The Genetic Basis of Abdominal Aortic Aneurysms: A Review

R.M. Sandford,* M.J. Bown, N.J. London and R.D. Sayers

Vascular Surgery Group, Department of Cardiovascular Sciences, University of Leicester, UK

Introduction. The pathogenesis of abdominal aortic aneurysm (AAA) remains poorly understood, however significant evidence has emerged in recent years to suggest a chronic inflammatory process. Observational studies have highlighted a familial trend towards AAA development among relatives of affected individuals and it is thought that inflammatory genes may influence an individual’s susceptibility. Conflicting reports exist over single gene versus multiple gene inheritance patterns in addition to a collection of studies examining individual inflammatory genes. This paper reviews the evidence for a genetic predisposition to aneurysm formation including familial and segregation studies in addition to experimental evidence investigating specific candidate genes.

Method. Medline and Pubmed database searches were conducted using the search terms abdominal aortic aneurysm and gene. Papers were reviewed and references manually searched for further relevant publications which were added to the data. Papers were categorised under the headings familial, segregation and candidate gene studies.

Results. A review of 58 papers is presented under sub-headings as above. In the case of the candidate gene section, a brief report of the functional relevance of each gene is included.

Conclusion. A summary of the evidence presented is given and the direction of future work in this field is briefly considered.

Keywords: Abdominal aortic aneurysms; genes.
Clifton in 1977 first reported a possible genetic component of aneurysm disease when he described a family in whom three brothers were all affected by AAA.\textsuperscript{11} Since then many familial studies have been conducted in an attempt to establish a genetic link. Several authors have also attempted to characterize the mode of inheritance through segregation studies.

As the inflammatory process has been increasingly implicated in AAA development, several studies have begun to investigate specific inflammatory genes, often those which code for key proteins in the cytokine cascade. This ‘candidate gene’ approach may provide insight into individual susceptibility to AAA and also advance understanding of the processes involved.

**Methods**

A search was conducted of the Medline and Ovid Embase databases from 1966 to the present day using the search terms ‘abdominal aortic aneurysm’ and ‘gene’, and these search results were then combined. This resulted in 53 human publications limited to the English language, of which 25 were felt to be relevant (i.e. relating familial or genetic factors with AAA). These papers were categorized according to their subject and study design into familial, segregation or candidate gene studies. Relevant references were extracted and collected manually. Papers were then reviewed and summarized. The following review adheres to the subheadings under which the publications were collected.

**Familial Studies**

One of the earliest population based studies to examine the aetiology of AAA compared coronary heart disease, stroke and aortic aneurysm.\textsuperscript{12} This was a prospective study of mainly white races from over 1000 counties in the United States. There were approximately 500 000 females and 350 000 males who were between 40 and 79 years old who were included in the analysis. Subjects completed a questionnaire at enrolment, detailing significant co-morbidity and smoking status, and were then followed up for 6 years. Any deaths occurring during this period were classified by the cause of death given on the death certificate. During the study, 431 men and 88 women died from aneurysm related disease. The death rate from AAA was found to be higher in men who were hypertensive. This study found significant associations between increased weight, low levels of exercise and smoking, and the development of aortic aneurysm. Although these common risk factors with coronary heart disease are still thought to be significant today, Clifton’s report of familial aneurysm in 1977 then provoked a series of studies into a possible genetic cause for aneurysms.

In 1986, Johansen and Koepsell compared the family histories of 250 patients with AAA and 250 controls. They found that 19.2% of patients with an aortic aneurysm reported having a first degree relative with a history of AAA. Only 2.4% of controls reported a positive family history of AAA. They therefore calculated an estimated relative risk of developing AAA if a first degree relative has already been affected of 11.6.\textsuperscript{10} This represented a significant clustering of AAA in families. In 1989 Darling and Brewster conducted a study to determine if two distinct subtypes of aortic aneurysm may exist: familial and non-familial. This was a nine year prospective study of 542 consecutive patients undergoing abdominal aortic aneurysm repair. Eighty-two of these patients reported a positive family history of AAA in between two and five first degree relatives. Four hundred and sixty patients therefore reported no previous incidence of aortic aneurysm in their family. There were some initial differences observed between the familial and non-familial groups. Firstly, the non-familial group had a higher male preponderance of AAA than the familial group (86% vs 65% male). Secondly, the mean age of the non-familial group tended to be higher than that of the familial group (67.8 years vs 62.4 years) and this difference was significant among the male patients. The two groups were however comparable in terms of smoking status, and number of patients affected by either hypertension or diabetes. They also found no difference in aneurysm morphology, either in terms of anatomy or aortic wall composition, suggesting that although some aneurysms may be the result of an unknown genetic factor, the final pathological process is likely to be similar to that in sporadic aortic aneurysm.\textsuperscript{13}

