ORIGINAL ARTICLE

Cardiac Imaging of Aortic Valve Area From 34,287 UK Biobank Participants Reveals Novel Genetic Associations and Shared Genetic Comorbidity With Multiple Disease Phenotypes

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BACKGROUND: The aortic valve is an important determinant of cardiovascular physiology and anatomic location of common human diseases.

METHODS: From a sample of 34,287 white British ancestry participants, we estimated functional aortic valve area by planimetry from prospectively obtained cardiac magnetic resonance imaging sequences of the aortic valve. Aortic valve area measurements were submitted to genome-wide association testing, followed by polygenic risk scoring and phenome-wide screening, to identify genetic comorbidities.

RESULTS: A genome-wide association study of aortic valve area in these UK Biobank participants showed 3 significant associations, indexed by rs71190365 (chr13:50764607, DLEU1, \( P = 1.8 \times 10^{-9} \)), rs35991305 (chr12:94191968, CRADD, \( P = 3.4 \times 10^{-8} \)), and chr17:45013271:C:T (GOSR2, \( P = 5.6 \times 10^{-8} \)). Replication on an independent set of 8,145 unrelated European ancestry participants showed consistent effect sizes in all 3 loci, although rs35991305 did not meet nominal significance. We constructed a polygenic risk score for aortic valve area, which in a separate cohort of 311,728 individuals without imaging demonstrated that smaller aortic valve area is predictive of increased risk for aortic valve disease (odds ratio, 1.14; \( P = 2.3 \times 10^{-6} \)). After excluding subjects with a medical diagnosis of aortic valve stenosis (remaining n=308,683 individuals), phenome-wide association of \( >10,000 \) traits showed multiple links between the polygenic score for aortic valve disease and key health-related comorbidities involving the cardiovascular system and autoimmune disease. Genetic correlation analysis supports a shared genetic etiology with between aortic valve area and birth weight along with other cardiovascular conditions.

CONCLUSIONS: These results illustrate the use of automated phenotyping of cardiac imaging data from the general population to investigate the genetic etiology of aortic valve disease, perform clinical prediction, and uncover new clinical and genetic correlates of cardiac anatomy.

Key Words: aortic valve • birth weight • humans • molecular epidemiology • odds ratio

The geometry of the aortic valve underlies cardiac structure and function relationships, including fluid dynamics, response to stress, and valvular pathology. Aortic valve stenosis (AS) is a common cardiovascular condition characterized by narrowing of the functional orifice of the aortic valve with an ensuing obstruction to
ejection of blood from the left ventricle and increased wall stress. In adult cohorts, AS is the most frequent valvular disease,² with prevalence estimates around 0.3% to 0.5% in the general population and markedly higher estimates in older individuals (up to 7% in >65-year-old subjects).³ As the natural history of adult-onset AS involves a relatively asymptomatic course followed by declining health after symptoms appear,⁴–⁷ there is a strong therapeutic potential for early detection of disease.⁸

A complex heritability pattern for AS involving multiple genes has been suggested,⁹ and larger genome-wide association studies (GWAS) have linked novel genomic loci to disease risk.¹⁰–¹⁵ However additional molecular genetic mechanisms of AS remain to be discovered. The advent of large population-based datasets that combine genetic data with cardiac imaging data such as the UK Biobank¹³ offers unprecedented opportunities to investigate heritable factors underlying AS pathogenesis to ultimately propose tools for the early identification of at-risk individuals.

While diagnosis of AS may be derived from a combination of findings from physical exam, auscultation, echocardiography, or functional data obtained during cardiac catheterization or surgery, recent findings support the clinical utility of software-based methods for magnetic resonance imaging (MRI) analysis.¹⁴ Novel MRI-based techniques to automatically distinguish between bicuspid and normal (tricuspid) aortic valve have potential to translate into clinical applications and to facilitate biomarker development.¹⁵–¹⁷ However, clinical utility of software-based methods for magnetic resonance imaging (MRI) analysis.¹⁴

