Valvular heart diseases are an important and growing public-health problem (1–4). Aortic valve diseases are frequently the consequence of congenital malformations or rheumatic fever (5). However, degenerative (senile) calcification of aortic valves, or calcific aortic valve disease, is increasing in prevalence and has become the most common indication for surgical valve replacement (6). Calcific aortic valve disease is characterized by pathological remodeling and calcification processes leading to varying degrees of morphologic changes of the aortic valve cusps, including irregular areas of increased thickening, distortion, rigidity, fibrosis, and the presence of cartilaginous or bone nodules. The disease has been divided into two functional categories, aortic valve sclerosis and aortic valve stenosis (AVS). This distinction is based on the obstruction of the left ventricular outflow track, which is absent in aortic valve sclerosis (morphologic changes of the valve without functional abnormality) and present in AVS (morphologic and functional valve abnormalities). Although this classification is useful in the clinical setting, it simply categorizes an early and more advanced stage of the same disease. Indeed, calcific aortic valve disease is recognized to be a slowly progressive disorder, with a disease continuum beginning with aortic valve sclerosis lesions sharing many similarities with early atherosclerotic plaques but which may subsequently progress toward severe calcification and valvular stenosis (7).

The prevalence of calcific aortic valve disease, with or without congenitally malformed valves, increases exponentially with age. In industrialized societies, aortic valve sclerosis is present in more than 25% of patients older than age 65 years (8), and is associated with a 50% increased risk of cardiovascular events (9). It is suspected that aortic valve sclerosis is a marker for a systemic atherosclerotic process. Moreover, it is generally assumed that aortic valve sclerosis represents an early stage of the disease process that may subsequently lead to the development of AVS. In fact, it is documented that over a short period of time (5 years) approximately 9% of individuals with an aortic valve sclerosis will progress to AVS (10). On the other hand, severe AVS is found in 2% to 5% of elderly subjects (8,11) and is associated with a poor prognosis, with a 80% 5-year risk of death, valve replacement, or progression to heart failure (12). Current management of these patients focuses on the development of symptoms to determine the timing of surgical valve replacement. Aortic valve stenosis has become the second most common indication for cardiac surgery (13). The American Heart Association Statistics Committee estimated that 99,000 valve proce-
dures were performed in the U.S. in 2004. The mean estimated cost for each surgery is nearly $120,000 (1). Accordingly, AVS is now considered to be a major societal and economic burden. With recent medical advances resulting in increased longevity, the prevalence of AVS is expected to rise significantly in the near future (14). Therefore, the health and socioeconomic burden associated with AVS is likely to increase substantially.

Many factors have been proposed to explain the cause of calcific aortic valve disease (Fig. 1). First, congenitally bicuspid aortic valve, present in 1% to 2% of the population, is a major factor contributing to AVS. During their lifetime, most individuals with congenital bicuspid valves develop aortic valve pathology, mostly AVS, whereas only 1% remain with a normal valve function (15). Subjects with a bicuspid valve develop AVS 1 or 2 decades earlier than those with a tricuspid valve. It is suspected that hemodynamic alterations induced by bicuspid aortic valves may accelerate the calcifying process. However, intrinsic biological abnormalities may coexist and contribute to early remodeling of valvuloarterial components in these patients. Whereas con-