A similar study conducted by Baird \textit{et al.} in 1995 utilized ultrasound scanning to screen relatives of both AAA patients and controls, in order to gain a more reliable estimate of family tendency to aneurysm development than relying solely on self reported incidence (which inevitably will miss some affected individuals). They recruited 126 unrelated patients consecutively admitted to hospital with AAA and 100 healthy controls undergoing cataract surgery. All of the controls, and 54 of the 427 siblings of aneurysm patients, underwent ultrasound scan, and this data was added to family history data obtained from interviews. They found that 4.4% of siblings of aneurysm patients had an aneurysm versus 1.1% of controls on the basis of family history alone. Following ultrasound scan, 19% of siblings of aneurysm patients...
were found to have AAA versus 8% of controls. The risk of aneurysm was shown to begin earlier and increase more rapidly for siblings of affected individuals compared with controls. Fitzgerald et al. agreed with this finding, demonstrating 22% of male siblings of AAA patients to have aneurysms on USS. The familial trend observed in the incidence of AAA particularly among male relatives has led to suggestions for targeted screening programmes for relatives of affected individuals.

Also in 1995, LaMorte et al. wrote the first report on racial differences in rates of AAA repair. They observed that atherosclerotic disease was more common in black than white Americans, but aortic aneurysm was more common in a white population. A multivariate analysis comparing atherosclerotic disease with a control group (undergoing appendicectomy) confirmed hypertension, age and smoking as significant risk factors for aneurysm disease, and reported a protective effect associated with diabetes. They found black people to be at less risk of aneurysm than white with an odds ratio of 0.29. They therefore concluded that this observation may suggest the influence of genetic factors.

Two further studies in 1999 and 2000 confirmed the increased incidence of AAA observed in first degree relatives of affected individuals, and quantified the odds ratios at 4.33 and 4.77 respectively.

Although these observational studies have identified a clear familial tendency for aortic aneurysm (see Table 1), most do not consider the effects of common familial factors such as socioeconomic status, dietary and lifestyle considerations. Further studies were therefore required to confirm and further investigate the genetic basis of AAA.

**Segregation Studies**

In view of the overwhelming evidence for a genetic link, several studies have attempted to characterize the pattern of inheritance of AAA. The earliest of these was Tilson and Seashore in 1984 who studied 50 families with clustering of AAA in 2 or more first degree relatives. Following segregation analysis, they concluded that if only one gene were responsible for aortic aneurysm, it is likely to be autosomal, however they could not exclude multigene mechanisms.

Following on from this, Majumder et al. 1991 performed a segregation analysis based on a population of patients with ruptured and surgically treated aneurysms. They found strong evidence to reject a sporadic model of aneurysm development and found the multifactorial effect to be minimal. A major gene locus was found to be likely and a recessive model was shown to best fit their data.

In contrast, Verloes in 1995 recruited 520 patients treated for AAA at a single centre and studied the 276 patients who had a positive family history of aneurysm. Although they also strongly rejected a sporadic model, and also found no better fit with a multifactorial model, a single dominant gene was felt to give the best explanation of their findings. In addition to this, they described an allele frequency of 1:250 for the morbid allele, with a sex-dependent penetrance which slowly increases with age to 0.3 in women and 0.4 in men over the age of 80 years. This would go some way to explaining the far greater incidence of aneurysms observed in men.

In 2003, Kuivaniemi et al. examined 233 families known to have at least 2 members affected by AAA from vascular centres in 7 different countries. They agreed with the Majumder study on the whole, reporting that the majority of their data fitted an autosomal recessive inheritance pattern. However, in approximately 25% of cases, an autosomal dominant pattern better explained their findings in agreement.