### RESULTS

### Participants and Aortic Valve Measurements

MRI-derived planimetric measurements of the aortic valve area (Figure 1) were obtained for a discovery set of 26,142 white British ancestry participants (51.5% women; mean [SD] age, 55.06 [7.4] years; mean [SD] aortic valve area, 435.8 [134.5] mm²) with genotyping data available through the UK Biobank. In addition, a replication set of 8,145 European ancestry participants was included (53% women; mean [SD] age, 54.69 [7.5] years; mean [SD] aortic valve area, 433 [135] mm²; Methods in the Data Supplement). The Table summarizes demographic and aortic valve features for the study cohorts. As displayed in Figure 1, the estimated aortic valve area indexed to body surface area was calculated at 2.28 cm²/m², concordant with aortic valve area measured directly at autopsy in a population of 4803 adults.¹⁸

### GWAS of Aortic Valve Area

Aortic valve measurements were submitted to genome-wide association testing (GWAS) for over 4.1 million markers using standard linear regression. A GWAS of aortic valve area within the MRI cohort (n=26,142) revealed 2 genome-wide significant associations (Figure 2); summary statistics did not show evidence of inflation (genomic inflation factor [λ], 1.02). The 2 observed associations were an intronic variant at the DLEU1 gene (chr13:50753830-50792591, lead variant: rs71190365 [chr13:50764607_C_CT]; minor allele frequency, 40%; \( β = -5.87; \) SE=1.06; \( P = 5.6 \times 10^{-8} \)) and a variant located on an intron of the CRADD gene (chr12:94184082-94201279, lead variant: rs35991305 [chr12:94191968_T_TG]; minor allele frequency, 40%; \( β = -5.87; \) SE=1.06; \( P = 3.4 \times 10^{-8} \)). Similar effect sizes and directions were observed in the replication cohort, although the variant on chromosome 12 did not meet nominal significance (Table V in the Data Supplement). Effect sizes and \( P \) for the top markers in all 3 loci were consistent when repeating the analysis with models adjusting for 2 genetic principal components.
and participants’ age (in addition to sex and body surface area; Table VI in the Data Supplement). In addition, exclusion of 86 images identified as bicuspid aortic valves by the weak supervision approach of Fries et al17 did not lead to substantial changes in the effect sizes or statistical significance of the results (models excluding bicuspid aortic valves and controlling for sex, age, body surface area, and 2 genetic principal components: chr13:50764607_C_CT: $\beta$=6.69, SE=1.13, $P$=3.4×10−9; chr12:94191968_T_TG: $\beta$=−6.38, SE=1.05, $P$=1.1×10−4; chr17:45013271_T_C: $\beta$=7.74, SE=1.42, $P$=4.9×10−8).

Interestingly, 2 of the 3 variants reported by Helgadottir et al11 as associated with higher risk of aortic stenosis also showed statistically significant associations with reduced aortic valve area (rs1830321: $\beta$=−3.88, SE=1.05, $P$=2.2×10−4; rs10455872: $\beta$=7.29, SE=1.88, $P$=1×10−6; Table IV in the Data Supplement). Similarly, the LPA variant rs10455872 displayed an association with reduced aortic valve area, consistent with the expectation from previous literature19 (rs10455872: $\beta$=−7.29, SE=1.88, $P$=1×10−6).

Additional insights on putative candidate genes and functional annotation and mapping were obtained through the FUMA platform.20 First, set-based analysis of 19148 protein-coding genes on the genome-wide aortic valve area results performed through MAGMA21 showed 7 genes significant at $P$=0.05/19148=2.611×10−6, in the following order: CRADD (chr12:94071151-94288616; Z=6.09, $P$=5.6×10−10), DLEU1 (chr13:50656307-51297372; Z=5.49, $P$=2×10−9), BRAP (chr12:112079950-112123790: Z=4.85, $P$=6.02×10−7), IQCH1 (chr15:67547138-67794598: Z=4.7628, $P$=9.55×10−7), GOSR2 (chr17:45000483-45105003: Z=4.7099, $P$=1.2394×10−6), RP11-162P23.2 (chr12:112191694-112229222: Z=4.6684, $P$=1.5175×10−6), and FER (chr5:10803523-108532542: Z=4.6156, $P$=1.96×10−6; Figure I in the Data Supplement). In addition, data from expression quantitative trait loci suggested that the genome-wide significant locus on chromosome 12 may impact the expression of MRPL42 and SOCS2, whereas the significant region on chromosome 13 might involve 6 genes (DLEU1, DLEU7, EBPL, KCNRG, RCBTB1, and TRIM13).

