysis of Icelandic and Dutch samples, but none of them were replicated in other sample sets.[20]

OTHER FINDINGS

Several studies have investigated the possibility that AAA could share genetic risk factors with other vascular diseases. In one such study, five different vascular phenotypes, AAA, intracranial aneurysms, coronary artery disease, peripheral artery disease and atherosclerotic stroke, were analyzed for SNPs found to be associated with myocardial infarction and type 2 diabetes mellitus.[208] The AAA study samples were from seven different geographical regions and included 2,836 AAA cases and 16,732 controls. The SNP previously associated with myocardial infarction and located in the *CDKN2BAS* gene, previously known as *ANRIL*, (which encodes an antisense RNA that regulates expression of cyclin-dependent kinase inhibitor 2B) at locus 9p21 was strongly associated with AAA, whereas the near-by SNP associated with diabetes was not associated with AAA (Table VI).[208] The latter finding is in agreement with clinical findings that type 2 diabetes is not a risk factor for AAA.[209]

The G allele of SNP rs10757278 on *CDKN2BAS* gene was associated with AAA in five of the seven geographically different (Iceland, Belgium, Canada, US-Pennsylvania, the Netherlands, UK and New Zealand) AAA study populations. Belgian and Canadian study populations did not reach statistical significance. In a meta-analysis of all seven populations the association was highly significant (Table VI).[208] The same SNP has also been investigated in other case-control sets from UK and Australia. A significant association with AAA phenotype was confirmed, but no correlation to aneurysm growth rate was found.[210]

In another study perlecan (officially known as heparan sulfate proteoglycan of basement membrane, *HSPG2*) and versican (known as chondroitin sulfate proteoglycan 2, *CSPG2*), which are susceptibility genes for intracranial aneurysms and located at 9p21, were investigated as potential risk loci for AAA.[211] The study examined 12 SNPs in the *HSPG2* gene and 22 in the *CSPG2* gene. No associations were found (Table VI).[211]

Another recently published study measured the telomere length of chromosomes in leukocytes in blood samples collected from 190 AAA patients and 183 age-matched controls and observed significantly shorter telomeres in the AAA group.[212] It is not immediately obvious how this relates to the disease pathogenesis, and it might just be an indication of vascular aging, since the same phenomena have been seen in other cardiovascular diseases.

CONCLUSIONS

AAA is a multifactorial disease, with both genetic and environmental risk factors contributing to the underlying pathobiology.[22, 152, 213, 214] The mutations responsible for the phenotype in syndromic forms of aortic aneurysms such as the Marfan syndrome are different from the common form of AAA. Many methodological challenges of genetic association studies,[204] such as the requirement of a large number of patients and controls,

have slowed down the progress of identifying genetic variants associated with AAA. Approximately half of the genetic association studies discussed in this review do not have the number of samples required to get reliable results, which are likely to be replicated (see Tables II–VI; Fig. 1). In addition to genome-wide studies, nearly 100 candidate genes have been investigated for potential role in the AAA pathogenesis, and approximately quarter of them have been found to be associated with AAA (Fig. 1). These genes cover a wide range of functional groups and biological pathways.

Genetic heterogeneity is likely to play a role in AAA and there might also be differences in different populations. From the clinical point of view, vascular surgeons have observed that AAA patients are a heterogeneous group. Most AAAs have some degree of atherosclerotic occlusive disease. A large number of AAA patients also have hernias suggesting that their condition might be due to a more generalized connective tissue disease.[215] Additional differences are that some AAAs grow faster than others, some lead to rupture, and some have large thrombi. Some AAAs have clinically obvious inflammatory reaction in the aortic wall, whereas in other cases the wall is only thinner without signs of inflammation. Some AAA patients have additional arterial aneurysms, most often in the popliteal artery. These variations in the clinical presentation suggest different subtypes and could help us determine which subgroups have better long-term outcomes in endovascular and open repair. In future genetic studies it will be useful to focus on well-defined subgroups. Here the interest and clinical expertise of vascular surgeons is needed to collect all the appropriate and relevant data. Future studies will include replication studies as well as detailed characterization of the genes and their potential role in AAA development.