**Figure 1** Pathogenesis of Calcific AVS

(A) Current understanding of factors leading to aortic valve stenosis (AVS). All of the genes reported to be associated with AVS in at least 1 published study are shown at the base of the triangle. The next layers show: 1) environmental and clinical factors; 2) metabolic and signaling pathways; and 3) cellular processes associated with AVS. Each layer affects subsequent layers and leads to the final manifestation of the disease. An extra level of complexity arises from the fact that all factors, both genetic and nongenetic, exist in a dynamic network that operates throughout the lifetime of an individual. (B) Two possible disease histories. The first individual (individual 1) carries a high genetic predisposition and develops AVS by the age of 65 years. In contrast, the second individual (individual 2) has a more favorable genetic makeup and develops AVS 2 decades later. (C) Drawing of an aortic valve illustrating the metabolic, signaling, and cellular processes involved in AVS. The potential interplay between cells, molecular mediators, and pathways is depicted in the blood compartment and in the subendothelial region. First, inflammatory cells and atherogenic lipoproteins infiltrate the endothelial layer. The extracellular lipids are subsequently taken up by macrophages to become foam cells. Activated T lymphocytes within the subendothelial region release cytokines, such as tumor necrosis factor-α (TNF-α), transforming growth factor-β1 (TGF-β1), and interleukin-1β (IL-1β). Interleukin-1β increases local production of matrix metalloproteins (MMPs), which contribute to extracellular matrix remodeling. Macrophages also express osteopontin (OPN), a bone-associated protein. The angiotensin-converting enzyme (ACE) that is colocalized with apolipoprotein B generates angiotensin II (AngII) from angiotensin I (AngI). Angiotensin II stimulates fibroblast expression of lipoprotein-retaining proteoglycan that trap lipids within the subendothelial compartment. The atherogenic milieu up-regulates the expression of bone morphogenic protein 2 (BMP2) and promotes osteogenic signaling pathways such as Runx2/Cbfal and Wnt/Lrp5/β-catenin pathways, which are involved in the differentiation of fibroblast/myofibroblast to an osteoblast phenotype. These modified cells then favor the development of calcium nodules and bone formation. Recently, it was shown that NOTCH1 inhibits osteoblast differentiation by repressing the Runx2/Cbfal pathway (67). BMI = body mass index.
genital abnormality and age are both irrefutable risk factors for AVS, other risk factors have been documented. In fact, epidemiologic studies have identified many clinical risk factors for AVS, including smoking, male gender, hyper-tension, hypercholesterolemia, elevated body mass index, and diabetes (8,16). In one study, serum creatinine and calcium concentrations were also correlated with the progression of AVS (17). More recently, the metabolic syndrome also has been associated with a higher prevalence of aortic valve sclerosis (18) and with faster disease progression and poorer clinical outcomes in patients with AVS (19). Finally, a genetic predisposition to AVS also was demonstrated (see subsequent text).

In this state-of-the-art review, we present a comprehensive overview of genetic studies conducted to elucidate the genetic architecture of AVS. Epidemiologic studies quantifying the genetic component of the disease are summarized. A compilation of candidate gene association studies is then provided. The findings derived from these studies are then incorporated into the current context of knowledge vis-à-vis the cellular processes and signaling pathways involved in AVS. Finally, recent developments in genomic research and technologies, which promise to accelerate the pace of discoveries in complex diseases such as AVS, are discussed.

**Molecular Understanding of AVS**

For many years, AVS has been regarded as a degenerative disease deriving from a “wear and tear” process (20). However, for the past decade molecular studies have laid some groundwork in defining the genes and molecular pathways involved in the pathological process. In this section, we describe how a disease previously known as a passive degenerative process is now convincingly demonstrated as a complex pathobiological disorder.

All molecular studies so far support the hypothesis that aortic valve calcification is an active cellular process involving multiple cell signaling pathways. In vitro experiments have clearly demonstrated that valve interstitial cells have the ability to form calcified nodules and to change their phenotype toward osteoblast-like cells when grown in appropriate conditions (21). Furthermore, histopathological features of human aortic valves removed at surgery or necropsy were the first to support the hypothesis that aortic valve stenosis is the result of an active inflammatory cellular process characterized by lipoprotein deposition and molecular mediators of calcification (22–27). Infiltration by inflammatory cells was observed in early degenerative valve lesions, including macrophages, T lymphocytes, and mast cells (28,29). In addition, these valves accumulate oxidized lipid and apolipoproteins (28,30). Aortic valve lesions also contain a number of proinflammatory cytokines, such as interleukin (IL)–1β (31) and tumor necrosis factor-α (32), as well as a number of matrix metalloproteinases (31–33) and neovascularization-promoting factors (34) believed to enhance tissue remodeling. Thus, an intricate process involving molecular and cellular responses that regulate extracellular matrix organization is involved in the pathogenesis of AVS (35). Taken together, these studies suggest a common cellular basis for the genesis of valvular and vascular diseases (36).