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>Number of Patients</th>
<th>Study Design</th>
<th>Ultrasound screening used?</th>
<th>Incidence of AAA among relatives (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1977</td>
<td>Clifton</td>
<td>3</td>
<td>Observational</td>
<td>No</td>
<td>3 brothers affected in same family 19.2%</td>
</tr>
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<td>Johansen et al.</td>
<td>250</td>
<td>Observational</td>
<td>No</td>
<td>15%</td>
</tr>
<tr>
<td>1989</td>
<td>Darling et al.</td>
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<td>Observational</td>
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<td>19%</td>
</tr>
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<td>Baird et al.</td>
<td>126</td>
<td>Case control</td>
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<td>11%</td>
</tr>
<tr>
<td>1999</td>
<td>Salo et al.</td>
<td>101</td>
<td>Case control</td>
<td>Yes</td>
<td>Odds ratio of 4.77 if relative affected</td>
</tr>
<tr>
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<td>Blanchard et al.</td>
<td>98</td>
<td>Case control</td>
<td>No</td>
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with the work of Verloes et al. They conclude that the lack of consistency in the mode of inheritance may be indicative of multifactorial disease.\textsuperscript{25}

In summary, there is overwhelming evidence of a genetic predisposition to development of AAA shown by clustering of aneurysms in families. Although no clear pattern of inheritance has yet emerged, it is generally agreed that an autosomal gene (or genes) is the most likely, although both dominant and recessive models may be feasible. Although studies have suggested a single gene may be responsible, others have suggested a multifactorial aetiology, and it is likely that the interplay between genetic predisposition and environmental factors such as smoking and hypertension are ultimately responsible for aneurysmal dilatation.

**Candidate Genes**

In order to further characterize the potential genetic component of AAA pathogenesis, several investigators have adopted a ‘candidate gene’ approach. This involves highlighting mechanisms involved in the inflammatory response and aneurysm formation, and studying the genes coding for key enzymes. Many of these genes have been shown to have polymorphic sites which may in part explain the genetic predisposition of some individuals, not just for aortic aneurysms, but for a whole range of chronic inflammatory conditions.

**Elastin and Elastases: MMP-2, -7, -9 & -12**

The degradation of medial elastin in the aortic wall appears to be an initiating step in the process of aneurysm formation. Matrix metalloproteinases (MMPs) digest both collagen and elastin, however MMP-2, -7, -9, and -12 are generally considered to be primarily elastases. Elevated levels of these MMPs have been shown to occur in aneurysmal aortic wall compared with normal aorta.\textsuperscript{26}

MMP-9, also referred to as gelatinase B, is both a type IV collagenase and elastase enzyme. A cytosine to thymidine substitution in position 1562 of the promoter region of the MMP-9 gene produces a 1.5 fold increase in promoter activity.\textsuperscript{27} It is therefore plausible that this polymorphism may be responsible for the upregulated MMP-9 activity seen in association with AAA.

Jones et al. compared 414 patients with AAA, 172 patients with peripheral vascular disease, and 203 healthy controls with respect to the C-1562T polymorphism. They found a greater proportion of T alleles amongst the aneurysm population than either of the other groups, and quantified the odds ratio of developing AAA with this allele to be 2.41 in comparison to the control group.\textsuperscript{27} However, other studies investigating the effect of MMP-9 have found no significant association between MMP-9 polymorphisms and AAA.\textsuperscript{28,29} It may be that the increased MMP-9 levels observed in the aneurysm wall are the result of increased local stimulus, rather than a genetic predisposition to MMP overproduction.

The MMP-12 gene has a polymorphic site in its promoter region involving a single nucleotide transition from Adenosine to Guanine in position -82. Human studies of this gene polymorphism were initially conducted in reference to aneurysmal coronary artery disease, however the allele frequencies did not differ significantly between the coronary aneurysm and control groups.\textsuperscript{30} Eriksson et al. later investigated the genotype-phenotype relationships of MMP-12 in addition to MMP-2, -3, and -9, and found no evidence that any specific MMP polymorphism had a clinically significant effect on aneurysm expansion,\textsuperscript{31} however experimental studies have suggested a clear role for MMP-12 in the development of aneurysms.\textsuperscript{32} Therefore, although MMP-12 is likely to be involved in aneurysm development, it is unlikely that the polymorphic locus is responsible for the upregulation seen.