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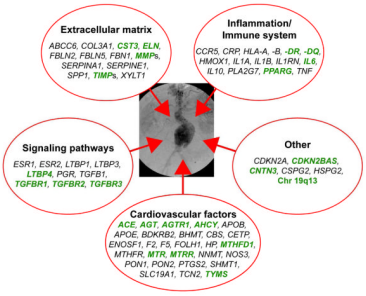

Fig. 1.

Summary on the biological pathways thought to be involved in AAA pathogenesis. The genes investigated for conferring genetic risk for AAA can be divided into five different functional groups. Genes with best evidence for contributing to AAA pathogenesis are shown in green. Studies on these genes had sufficient numbers of cases and controls making it likely that the results are not false positive associations. Details on the results of each gene are provided in Tables II through VI. To make it easier to find the genes in each functional group we have alphabetized the gene symbols, which are available from the National Center for Biotechnology Information (NCBI; http://www.ncbi.nlm.nih.gov/).

Table I

AAA candidate genes investigated by DNA sequencing

Gene	Sequence variant	Number of AAA patients/controls	
		with mutations	without mutations
COL3A1	G619R	1 Family[15]	
	G136R, T501P	1 Family[16]	49 Families[16]
	607 C>T	1[13]	39/29[13]
	G+1 IVS20	1 Family[14]	
FBLN2	1203 G>A, 1295 C>T, 500/502 G>A, 1115 G>A, 1150 A>G, 1229 A>C, 1278 A>G, 1779 C>T, 2574 G>A, 2629 G>A, 2754 C>T, 3408 G>A, 3540 T>C		11/2[28]
MMP2	IVS1+31 C>G, IVS7−18 G>A, IVS10+26 C>T, 124 G>A, 1368 C>T, 1860 C>T, −1586 C>T, −1070 T>G, −61 G>C, 228 G>A, 678 G>C, 750 C>T, IVS512 C>T, C1149 C>T, 1380 G>A, rs243834, rs11541998, rs10775332		51/48[32]
TIMP1	434 C>T	6/0[36]	64/29 (only males)[37]
		20/22 (only females)[37]	
	rs4898	50/44[38]	96/89[38]
	rs1043428, 328+16 C>T		50/44[38]
	323 C>T		84/51[37]
TIMP2	573 G>A	64/29 (only males)[37]	20/22 (only females)[37]
	306 C>T		84/51[37]
	−621 C>T, −596 A>C, rs8179096, −261 G>A, 231+23 C>T, rs2277698		50/41[41]
CETP	4 microsatellite loci		82/79[42]
	Exon 9 nt 170 A>T, Intron 12 nt 312 C>T, Exon 14 nt 16 G>A, Intron 15 nt 151 G>A		85/34[43]

Gene symbols available from the National Center for Biotechnology Information (NCBI; http://www.ncbi.nlm.nih.gov/) were used.

Table II

Genes of the extracellular matrix (ECM) – structure and remodeling of the aortic wall

		Number of studies*	
Gene	**Polymorphisms**	**Associated**	**Not associated**
COL3A1	G619R		3 (0)[44] in 28 AAA-families, [45],[46]
	A531T		3 (0)[44],[45],[47] one study on AAA+PAA
	581 T>C		1 (1)[48]
	Ava II rare allele		1 (0)[45]
FBN1	4 allele repeat	1 (0)[47] AAA vs AAA +PAA	
ELN	422 G>A	1 (1)[48] in males with family history	2 (1)[48],[56]
ABCC6	31 mutations, c.1964 A>G, c.2171 G>A, c.2175 A>T, c.2224 A>T, c.4254 G>A		1 (1)[57]
FBLN5	rs2498834, rs2430366, rs2254320		1 (1)[65]
MMP1	−1670 G/GG		1 (1)[48]
MMP2	−955 A>C		1 (1)[48]
	−1360 C>T		2 (2)[67],[68] AAA expansion
	rs243865, rs2053605		1 (1)[216]
MMP3	−1612 5A/6A	2 (2)[48] in males with family history,[70]	3 (2)[48],[67],[71] one study on AAA expansion
	−1171 5A/6A		1 (1)[68] AAA expansion
MMP9	rs3918242	1 (1)[74] AAA vs PVD	8 (6)[48],[67],[68],[71],[75],[76] two studies on AAA expansion
	−131 to −90 (CA repeat)		2 (0)[76],[77]
MMP10	180 A>G		1 (1)[48]
MMP12	−82 A>G		3 (3)[48],[67],[68] two studies on AAA expansion
MMP13	−77 A>G		1 (1)[48]
TIMP1	434 C>T	1 (1)[48] males *without* family history	1 (1)[48] males *with* family history
	−372 C>T		1 (1)[68] AAA expansion
	rs2070584	1 (1)[48] males *without* family history	1 (1)[48] males *with* family history
TIMP2	rs2009196		1 (1)[48]
TIMP3	−1296 T>C		1 (1)[48]
SERPINA1	α1-AT P1 deficiency	1 (0)[82]	1 (0)[81] AAA vs IA
SERPINE1	−675 4G/5G	1 (0)[217] AAA families	3 (3)[67],[68],[71],[86] three studies on AAA expansion
	−847 A>G		1 (1)[68] AAA expansion