A number of studies have also suggested that the renin-angiotensin system is involved in aortic valve lesion pathogenesis (26,29). All major components of the renin-angiotensin system are found in valve lesions, including angiotensin-converting enzyme, angiotensin II, and angiotensin II type 1 receptor. This system is believed to promote lesion progression by stimulating cellular proliferation and proteoglycan synthesis by fibroblasts, which in turn stimulates the production of reactive oxygen species, including peroxynitrite, through the inducible nitric oxide synthase pathway (37). Recently, in a rodent model of AVS, Weiss et al. (38) reported that aging was associated with increased production of superoxide within calcified aortic valves. On the other hand, in hypercholesterolemic rabbits, expression of endothelial nitric oxide synthase is decreased (39), and the absence of this enzyme in mice causes abnormal congenital aortic valve development (40). Therefore, complex interactions regulating nitric oxide production are likely to play an active role in the pathogenesis of calcific aortic valve diseases.

Calcification and matrix remodeling is a defining feature of AVS (41). Moreover, bone and cartilage formation occur in 10% to 15% of explanted AVS valves. A growing body of evidence is now supporting that ectopic calcification is a cell-regulated process involving the transformation of valve fibroblast into osteoblast-like cells (21,22,27). Earlier molecular studies performed in human aortic valves demonstrated the up-regulation of molecular calcification markers, including osteocalcin, osteopontin, and Runx2 (27,42,43). Runx2, also known as Cbfa1, is a central transcriptional regulator of osteoblasts. Runx2/Cbfa1 is also up-regulated in mouse and rabbit models of valvular calcification (44,45). The importance of Runx2/Cbfa1 in calcification was demonstrated in knockout mice characterized by bones that do not calcify and remain cartilaginous (46). Runx2/Cbfa1 can be activated by the bone morphogenetic protein 2, which is present in human aortic valve lesions (47). The protein is activated by atherogenic factors, such as oxidized lipids, which are found in valvular lesions (30). Accordingly, lipid-derived products from oxidation present in valve lesions can promote calcification by activating the osteogenic Runx2/Cbfa1 pathway via BMP2 (23). Interestingly, BMP2 is also known to up-regulate the transcription factor Msx2, which is an activator of the Wnt signaling pathway. Recently, Rajamannan et al. (48) suggested that the Wnt/low-density lipoprotein receptor–related protein 5 (Lrp5)/β-catenin pathway may be involved in valvular calcification. Taken together, these results suggested that the activation of BMP2 by atherogenic factors found in valve lesions stimulate 2 osteogenic signaling pathways, namely the Runx2/Cbfa1 and the Wnt/Lrp5/β-catenin pathways.
These activated pathways subsequently promote osteoblastogenesis and the formation of extraosseous calcification.

Molecular studies conducted over the past decade provided evidence that supports the implication of active molecular and cellular processes in the pathogenesis of AVS. This includes specific cell signaling pathways regulating vascular calcification, inflammation, and remodeling as well as other biological processes such as subendothelial deposition and retention of atherogenic lipoproteins, activation of the renin-angiotensin system, and neovascularization. The implication of all these cellular, metabolic, and signaling pathways provides a strong impetus for the realization of future research to quantify the genetic contribution in the development and progression of AVS and to identify the causal or susceptibility variants.