Aortic Valve Area PGS and PheWAS

From the summary statistics of the aortic valve area GWAS, we then created a PGS for aortic valve area for all European ancestry subjects as the weighted sum of alleles associated with aortic valve area. The score was then validated in a separate set of 8151 UK Biobank

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**Aortic Valve Area Measurement from Magnetic Resonance Imaging (MRI) Sequence Data.**

**A**, MRI frames for raw anatomical images (CINE) and magnitude (MAG) series in an oblique coronal plane of the thorax centered upon an en face view of the aortic valve at sinotubular junction (red boxes). **B**, Distribution of aortic valve area measurements in men and women. Estimated aortic valve area indexed to body surface area is calculated at 2.28 cm²/m², which is concordant with aortic valve area measured directly at autopsy in a population of 4803 adults.18

**Table. Demographic and Aortic Valve Features for the Study Cohorts**

|                | Age, y | BSA | Aortic valve size, mm² | Sample size, n |
|----------------|--------|-----|------------------------|----------------|
|                | Mean (SD) | Range | Mean (SD) | Range | Mean (SD) | Range | Women/men |
| Discovery set  | 55.06 (7.04) | 40–70 | 1.47 (0.09) | 1.16–1.87 | 435.8 (134.5) | 122–1085 | 13463/12679 |
| Replication set| 54.69 (7.5) | 40–70 | 1.46 (0.09) | 1.18–1.83 | 433 (135) | 122–1049 | 4317/3828 |

BSA indicates body surface area.
participants with cardiac MRI who did not contribute to the original variant effect estimate for the PGS (see Methods). Furthermore, among the UK Biobank participants of European ancestry who did not have MRI data (n=308 683), we identified 1406 participants with aortic valve disease as defined by inpatient diagnosis codes.22 For each SD decrease in the PGS for aortic valve area, there was a strong and statistically increased risk for clinically defined aortic valve disease ($\beta=0.12; SE=0.03; P=8.5\times10^{-6};$ area under the curve, 0.7486; and $R^2=0.006$). Consistently, survival analysis showed that individuals with the lowest PGSs for aortic valve area (smallest valve area) displayed the largest incidence AS or procedure over time (hazard ratio, 1.14 per SD PGS; $P=0.002$ in a model adjusted for sex, smoking, and hypertension; Figure 4).

To better understand the clinical correlates and predictors of aortic valve area, we conducted a PheWAS relating the genome-wide PGS with 2976 phecodes and phenotypes from the Global Biobank Engine, applied to the subset of healthy controls without MRI images (n=308 683 individuals). As displayed in Figure 5, a higher PGS for aortic valve area was related to a lower risk for multiple types of diseases: digestive (eg, celiac disease), metabolic and endocrine (eg, diabetes and hypothyroidism), circulatory (eg, angina pectoris and ischemic heart disease), and respiratory (eg, bronchitis). It also showed the inverse association (risk increasing) for foot deformities and disorders of iron metabolism. PheWAS results for the 2 lead markers on chromosomes 12 and 13 are included in Figure II in the Data Supplement and Tables I and II in the Data Supplement.

Finally, we performed genome-wide correlation analysis of aortic valve area with 597 UK Biobank GWAS results along with 258 independent studies using the LDHub tool. Figure III in the Data Supplement shows significant correlations at a false discovery rate of $P=0.05$ separately for published research studies (non-UK Biobank) and UK Biobank GWAS results (http://www.nealelab.is/uk-biobank, which is complicated by phenotypic and sample overlap between the laboratory GWAS traits and comorbidities in subjects from the current MRI study). After correction for multiple testing, the correlation with UK Biobank summary statistics indicated that alleles associated with larger aortic valve area show a positive correlation with birth weight and a number of functional measures including pulmonary function (forced vital capacity, forced exploratory volume in 1 second), hand grip strength, and walking pace similar to the results from the PheWAS. The same alleles displayed a negative correlation (apparent protective effect) with a personal and family history of diabetes and heart disease, visual problems, and anthropometric measures linked to cardiometabolic disease (fat percentage, waist circumference, and body mass index). Among the independent 258 genetic correlation coefficients, alleles
Figure 3. Locus zoom plots for 2 genome-wide significant loci identified through the aortic valve area genome-wide association studies.