		Number of studies*	
Gene	**Polymorphisms**	**Associated**	**Not associated**
SPP1	rs1126772, rs9138, rs4754, rs1126616, rs11730582		1 (1)[91]
XYLT1	343 G>T	1 (0)[92]	
CST3	−148 G>A	1 (1)[96] AAA expansion	
	−82 G>C		1 (1)[96] AAA expansion

*Number in parenthesis indicates the number of studies with a sample size of at least 150 cases and 150 controls.

If multiple sample sets were used in one publication, they were treated as independent studies.

AAA, abdominal aortic aneurysm; PAA, popliteal artery aneurysm; IA, intracranial aneurysm; PVD: peripheral vascular disease

Gene symbols available from the National Center for Biotechnology Information (NCBI; http://www.ncbi.nlm.nih.gov/) were used.

Table III

Genes of the cardiovascular system

		Number of studies*	
Gene	**Polymorphisms**	**Associated**	**Not associated**
ACE	insertion/deletion intron 16 (rs4646994)	4 (2)[103_106]	7 (4)[101_103,107,108§]
AGT	rs699	1 (1)[107]	2 (2)[107]
AGTR1	rs5186	2 (2)[107]	3 (3)[105,107,109]
BDKRB2	rs5223		3 (3)[107]
APOB	ApoB (Xbal)		1 (0)[47] AAA vs AAA+PAA
APOE	APO E3E3 and E3E4	1 (0)[113] AAA expansion	1 (1)[114] AAA expansion
	rs405509, rs429358, rs4420638, rs7412, rs8106922		1 (1)[114]
CETP	TaqIA RFLP	1 (0)[42]	
F2	FII G20210A		1 (1)[115]
F5	Factor V Leiden		1 (1)[115]
MTHFR	rs1801133	4 (0)[120_123]	6 (3)[115,118,123_126]
	rs1801131	1 (0)[126] male and non-smoker	2 (1)[125,126]
	rs2274976, rs48846049		1 (1)[125]
MTHFD1	rs8003379	1 (1)[125]	
	rs2357481, rs1076991, rs3783732, rs1950902, rs4902283, rs2236225		1 (1)[125]
MTR	rs2853523	1 (1)[125]	
	rs4659725, rs1805087, rs2275566, rs6676866		1 (1)[125]
MTRR	rs326118	1 (1)[125]	
	rs1801394, rs1532268, rs2303080, rs10064631, rs16879334, rs8659		1 (1)[125]
TYMS	rs16430	1 (1)[125]	
	rs502396		1 (1)[125]
ENOSF1	rs8423		1 (1)[125]
AHCY	rs819149,	1 (1)[125]	
	rs7271501		1 (1)[125]
FOLH1	rs202680	1 (0)[125] subgroup AAA diameter	1 (1)[125]
	rs202676		1 (1)[125]
BHMT	rs651852, rs567754, rs3733890, rs585800		1 (1)[125]
BHMT2	rs644191, rs682985		1 (1)[125]
CBS	8344 C>T, 1542 C>T, 3753 C>T, 3758 G>A, rs1051319		1 (1)[125]
NNMT	rs566775, rs10891639, rs4646335, rs3819100		1 (1)[125]