**Genetics of AVS**

**Genetic epidemiology.** Most of the genetic epidemiologic studies performed on valvular diseases have focused on congenital valve defects. Bicuspid aortic valve, the most common congenital cardiovascular abnormality, was long considered to be a sporadic and isolated event. However, earlier studies described familial patterns compatible with genetic inheritance (49), along with a higher rate of occurrence in the first-degree relatives of affected patients (50). Subsequently, a larger study estimated the heritability coefficient at 89%, suggesting that the bicuspid aortic valve is almost entirely genetic in nature (51). Interestingly, a recent genome-wide linkage scan performed in 38 families identified 3 loci on chromosome 18q, 5q, and 13q which likely harbor genes responsible for bicuspid aortic valve (52). Strong inheritance was also observed for nonsyndromic left ventricular outflow tract obstruction, which consists in an anatomically varied set of defects including bicuspid aortic valve, coartation of the aorta, aortic valve stenosis, and hypoplastic left heart (53,54). Similarly, a population database from Utah, composed of large pedigrees, demonstrated that death resulting from aortic and mitral valve diseases clustered among relatives, suggesting a significant genetic effect for death caused by valvular diseases (55). Despite this clear genetic contribution, however, the mode of inheritance of valvular diseases is unclear and is most likely explained by the action of many genes. Nevertheless, these studies demonstrated that valvular diseases aggregate within families and clearly support the genetic hypothesis of AVS.

**Genetic association studies.** A small number of studies have tried to elucidate the genetic variants and genes associated with AVS (Table 1). These studies have provided some preliminary data suggesting the contribution of a few genes. The first of these reports was conducted on a genetic variant located in the vitamin D receptor gene, called BsmI (58). This study was performed in a case-control series of 100 patients with AVS (aortic valve area <1.0 cm² or mean aortic valve gradient >40 mm Hg) and 100 control subjects. This association was independent of age, gender, and coronary artery disease. Association analyses indicated that the B allele frequency was significantly higher in patients than in control subjects. A second study conducted in 802 patients undergoing transthoracic echocardiography identified 43 patients with AVS defined as an aortic valve area of ≤1.8 cm² and a mean aortic valve gradient of ≥10 mm Hg (59). A greater prevalence of APOE 2/4 and 3/4 genotypes was observed in patients with AVS compared with patients without AVS. This association was independent of age, gender, coronary artery disease, and low-density lipoprotein cholesterol. A third study investigated whether polymorphisms in the estrogen receptor (ER) α gene and in the transforming growth factor (TGF)-β1 gene were associated with aortic valvular sclerosis in a small case-control series of post-menopausal women (60). All case subjects underwent aortic valve replacement with an aortic valve area of <1.3 cm². Control subjects were matched for age and gender and were free from significant aortic sclerosis as determined by echocardiography. The PvuII polymorphism of the ERα gene was independently associated with an increased risk of
The combination of the PvuII and the AocI polymorphisms in the ERα and the TGFB-β1 genes, respectively, was also associated with aortic sclerosis. A fourth study found a higher prevalence of the apo B XbaI polymorphism and the apo E2 allele in nondiabetic patients with severe isolated AVS (aortic valve gradient >60 mm Hg) compared with a control group free of AVS as assessed by echocardiography and matched for age, gender, body mass index, hypertension, and lipid/lipoprotein levels (61). Finally, 3 promoter polymorphisms (−1082, −819, and −592) in the IL-10 gene were significantly associated with the degree of calcification measured by atomic absorption spectroscopy in 187 surgically excised stenotic aortic valves (62). In the same study, a 32-basepair deletion in the chemokine receptor 5 and a promoter polymorphism (−447) in the connective tissue growth factor genes were also shown to influence the degree of calcification.