There is a polymorphic site in the promoter region of the MMP-2 gene with a cytosine to thymidine transition at the -1306 locus. Although this has not been investigated with respect to aortic aneurysm disease, it has been shown to be significant in the development of coronary artery aneurysms, with patients affected by aneurysm tending to have a higher proportion of cytosine alleles than thymidine.\textsuperscript{30} This may be a potential area for further investigation.

**Collagen and Collagenases: MMP-1, -8 & -13**

Types I and III collagen are found in abundance in the aortic wall and provide structural integrity and strength. Defects in the collagen I gene are known to cause problems such as Osteogenesis Imperfecta but are not known to be associated with vascular defects.\textsuperscript{26} In contrast with collagen I, alterations in collagen III turnover are likely to be pivotal in the weakening of the aortic wall and aneurysmal dilatation.

Collagen III is secreted as a procollagen, and the aminoterminal propeptide (PIIINP) is then cleaved to produce the mature collagen molecule. The propeptide is detectable in the extracellular matrix following
cleavage, and if collagen turnover increases rapidly, large amounts of PIIINP are found. A study conducted in 1995 by Satta et al. found significantly higher levels of PIIINP in patients with AAA than those with aorto-occlusive disease, indicating increased collagen turnover. Anderson et al. also described an increased collagen I to collagen III ratio in a patient with multiple large vessel aneurysms. They associated this with a polymorphism of the collagen III gene resulting in an amino acid switch from leucine to phenylalanine, which was present in the patient, but absent in other asymptomatic family members or control subjects. This has not been further investigated by other authors.

Matrix metalloproteinases are largely responsible for the alterations in matrix turnover seen in AAA. Their activities are regulated at several levels: firstly the transcription and translation of inactive precursors (zymogens); secondly the post-translational activation of zymogens by proteolysis; and lastly by the interaction of mature MMPs with their tissue inhibitors (Tissue Inhibitors of MetalloProteinases, TIMPs). Higashikata et al. used real-time reverse transcriptase polymerase chain reaction (RT-PCR) to quantify gene expression and found MMP-1 and -3 to be elevated in aneurysmal compared with normal aorta. They also found the ratio of MMP-1 to TIMP-1 and -3 was significantly elevated, indicating increased tendency to matrix degradation with decreased regulation by the usual control mechanisms. These findings were previously reported by Tamarina et al. in 1997 when they described elevated levels of MMP-1 mRNA and an increased MMP-1 to TIMP-1 ratio. MMP-8 is a potent type I collagenase, which has also been shown to be upregulated in the aneurysm wall.

To date, there is no clear evidence that the upregulation of MMPs seen in association with AAA results from a genetic predisposition. Although polymorphic sites have been identified in the promoter regions of several MMPs, no particular polymorphism has been found with increased frequency in association with aneurysmal disease. Although experimental work with knockout mice has demonstrated a protective effect from complete lack of MMP-12, it is unlikely that any naturally occurring polymorphism would have such a dramatic effect on the gene function and consequent protection from AAA formation.

Tissue Inhibitors of MetalloProteinases

The balance between MMPs and their tissue inhibitors (TIMPs) determines the composition of the extracellular matrix. There are currently four TIMPs which have been characterized and named TIMP-1 to -4. TIMP-1 is a specific inhibitor of MMP-1 and -9.

Tilson et al. in 1993 conducted a study to determine whether the relative decrease in TIMP expression seen in aneurysmal aorta occurs as a result of decreased tissue expression or a primary genetic predisposition. They found a point polymorphism from cytosine to thymidine in the third position of codon 101, but demonstrated that the amino acid for which it coded was preserved. They also demonstrated normal fibroblast expression of TIMP mRNA in association with this polymorphism, and therefore concluded that there was no evidence to suggest that the TIMP-1 deficiency seen in aneurysmal aorta results from a primary gene deficiency.

More recently however, two studies have demonstrated a significant difference in the allele frequencies expressed in patients with AAA compared with control groups. Ogata et al. found an association between the TIMP-1 polymorphism and AAA in male patients without a family history of aneurysm, and Wang et al. found a significant difference between aneurysms and controls in the frequency of the TIMP-2 polymorphism, which occurs in the same position as in the TIMP-1 gene, and is also a neutral polymorphism with no effect on translation.