		Number of studies*	
Gene	**Polymorphisms**	**Associated**	**Not associated**
PON1	−108 C>T	1 (0)[126] only > 65 years and smoker	1 (0)[126]
	rs854560, rs662, rs3917594		1 (1)[125]
PON2	rs12026		1 (1)[125]
SLC19A1	rs3788205, rs3177999, rs1051266		1 (1)[125]
SHMT1	rs638416, rs1979277		1 (1)[125]
TCN2	rs5749131, rs1801198, rs10418		1 (1)[125]
NOS3	Intron 4 27–bp repeat (4a/4b)		2 (1)[135,141]
	894 G>T	2 (1)[135,136]	
	−786 T>C		1 (1)[135]
PTGS2	rs20417, rs4648307		1 (1)[146]
HP	Variant α-chains α1/α2	2 (0)[42,148] one study on AAA expansion	2 (0)[44,147] in 28 AAA families
Blood groups			
ABO	A		1 (0)[12] 117/59862
RHD/d	Rh-	1 (0)[12]	
KEL	positive	1 (0)[12]	
MNS	MNss	1 (0)[12]	

*Number in parenthesis indicates the number of studies with a sample size of at least 150 cases and 150 controls.

§Study with 1,000 cases and controls

If multiple sample sets were used in one publication, they were treated as independent studies. AAA, abdominal aortic aneurysm; PAA, popliteal artery aneurysm

Gene symbols available from the National Center for Biotechnology Information (NCBI; http://www.ncbi.nlm.nih.gov/) were used.

Table IV

Genes of the immune system

Gene	Polymorphisms	Number of studies*	
		Associated	Not associated
HLA	-A, -B		1 (0)[12]
	-DRB1*15	1 (0)[155]	
	-DQB1, -DRB1*0404		1 (0)[155]
	-DRB1*04, -DRB1*02	2 (0)[156,157]	
	-DQA*0120, -DQA1, -DRB1, -DRB1,3-5	1 (1)[162] in male Belgians	1 (1)[162] in male Canadians
	-DR2(15)	1 (0)[158]	
	-DQ3	1 (0)[159]	
	-DRB1*0401	1 (0)[160]	
	-DQA1*0102	1 (1)[218]	
	-A, -A2, -B, -B61, -DRB1*, -B1*1502	1 (0)[161]	
	-A1, -A3, -A11, -A24, -A26, -A30, -A31, -A33; -B7, -B13, -B62, -B75, -B71, -B35, -B37, -B38, -B39, -B60, -B40, -B44, -B47, -B46, -B48, -B51, -B52, -B54, -B55, -B56, -B58, -B59, -B67; -DRB1*0101, -1501, -1602, -0301, -0302, -0401, -0404, .0405, -0410, -0403, -0406, -0407, -1101, -1102, -1201, -1202, -1301, -1302, -1401, -1402, -1405, -1407, -1403, -1406, -0701, -0803, -0801, -0802, -0804, -0811, -0901, -1001		1 (0)[161]
	-A*11, -B*08, -B1*11		1 (1)[163]
CCR5	−308 (32 pair deletion)	1 (0)[170] in subgroups AAA vs PVD, AAA vs carotid stenosis, rAAA vs eAAA	2 (1)[170,171]
IL1A	−889 C>T, 4845 G>T		1 (0)[176]
IL1B	−511 C>T, −31 C>T		1 (0)[176]
	3953 C>T		2 (0)[176,177]
IL1RN	2018 C>T		1 (0)[176]
IL6	rs1800796	1 (1)[179] recessive model	1 (1)[179]
	rs1800795		3 (2)[177_179]
	rs1800797		1 (1)[179]
IL10	−1082 G>A	1 (0)[177]	1 (1)[182]
	−592 C>A		1 (0)[177]
PLA2G7	G994T	1 (0)[183]	
TNF	−308 G>A		1 (0)[177]
PPARG	rs1801282	1 (1)[187]	
	rs3856806		1 (1)[187]
CRP	rs3091244		1 (1)[193]
HMOX1	−258 to −195 GT length polymorphism	1 (0)[197]	

* Number in parenthesis indicates the number of studies with a sample size of at least 150 cases and 150 controls.