Taken together, these studies suggest that individuals with a certain genetic background may be at higher risk of developing AVS. However, these studies suffer from major limitations and do not meet the current criteria for high-quality genetic association studies (63,64), although this was not necessarily obvious at the time of their publication. First, the number of patients in these studies is relatively small. The small sample sizes may reflect the complexity of collecting and phenotyping patients with AVS. Nevertheless, small sample sizes are more likely to give false-positive results (65). Accordingly, the role of the polymorphisms must be confirmed in larger studies before firm conclusions can be drawn. Another major limitation is the use of only 1 or a few polymorphisms in each gene. Lessons from the International HapMap Project (66) indicate the proper number of genetic variants that need to be genotyped to capture most of the genetic information within a gene. In most cases, many variants need to be genotyped to test a gene comprehensively. So far, all the gene association studies with AVS have been performed incompletely. It is also unclear whether genes associated with AVS act directly in the disease process or mediate their effect via other traditional risk factors. For instance, polymorphisms in the apolipoprotein genes may alter blood lipids that are known risk factors for AVS. To rectify this problem, large sample sizes of patients who are very well characterized at the clinical and environmental levels will be essential. Standards to determine the disease status are also urgently needed. None of the genetic studies described above used the same criteria to establish the disease status. Replication of positive genetic findings in different populations may be very difficult if patients are defined using different criteria.

**Discovering NOTCH1 as a causal gene for AVS.** Recently, a major breakthrough in the genetics of aortic valve disease was made when the Notch1 signaling pathway was identified (67). From a genome-wide scan of a 5-generation family suffering from aortic valve diseases (Figs. 2A and 2B), the authors identified linkage on chromosome 9q34–35. After reviewing genes in the region, they focused on the NOTCH1 gene. They then identified a specific mutation labelled R1108X, which causes a premature stop codon (Fig. 2C). All affected subjects had the mutant allele, which was not detected in unaffected family members or in 1,136 unrelated subjects of diverse ethnicity. The same authors also found a second mutation in the NOTCH1 gene segregating with aortic valve diseases in a smaller Hispanic family characterized by bicuspid aortic valve and aortic valve calcification (Figs. 2D and 2E). The mutation, labeled H1505del, causes a frameshift that alters 74 amino acids of
the protein before ending its formation prematurely (Fig. 2F). Recently, 2 novel likely pathogenic NOTCH1 mutations (p.T596M and p.P1797H) were reported in 2 sporadic cases of bicuspid aortic valve (68). The Notch pathway is known to be involved in embryonic patterning, and from these genetic studies it has been documented to be highly expressed within the developing aortic valve. Moreover, Notch1 has been identified as a repressor of Runx2, a critical regulator of osteoblast development. Thus, the discovery of the Notch pathway in aortic valve disease supports the concept that a developmental program might be reactivated in disease processes. Taken together, these results provide compelling evidence that functional deoxyribonucleic acid variants at the NOTCH1 locus result in human valve diseases. However, a very limited number of patients as well as deoxyribonucleic acid variants in the NOTCH1 gene have been studied. Whether genetic variants in that gene contribute to AVS in the population at large still remains to be determined. Nevertheless, this work demonstrates the utility of genetic research to identify new molecular targets.

**Global perspective of genetic research on AVS.** Collectively, molecular and genetic studies have clearly demonstrated that AVS is not merely the result of a passive process associated with aging but rather an active pathobiological disorder with several potential therapeutic targets. As previously emphasized, many factors are involved in the development of AVS. At the moment, convincing evidence supports the hypothesis that, in at least a subset of individuals, genetic predisposition co-exists along with environmental factors to create a biological substrate prone to early calcification of the aortic valve. In fact, genetic association studies performed with candidate genes and the identification of signaling pathways such as Runx2/Cbfa1, Wnt, nitric oxide, and Notch1 provide some landmarks for understanding the pathogenesis of AVS (Fig 1). However, further research will be required to understand the molecular basis of the disease.