On each subplot, there is only 1 lead SNP per locus, hence overlapping with each top lead SNP. Markers with linkage disequilibrium (LD) $r^2$ below 0.1 are shown in gray. Detailed gene mapping information can be found in Table III in the Data Supplement. SNP indicates single nucleotide polymorphism.
related to larger aortic valve area overlap with the genetic determinants of birth weight.\textsuperscript{27,28}

**DISCUSSION**

In this work, computationally derived MRI measures of aortic valve area were screened to find genetic associations among European ancestry subjects from the UK Biobank. Through GWAS of common variants, 2 loci were identified: a signal indexed by an intronic \textit{DLEU1} variant (rs71190365, chr13:50764607, \(P=1.8\times10^{-9}\)) and a second region led by a marker intronic within the \textit{CRADD} gene (rs35991305, chr12:94191968, \(P=3.4\times10^{-8}\)). A lower PGS for aortic valve area was predictive of clinically defined aortic valve disease in the set of UK Biobank subjects without an MRI scan available (1406 and 308,683 subjects with and without a history of aortic valve disease, respectively). Finally, in individuals without a diagnosis of aortic valve disease (n=308,683), PheWAS results suggested links between genetic markers related to aortic valve area and cardiovascular complications.

Supporting our computational approach to measurement of aortic valve area, the 2 novel loci identified through GWAS findings have been described previously in the literature. The identified region on chromosome 12 displays an intronic variant in the \textit{CRADD} gene as a top marker. Variation mapping to \textit{CRADD} in a Black cohort has been previously been related to coronary artery calcification,\textsuperscript{29} a phenotype strongly linked to calcific aortic valve disease and aortic stenosis,\textsuperscript{30} and a recent analysis of the UK Biobank also shows an association between rs58899389 (chr12:94199513; \textit{CRADD} gene) and ascending thoracic aorta.\textsuperscript{31} The PheWAS data for rs71190365 indicate a link to known cardiac comorbidities such as forced expiratory volume and body mass, which may represent a pleiotropic effect—decreased area of the aortic valve is a determinant of cardiac output, which governs cardiac output and exercise capacity.\textsuperscript{32} Functional expression quantitative trait loci information indicates that this GWAS signal may involve \textit{SOCS2} as a causal gene, which has been implicated in early body growth processes.\textsuperscript{33,34} In this regard, PheWAS results (Figure II in the Data Supplement) also suggest a role for the lead single nucleotide polymorphism (SNP) in body mass and height. The second locus retrieved from the GWAS is indexed by an intronic SNP on \textit{DLEU1}, which has been linked to echocardiographic measures of aortic root diameter.\textsuperscript{35}

Importantly, the PGS derived from genome-wide alleles related to aortic valve area was associated with a clinical history of aortic valve disease, suggesting that the genetic signals from population-based cardiac MRI measurements may predict risks for health and disease. The initial course of disease in aortic stenosis is often clinically silent,\textsuperscript{36} and a PGS may represent an opportunity for screening and identification of patients with early-stage disease. Adverse changes in hemodynamics result from progressive narrowing of the aortic valve in.

**Figure 4. Survival analysis of polygenic scores for aortic valve area and aortic valve stenosis.**

For visualization, all participants were divided by polygenic score. In a competing-risks survival model, 1 SD lower polygenic score (corresponding to a smaller valve area) was associated with a 1.14 increased hazard ratio ([95% CI, 1.05–1.24] \(P=0.002\)) for accruing a diagnosis or procedure specific to aortic valve stenosis independent of smoking status, hypertension, or genetic sex. Median follow-up time was 29 y, and proportional hazards assumption was met. AoV indicates aortic valve.
Non albumin protein

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Aortic valve disease may also accompany component

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other clinically relevant phenotypes identified here.