These single point polymorphisms do not affect the amino acid sequence of the TIMP protein and therefore are unlikely to be significant in AAA pathogenesis, however other polymorphisms also exist. Several novel single nucleotide polymorphisms of the TIMP-2 gene have been found including the -418 guanine to cytosine locus, the -177 cytosine to thymidine locus and the +34 cytosine to adenosine locus. Whilst these have not been investigated in relation to AAA, they have been found to be linked and possibly significant in relation to chronic obstructive pulmonary disease. It may be therefore, that although the single polymorphisms studied by Ogata and Wang are not in themselves responsible for the alteration in TIMP activity, they may be markers for another polymorphism which does affect translation.

Plaminogen Activator Inhibitor-1

Regulation of the MMP/TIMP system is partly controlled by the plasmin system. The inactive pro-enzyme of plasmin, plasminogen, is converted to its active form by plasminogen activators, either tissue type plasminogen activator (tPA) or urokinase plasminogen activator (uPA). Plasmin (the active enzyme) in turn activates MMPs. The actions of plasminogen
activators are regulated by plasminogen activator inhibitors (PAI-1 and -2).

There is a polymorphism of the PAI-1 gene in position -675 where the wild type gene has a 4G pattern, but a 5G insertion may also be seen. The 4G allele binds only an activator of transcription, whereas the 5G allele binds both an activator and a repressor, and is therefore associated with relatively reduced transcription of PAI-1. The frequency of the 5G allele has been shown to be greatest among patients with familial aneurysms at 53%, in comparison to 39% in a control population and 38% in patients with non-familial aneurysms.

The 5G allele has also been analysed in relation to aneurysm progression and patients homozygous for the 5G insertion were found to have faster aneurysm growth than those with a 4G allele.

It is likely therefore, that the plasmin system may be involved in progression of AAA and this makes it a potential target for the development of medical therapies to suppress aneurysm growth.

**Interleukins**

It is now generally accepted that AAA arises as a result of a chronic inflammatory process. Bown et al. therefore studied a range of inflammatory cytokine polymorphisms in relation to their prevalence in AAA. Although polymorphisms of the interleukin (IL)1β, IL-6, IL-10 and tumour necrosis factor alpha (TNFα) genes were studied, only the IL-10 polymorphism appeared in higher frequency among aneurysm patients than healthy controls. Interleukin-10 is an anti-inflammatory cytokine, and the -1082 polymorphism is associated with decreased IL-10 production, thus limiting the ability of the subject to regulate the inflammatory process which leads to AAA formation.

Several other studies have confirmed the findings of non-significant interleukin gene polymorphisms. Marculescu et al. compared 135 patients with aneurysms to 270 patients with coronary artery disease with respect to six known polymorphisms in the IL-1 gene. They found no significant differences in any of the polymorphisms between groups and therefore concluded no role for IL1 polymorphisms in the pathogenesis of AAA.

Similarly, Jones et al. assessed the role of the -174G to C substitution in polymorphic locus of the IL-6 gene. This is known to be a functionally significant polymorphism as lower IL-6 levels have been reported with the homozygous G genotype than when a C allele is present. The authors found no link between IL-6 genotype and aneurysm progression, however, the G allele did appear to be a predictor of cardiovascular mortality.

**Angiotensin Converting Enzyme**

The renin-angiotensin-aldosterone system plays a major role in the conservation of salt and water and as such is a useful therapeutic target for antihypertensive agents. The angiotensin converting enzyme (ACE) which converts angiotensin I into the active angiotensin II has been shown to be highly expressed in human aneurysmal aorta, and experimental studies have demonstrated that infusion of angiotensin II produces large aortic aneurysms. This evidence is suggestive that high local levels of angiotensin II may play a significant role in AAA development.

There is a polymorphic site in the ACE gene which consists of the presence or absence of a 287 base pair DNA fragment corresponding to an alanine repetitive sequence in the intron of the ACE gene. The polymorphism has been termed I for insertion of the fragment and D for its deletion. The alleles are co-dominant with an additive effect on plasma levels, so homozygotes for the deletion allele have the highest plasma levels of ACE and homozygotes for the insertion have the lowest. Fatini et al. compared the genotypes of 250 patients with AAA and 250 age and sex matched controls. They found an increased D allele frequency in the AAA group of 0.63 compared with 0.49 in the control group and this difference was found to be highly significant.