Except for NOTCH1, all of the genes investigated so far were identified by a candidate gene strategy. In this approach, genes are selected according to their known functions. As a result of current concepts of AVS pathogenesis, geneticists have studied genes involved in calcification (VDR and CTGF), inflammation (IL-10 and CCR-5), and tissue remodeling (TGF-β1) as well as genes influencing lipids and lipoprotein metabolism (APOE, APOB, and ESR1). It is still too early to know whether a final common pathway will be identified from genetic research or whether it is a true polygenic disease. To elucidate this question, many more genes encoding components of pathological pathways leading to AVS remain to be tested. These include genes involved in subendothelial deposition and retention of atherogenic lipoproteins, chronic inflammation, the reinf-
angiotensin system, remodeling, fibrosis, and neovascularization as well as specific cell signaling pathways regulating nitric oxide and ectopic calcification. In addition, different genes may act at different stages of the disease. For example, it is expected that the genes involved in early lesion formation will be found to differ from those involved later in the calcification process. Obviously, a substantial amount of genetic research will be required to answer these critical questions. Recent developments in genomic research and technologies are particularly promising and may well accelerate the pace of discovery. Unfortunately, these tools have yet to be applied to AVS.

**Advances in Genomic Research and Applications in AVS**

Individualized medicine has been marked as one of the benefits of the Human Genome Project (69) and the ensuing International HapMap Project (66). Early genetic studies were impaired by our inability to comprehensively capture genetic variability. The bottleneck was our misunderstanding of human genetic variations and our incapacity to measure them. With the premise of the International HapMap project and the recent boost in technology developments, these limitations have been overcome to some extent. It is now possible to interrogate the entire human genome and capture most of the genetic information in 1 simple assay. The power of these new genomic approaches is in the ability to interrogate the genetic component of a particular disease without prior knowledge of the biological basis governing it. In the subsequent sections, we briefly describe these new tools. In particular, we show how they can be applied to improve our understanding of AVS, including the diagnosis, prevention, and treatment of patients.

**RNA profiling with microarrays.** Recent developments in genomic technologies have motivated many researchers to compile gene expression profiles in different tissue samples using microarray technology. This powerful technology serves 2 main purposes in the disease state: 1) gene discovery and; 2) molecular signature analysis. Substantial improvement and standardization have been achieved in gene expression research in the last few years. The arrays that are currently available can scan the expression levels of almost all genes in the human genome simultaneously, and they exhibit good intraplatform consistency and a high level of concordance in term of the genes identified as being differentially expressed (70). In addition, new bioinformatics tools are now available to visualize gene expression data in the context of biological pathways (71,72). Previous microarray studies showed that gene expression profiles differed considerably among patients at various temporal and spatial points of the disease. For example, heart failure profiles varied among patients of different age and gender (73). Similarly, different gene expression signatures were observed in transgenic mice at different stages of heart failure (74). Future application of this technology on a range of healthy to severely affected aortic valve tissues is likely to produce a comprehensive list of dysregulated genes and highlight the transcriptional profile leading to the disease.

Recent studies suggested that blood-cell–derived ribonucleic acid can be used as an alternative to direct sampling of tissue biopsies to find molecular signatures of internal diseases (75–79). It is likely that the calcification and the inflammatory processes involved in AVS are reflected in blood cells. The gene expression profiles of circulating cells can potentially provide an early warning of eventual threats. Blood-cell–derived ribonucleic acid offers many advantages for research and clinical applications. First, human blood is a noninvasive readily available source of clinical materials that can be collected in sufficient quantity. In contrast to valve tissues that are obtained from patients only after explantation, human blood can be collected at various time points and consequently has more direct clinical applications for disease management. In addition, the investigation of peripheral blood allows for gene profiling of larger samples. Accordingly, exploring deoxyribonucleic acid microarray gene expression in whole blood may potentially become a powerful tool for researching, diagnosing and treating human AVS.

