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Genetic analysis of cardiac dynamic flow volumes identifies loci mapping aortic root size

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An open-source automated algorithm called DeepFlow enables large-scale derivation of aortic flow measurements, and genetic analysis of aortic flow, structural and functional traits demonstrates a causal relationship between aortic size and aortic valve regurgitation.

Nearly 10 years ago, the UK Biobank imaging study began, with the aim of capturing magnetic resonance imaging (MRI) data from the heart, brain and abdomen from up to 100,000 individuals, including repeat imaging of 60,000 of them[1]. With over 70,000 participants now scanned, the resource is providing geneticists with unprecedented opportunities for large-scale studies of well-recognized clinical cardiac phenotypes (for example, left ventricular mass and left ventricular ejection fraction) and for developing algorithms for new phenotypes at scale. In this issue of *Nature Genetics*, Gomes et al.[2] derive cardiac dynamic flow and volume measures using DeepFlow, a deep learning system they developed, to perform genome-wide association studies (GWAS) in 37,653 individuals for 17 cardiovascular traits and demonstrate, using Mendelian randomization, a causal relationship between aortic root size and aortic regurgitation.

The authors crafted an automated software solution (DeepFlow) to extract aortic flow measurements, and performed left ventricular volumetric quantification using a previously published algorithm[3]. At the heart of DeepFlow is a U-Net-based segmentation architecture, finely tuned through training on 150 randomly selected participants from the UK Biobank, corresponding to 4,500 frames of aortic cine images. The authors conducted out-of-sample testing on 15 participants, totaling 300 cine images. The comparative analysis explored alternative networks such as the feature pyramid network (FPN) and the mask-region-based convolutional neural network (Mask-R-CNN), showing no discernible advantage for these over the simple U-Net architecture. DeepFlow segmentation, combined with the algorithm developed by Bai et al.[3], yielded several left-sided volumetric and flow traits encompassing total left ventricular stroke volume (LVSV), forward LVSV, net LVSV, aortic valve regurgitant volume, aortic valve regurgitant fraction and mitral valve regurgitation volume (estimated using a standard method by subtracting the forward LVSV from the total LVSV). Though the task that DeepFlow performs is arguably simple (that is, segmentation of a circular structure with slight anatomic variation), the results underscored the suitability of U-Nets for biomedical image segmentation.

The training dataset comprised phase-contrast cardiac magnetic resonance (CMR) studies obtained from a single scanner type (1.5-T Siemens scanner) within the UK Biobank cohort, a population known for healthy-volunteer selection bias, reflected by a limited representation of aortic pathology: only a small proportion exhibited moderate to severe aortic regurgitation, and a mere four cases reported with congenital aortic valve disease. Therefore, caution should be taken when extending the application of DeepFlow to patient cohorts or CMR studies from other scanner types. Several technical considerations also merit acknowledgment, as they may influence the overall accuracy of flow estimation. Notably, the velocity encoding was largely set at 250 cm s^{-1} to mitigate the risk of flow-related aliasing, at the expense of a potential reduction in overall measurement accuracy. Additionally, no background correction was applied to mitigate phase-offset errors. Within these limitations, the authors presented a robust open-source algorithm for the segmentation of two-dimensional phase-contrast images, which facilitates large-scale quantification of aortic flow measurements in the mostly healthy UK Biobank study population.