These findings were confirmed by Pola et al. They segregated the aneurysm group into those with hypertension and those without, in order to determine whether the ACE polymorphism was acting via an effect on blood pressure (which is already known to predispose to aneurysm formation). Interestingly, they found a high incidence of the DD genotype in normotensive patients with aneurysms (70%), but only 32% of hypertensive patients with co-existent AAA had this genotype. This does suggest that the polymorphism affects AAA development independently of any association with blood pressure.

In agreement with this finding, experimental studies have shown that whilst infusion of angiotensin II produces AAA, infusion of incremental doses of aldosterone produces no effect on aortic diameter. This is significant as it suggests that the increased ACE levels seen in the aneurysm wall may be stimulated by a different pathway to the physiological renin-angiotensin-aldosterone system.
As angiotensin converting enzyme inhibitors (ACEI) are already in routine clinical use in the treatment of hypertension and are generally well tolerated, studies into the effects of ACEI on aneurysms in patients with differing ACE genotypes would be interesting as this represents a potential therapeutic target for future medical treatment of small aneurysms.

**Methylene Tetra Hydro Folate Reductase**

Homocysteine is a non-protein amino acid which is involved in carbon metabolism and methylation reactions. High plasma levels are toxic to vascular tissues, and hyperhomocysteinaemia is known to be a risk factor for early onset vascular disease. Excessive homocysteine is re-methylated by methionine synthase and in this reaction, 5-methyltetrahydrofolate serves as a methyl donor. This compound is produced by methylenetetrahydrofolate reductase (MTHFR) and therefore a defect in this enzyme may lead to hyperhomocysteinaemia.

There is a polymorphism in the MTHFR gene at the 677 locus which involves substitution of a cytosine nucleotide for a thymidine. Strauss et al. demonstrated an elevated T allele frequency amongst patients with AAA compared to a control group (0.37 vs 0.21) with an odds ratio for AAA of 4.4 if a T allele was present. More recently, a large study of 428 patients with aneurysms failed to demonstrate an association between the C677T polymorphism and aneurysm formation, however they did demonstrate significantly larger aneurysms amongst patients who were homozygous for the T allele compared with those who had a C allele.

**Nitric Oxide Synthase**

Nitric oxide (NO) is responsible for most vasodilatation induced by the endothelium and a decrease in NO production may cause abnormal vascular function. NO is produced by endothelial NO synthase (eNOS), the gene coding for which is located on chromosome 7. A 27 base pair repeat is present in intron 4 of the eNOS gene and it is possible that this polymorphism may affect function of the enzyme. Kotani et al. studied an aneurysm and a control group, dividing the aneurysm group into surgical and non-surgical patients. They found that 10% of the control group had 4 repeats present compared to 14% of the aneurysm group. The remainder in each group had 5 repeats at the polymorphic site. When the aneurysm group was subdivided, 21% of the surgical patients were found to have 4 repeats in contrast to only 4% of the non-surgical group, and the authors conclude that the 4 repeat genotype may be associated with rapid progression of AAA.

Two further polymorphisms of the eNOS gene have been described: a T substitution to C at the -786 locus and a G substitution to T at the 894 locus. Although a significant association has been found between the G894T allele and AAA, no such link was demonstrated for the T786C allele.

**Human Leucocyte Antigens**

The Human Leukocyte Antigen (HLA) system is a recognition system which controls a variety of cell-cell interactions. Although not directly part of the inflammatory response, it determines T cell function, which is in turn central to chronic inflammatory processes. There are two arms to the HLA system: HLA class I which comprises HLA-A and -B molecules and is recognized by receptors on CD8 positive cells (suppressor T cells); and HLA class II (HLA-DR) which are recognized by receptors on CD4 positive T helper cells. Certain HLA subtypes have been associated with a number of chronic inflammatory conditions, and represent the genetic basis of a number of well known diseases such as diabetes and rheumatoid arthritis.
HLA alleles have been studied in relation to aortic aneurysm. Rasmussen et al. studies the HLA-DR B1 locus which has 12 associated alleles. They found B1*02 and B1*04 subtypes to be more common amongst the aneurysm group compared to a control group, and the B1*01, B1*08 and B1*14 alleles to be more frequent among the controls.62 These findings were confirmed by Monux et al. whose results did not reach statistical significance, but suggested HLA-DR B1*01 to be protective and HLA-DR B1*04 to predispose to AAA.63 Increased frequency of the HLA-DR2(15) allele has also been described amongst aneurysm patients compared with controls (58.7% vs 28%) in a Japanese population.64