**Genotyping technologies and genome-wide association studies.** The technology boost in genomic research can be truly appreciated in genotyping applications (80). Genotyping refers to the process of determining the genotype of an individual and is used to identify disease-associated genes. Many methodologies have been developed, using different chemistries and instrumentations. The majority of these methods genotype only a tiny fraction of the human genome. For example, genetic association studies conducted on AVS genotyped 1 to 3 single nucleotide polymorphism (SNPs) per gene (Table 1). This is a very limiting approach, given that millions of such variants exist in the human genome. At the time of writing (October 2007), the public SNP database known as dbSNP contained 11.9 million candidate human SNPs. According to the International HapMap project (66), a large fraction of these SNPs provide redundant information, which gives rise to the concept of linkage disequilibrium. The high level of linkage disequilibrium in the human genome is encouraging as far as genome-wide association studies are concerned. A maximally informative set of SNPs, or a scientifically selected subset of all SNPs, can be genotyped to capture nearly all common variations in the human genome. Previous estimates suggested that 300,000 to 500,000 SNPs are required to achieve this level of coverage (66). Although these numbers seem impressive, current technologies can afford a lot more. Different platforms now allow millions of SNPs to be assessed in a single assay. With this high-density coverage, these platforms can also identify copy number variations that are likely to be involved in complex diseases (81,82). Thus, unprecedented capabilities are currently available to interrogate the human genome. The power of such hypothesis-free study designs in
identifying the genetic factors of complex diseases is only just beginning to emerge for certain diseases, such as obesity (83), type 2 diabetes (84), and Crohn disease (85). However, intensive effort will be required, and resources will have to be consolidated, for a genome-wide association study on AVS.

Although promising, the cost of failure with genome-wide association scans is potentially huge for studies that are designed and executed with low statistical power and inadequate quality control (86). In addition, the approach is currently biased to detect common susceptibility variants rather than the entire allelic spectrum of human diseases (87). For example, susceptibility alleles with minor allele frequencies of <5% or with effect sizes of <1.2 odds ratio are not likely to be found unless they are tested in unrealistically large sample sizes. However, the major limitation of genome-wide association studies is the cost of phenotyping and genotyping thousands of individuals. The establishment of an international consortium is timely to share the enormous research resources required to conduct a well-powered genome-wide association screen on AVS. Consortia studies conducted with methodologic rigor are a practical approach to achieve sufficiently large sample size (88). With the anticipation of such an endeavor in AVS, potential participating centers must adopt a clear classification for case and control subjects that is based on standards and widely accepted criteria. Genome-wide association scan studies on AVS would certainly accelerate susceptibility locus discovery and are worth pursuing even if they are not expected to fully resolve the allelic architecture that underlies this multifactorial human disease.

Conclusions

A clear genetic component of AVS is anticipated. So far, only a handful of studies have attempted to unravel the genetic architecture of AVS. A small number of candidate genes, such as VDR, APOE, APOB, IL10, and ESP1, have been identified but need to be confirmed in larger samples. Genetic research has also identified defects in the Notch1 signaling pathway causing aortic valve diseases in a restricted number of families. Basically, all genetic/genomic work on AVS is still at the embryonic stage. A major factor limiting the progression of the field is the lack of large and well-defined case-control series of patients with AVS. Resources must be allocated to build these cohorts, because the bottleneck in genomic research has shifted from an incapacity to measure genetic variations to an inability to evaluate them in appropriate cohorts. In fact, with technologic progress in genomic research, we are now able to comprehensively interrogate the human genome and review the pathogenesis of AVS using powerful tools. These tools can confirm suspected targets and identify unsuspected targets. These new targets improve our understanding of the disease etiology and can be translated into many patient benefits. In fact, drug targets can lead to the development of new drugs that, in the longer term, have the potential to produce new therapeutic options. For patients, identification of causal genes means that new clinical counselling guidelines, including prevention strategies and better diagnosis in families at greater risk, can be built.

Echocardiographic and clinical variables are not sufficient to accurately predict the hemodynamic progression rate of the stenosis. Therefore, the important interindividual variation in AVS progression rate remains largely unexplained. In this context, genomic research also has the potential to discover genetic variants or biomarkers that would help the clinician to identify AVS patients who are likely to have rapid hemodynamic progression versus slow or no progression.

Further insights into the genetic factors associated with AVS may also allow us to custom-tailor future medical treatments. Ultimately, finding the causal genes will represent a major step forward in disease prevention and treatment. However, to achieve its promise, genomic research will require large well designed studies that incorporate high-throughput genomic data and carefully collected phenotypes.

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