The predictive characteristics for aortic valve disease and

of this PGS in other large cohorts is needed to confirm

traits or clinically correlated epiphenomena. Validation

some aspect of shared genetic architecture between 2

ever, causal relationships with aortic valve area are not

sequences of end-stage disease.37,38

asymptomatic patients, and early detection could offer

an opportunity to improve risk stratification for catheter

or surgical intervention to prevent or postpone the con-

sequences of end-stage disease.37,38

Exploring this score via a PheWAS, the same PGS

estimates were linked to higher risk for several other conditions (notably, multiple sclerosis) and lower risk for celiac disease, angina, and cardiovascular conditions (Figure 5; Figure IV in the Data Supplement). Aortic valve dysfunction is a common feature of Turner syndrome along with autoimmune celiac disease,47,48 while aortic valve disease may also accompany component autoimmune phenotypes of multiple sclerosis.41,42 However, causal relationships with aortic valve area are not revealed by these analyses; the observed associations between a PGS and a second phenotype may represent some aspect of shared genetic architecture between 2 traits or clinically correlated epiphenomena. Validation of this PGS in other large cohorts is needed to confirm the predictive characteristics for aortic valve disease and other clinically relevant phenotypes identified here.

The findings from the PheWAS are supported by the genetic correlation analyses from the UK Biobank studies; although not passing a strict multiple testing correction, they are internally consistent with the 258 independent-trait analyses. Aortic valve area alleles also display a negative enrichment (apparent protective effect) for coronary artery disease (rg=−0.211, \( z=−3.0126, P=0.002630 \)) and type 2 diabetes (rg=−0.2347, \( z=−2.2619, P=0.023743 \)) and a positive correlation with forced vital capacity (rg=0.1972, \( z=2.5913, P=0.009616 \); and rg=0.2481, \( z=2.2151, P=0.026843 \)). These findings are also likely to represent pleiotropy—lung function and aortic valve area are tightly linked to body size, while aortic valve flow is a functional determinant of blood flow in the coronary arteries.47

Some limitations of this study deserve mention. First, since the UK Biobank is not a hospital-based sample, the range of aortic valve areas may be narrower than what is observed in clinical datasets, and it is certain that selection and survivorship biases have influenced the GWAS results.48 While the aortic valve measurements were

Figure 5. Phenome-wide association results for the aortic valve area polygenic score using International Classification of Diseases, Tenth Revision, codes mapped to phecodes.

Additional results from the Global Biobank Engine44 are included in Figure IV in the Data Supplement. Phenotypes are colored by category (shown on the horizontal axis), and each triangle points up or down depending on the direction of effects (positive or negative associations). BMI indicates body mass index; BP, blood pressure; conc, concentration; DXA, dual-energy x-ray absorptiometry; eGFR, estimated glomerular filtration rate; FEV, forced expiratory volume; FVC, forced vital capacity; HbA1C, glycated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; med, medication; MRI, magnetic resonance imaging; NS, non-syndromic; PEF, peak expiratory flow; PHEWAS PRS AoV, phewas using polygenic scores of aortic valve size; RBC, red blood cell; SHBG, sex hormone-binding globulin; and UKBB, UK Biobank.
almost entirely automated, systematic errors related to the underlying computational approach may introduce inaccuracies. However, the fact that the findings are biologically relevant likely reflects that true genetic effects were present in the observed signals. Also, although the main genetic associations are robust to adjustments for sex, age, body surface area, and genetic principal components, BMI might have partly contributed to the observed effects.

Overall, the outcomes suggest novel candidate loci as determinants of aortic valve area in the general population and indicate a shared genetic architecture with different traits across the health-disease spectrum. Leveraging imaging and diagnostic information from large-scale public records offers an unprecedented opportunity to study the genetic architecture of variability in cardiac morphology and its link to aortic valve disease.

ARTICLE INFORMATION
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