Class I HLA antigens may also be significant, and a case control study found HLA-A2 to be present in 60.4% of patients with aneurysms but only 42.6% of controls (P = 0.036); and HLA-B61 to be present in 30.4% of patients with aneurysms but only 11.4% of controls (P = 0.002).65

Although the precise mechanism by which HLA genotype affects individual susceptibility is not yet fully understood and is likely to be a complex interplay between genetic predisposition and environmental exposure, it may be possible to identify an HLA allele, or combination of alleles, which function as a genetic marker for AAA.

**Inflammatory Receptors: CCR2 and CCR5**

Many inflammatory cytokines have cell signaling or chemotactic properties and attract inflammatory cells to the site of injury. This family of cytokines are often termed chemokines and share a common C-C structure. Many chemokines, such as monocyte chemoattractant protein 2 (MCP-2), macrophage inflammatory protein 1 alpha (MIP-1α) and beta (MIP-1β), and Regulated on Activation Normal T cell Expressed and Secreted protein (RANTES), effect their function through ligand binding with a C-C chemokine receptor.

Chemokine receptors have attracted much scientific interest in recent years as they function as a coreceptor for the Human ImmunoDeficiency Virus (HIV) into CD4 positive cells and anti-chemokine receptor therapies are being trialed in this context. As they are central to cell signaling and the inflammatory process, CCR (C-C chemokine receptors) have also been studied with respect to their potential role in chronic inflammatory conditions including AAA.

There are two chemokine receptors in particular, CCR2 and CCR5, which are structurally similar to one another and are known to have gene polymorphisms which affect protein translation.66 Studies of these polymorphisms in relation to HIV susceptibility have demonstrated a relative resistance amongst patients who are homozygous for the polymorphic alleles compared to those who have a wild type gene.67

CCR5 has a 32 base pair deletion (Δ32) polymorphism in the promoter region of the gene. This results in a frameshift and premature termination of the protein.68 The role of this polymorphism in susceptibility to AAA has been investigated, and a higher incidence of the Δ32 allele was observed among patients with aneurysms than patients with other vascular pathology (carotid stenosis and peripheral vascular disease) or healthy controls.69 Further understanding of the role of chemokine receptors in AAA may provide a potential target for modulation of the inflammatory response through the development of agents to block these receptors.

**Conclusion**

Although there is overwhelming evidence for a genetic predisposition to AAA formation demonstrated by both familial and segregation observational studies, no single gene has yet emerged as the key to understanding this relationship. Cytokine pathways are extremely complex, and the regulation of this system may underlie the development of AAA. Many of the cytokine genes contain polymorphic loci, and although significant associations have been found between certain gene polymorphisms and AAA, it is unlikely that any one single gene will emerge as a critical factor. It is likely that downregulation of any particular cytokine or pathway due to a genetic polymorphism will be counterbalanced by upregulation of a similar pathway to compensate. As such, it may be that a particular combination of polymorphisms predisposes to AAA formation, but any individual gene has a limited effect.

The role of hypertension, smoking and male sex must also be taken into consideration as the evidence supporting involvement of these risk factors is overwhelming. It is likely that the true mechanism underlying aneurysm formation will involve the interplay between a genetic predisposition and environmental risk factors such as these.

Understanding the genetic predisposition to AAA development will provide a greater understanding of the condition as a whole and may provide potential targets for therapeutic intervention to modulate the inflammatory response. Although the candidate gene approach has led to significant advances in
understanding the pathogenesis of AAA, it is unlikely that a single gene polymorphism will hold the key to aneurysm formation. Whole genome studies are likely to be required in order to fully understand the pathogenesis of abdominal aortic aneurysm.

References