If multiple sample sets were used in one publication, they were treated as independent studies. AAA, abdominal aortic aneurysm; rAAA, ruptured AAA; eAAA, elective repair of AAA; PVD, peripheral vascular disease

Gene symbols available from the National Center for Biotechnology Information (NCBI; http://www.ncbi.nlm.nih.gov/) were used.

Table V

Genes of signaling pathways

Gene	Polymorphisms	Number of studies*	
		Associated	Not associated
TGFB1	Bsu361 RFLPs		1 (0)[56]
	−1347 G>A, 7440 A>C, 11089 G>A, 13077 A>G, 20743 G>A, 25782 C>T, 26718 G>A		3 (3)[199] AAA expansion
	−509 T>C		1 (1) [48]
TGFBR1	rs10819634		2 (2)[200]
	rs1571590	1 (1)[200]	1 (1)[200]
	rs1626340	1 (1)[200]	1 (1)[200]
	9A/6A		1 (1)[105]
TGFBR2	rs1078985		2 (2)[201]
	rs764522, rs3087465, rs13075948, rs9831477, rs1346907, rs9843143	1 (1)[200]	1 (1)[200]
	rs1036095, rs4522809	2 (2)[200]	
	rs304839		2 (2)[200]
TGFB3	−614 G>A	1 (1)[199] AAA expansion	2 (2)[199] AAA expansion
	715 T>G, 2469 T>C, 7602 T>C, 17368 A>G, 19456 A>T, 23653 G>A		3 (3)[199] AAA expansion
LTBP1	−256 G>C		3 (3)[199] AAA expansion
LTBP3	4598 A>G, 9048 T>C, 22537 G>A		3 (3)[199] AAA expansion
LTBP4	−4234 A>G, 10384 G>A, 21011 A>T, 25859 C>T, 32603 C>G	1 (1)[199] AAA expansion	2 (2)[199] AAA expansion
	1334C>G, 573 G>A, 20757 C>T		3 (3)[199] AAA expansion
ESR1	−397 T>C, −351 A>G		1 (0)[56]
ESR2	1730 A>G	1 (0)[56]	
PGR	TaqI RFLPs		1 (0)[56]

*Number in parenthesis indicates the number of studies with a sample size of at least 150 cases and 150 controls.

If multiple sample sets were used in one publication, they were treated as independent studies. AAA, abdominal aortic aneurysm

Gene symbols available from the National Center for Biotechnology Information (NCBI; http://www.ncbi.nlm.nih.gov/) were used.

Table VI

Family-based DNA linkage studies, genome-wide association studies (GWAS) and follow-up studies

		Number of studies*	
Locus	**Polymorphisms**	**Associated**	**Not associated**
19q13[17, 18]			
	608 SNPs		1 (1)[203]
	rs16968029, rs281407, rs1075453, rs6509496, rs1530878, rs285676, rs576556, rs4802552	1 (1)[203]	1 (1)[203]
9p21[208]			
	rs10116277, rs1333040, rs2383207	2 (2)[20]	
	rs7025486		2 (2)[20]
CDKN2BAS	rs10757278-G	5 (5)[208]	4 (4)[208,210]
CDKN2A	rs10811661-T		7 (7)[208]
HSPG2	rs2270701, rs3767137, rs7556412, rs7355045, rs2305562, rs12404444, rs2454290, rs11810496, rs2501255, rs6698486, rs4654773, rs12081298		1 (1)[211]
CSPG2	rs2652106	1 (1)[211]	1 (1)[211]
	rs28899, rs962066, rs11746859, rs33599, rs6452540, rs160380, rs13686, rs17348129, rs188703, rs2445874, rs647873, rs309596, rs309590, rs309587, rs12653308, rs17205986, rs160187, rs160280, rs309584, rs309578, rs11726		1 (1)[211]
3p12.3[19]			
	rs9876789, rs6549604, rs4076052	1 (1)[207]	
CNTN3	rs7635818 (upstream to CNTN3)	2 (2)[19]	3 (3)[20,207]
9p33[20]			
	rs7025486	4 (4)[20]	6 (6)[20]

*Number in parenthesis indicates the number of studies with a sample size of at least 150 cases and 150 controls.

If multiple sample sets were used in one publication, they were treated as independent studies.

Gene symbols available from the National Center for Biotechnology Information (NCBI; http://www.ncbi.nlm.nih.gov/) were used.