The authors performed GWAS on 16 traits: 8 from the DeepFlow algorithm, total LVSV and 7 additional left and right ventricular parameters. Aortic area, forward peak velocity at the aortic annulus ($f_{V\mathrm{max}}$) and total LVSV were the most heritable (>20%), and strong genetic correlation across some traits was observed (aortic area and $f_{V\mathrm{max}}$, $r^2 > 0.8$). Taking a genome-wide significant threshold ($P < 5 \times 10^{-8}$), loci were identified for six traits (aortic area, $f_{V\mathrm{max}}$, total LVSV, forward LVSV, aortic valve regurgitant volume and fraction). Common variants were observed at three loci with genes relating to connective tissue disorders (*FBN1*, *ELN* and *PRDM6*). One locus was found for forward LVSV, and the candidate gene *SLC12A9* was highlighted; the same variant is also associated with heart rate. Aortic area and $f_{V\mathrm{max}}$ (>70%) loci overlap, as expected, with the high genetic correlation. A review of the lead variants for each trait for associations with traits measured using CMR[4–7] and aortic distensibility measured using echocardiogram (ECHO)[8] indicated that at 33 of the 34 shared loci, there is a variant associated with at least one CMR or ECHO trait (Fig. 1). Similarly, looking at variants only significantly associated with aortic area, 17 out of 20 loci showed overlap with other CMR and ECHO traits, and there was overlap with 3 of the 4 loci for $f_{V\mathrm{max}}$. The traits most represented were the diameter of the aorta along with aortic distensibility measures, and there was little overlap with structural cardiac measures.

The authors then tested for plausible causal relationships between aortic area and aortic valve regurgitant fraction. For this, they performed Mendelian randomization using the CAUSE algorithm, a recently proposed method to address both correlated and uncorrelated horizontal pleiotropic effects[9]. They observed a positive causal association between aortic area and aortic valve regurgitation (0.23% per cm^2 m^{-2} of body surface area-indexed aorta area, $P = 0.0003$), which was confirmed by three other well-established Mendelian randomization methods. They also tested for reverse causality but did not find significant support for association. Although these results were partially expected given the known pathophysiologic relationships between aortic root dilatation and severity of aortic regurgitation[10], as

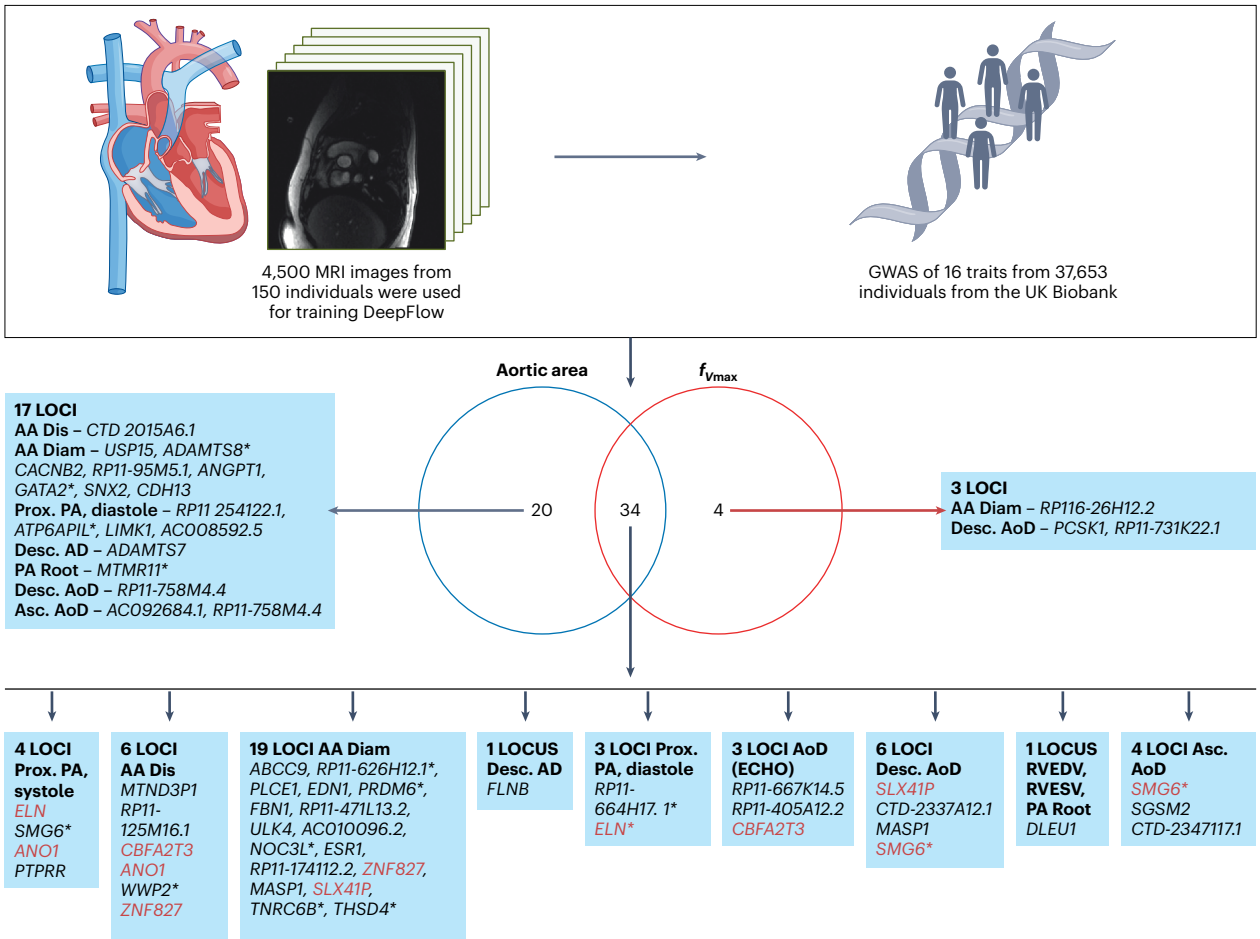

Fig. 1 | Overlap of loci associated with aortic area and forward peak velocity (f_{Vmax}) with cardiac magnetic resonance traits and aortic distensibility measured using echocardiography. Overlap of loci is reported if the lead variant for aortic area or f_{Vmax} is located within 500 kb of a locus that is genome-wide significant for a cardiac magnetic resonance trait or aortic distensibility measured using ECHO. Asterisks denote instances in which the variant for aortic area and f_{Vmax} is the same variant as reported for a CMR trait or aortic distensibility measured by ECHO. AA Dis, ascending aortic distensibility[4]; AA Diam, ascending aorta diameter[5]; Asc. AoD and Desc. AoD, ascending and descending aortic distensibility, respectively[7]; AoD (ECHO), aortic distensibility measured by ECHO[8]; Prox. PA, diastole, proximal pulmonary artery diastole[6]; Desc. AD, descending aortic diameter[5]; PA Root, proximal artery root[6]; Prox. PA, systole, proximal pulmonary artery systole[6]; RVEDV, right ventricular end diastolic volume[6]; RVESV, right ventricular end systolic volume[6]. Red type indicates loci associated with more than one CMR or ECHO trait. This figure was created using data from supplementary tables s6 and s7 of Gomes et al.[2].

the authors emphasize, the new genetic information may guide alternative therapeutic strategies thanks to the biological understanding of key mechanisms for aortic valve regurgitation. Nevertheless, the nonsignificant causal association between aortic valve regurgitation fraction and aortic area should be interpreted with care, given the low heritability of aortic valve regurgitation fraction and the fact that only a single locus was found to be significant genome-wide for the exposure trait. Finally, given the previous evidence for bidirectional causality between aortic area and hypertension, it would have been very interesting to test and compare causal associations between hypertension and aortic valve regurgitation fraction.

In summary, this paper provides a new tool for measuring aortic flow and supports a causal relationship between aortic area and aortic valve regurgitation. To drive the field forward, investigations of aortic flow, structure and functional measures in patients are also required at scale, and we need to probe the genetic relationships across all CMR traits to understand the biology. Equally, extrapolating the genetic insights from aortic or mitral flow phenotypes to distinct disease processes such as degenerative valvular disease or rheumatic valve disease – key determinants of valvular dysfunction globally – requires careful consideration.

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Competing interests

The authors declare no competing interests.