Integrated analysis identifies hypertension-GWAS-loci regulated, differentially expressed genes in aorta and blood of aortic dissection

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Research

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Abstract

Background: Aortic dissection is a life-threatening condition caused by a tear in the intimal layer of the aorta. Hypertension is the most common risk factor of aortic dissection. However, only a small proportion of subjects with hypertension will develop aortic dissection. Genetic basis and effect genes determining the development and progression of aortic dissection remained to be identified. In this study, we attempted to recognize the underlying effect genes from reliable large-scale genome-wide association studies (GWASs) of hypertension.

Methods: As most GWAS locus functions through its biological role in gene expression regulation, we initially converted the GWAS signals to transcriptomic profiles in aorta using the Functional Summary-based Imputation (FUSION) algorithm. The FUSION derived genes were then checked whether they were differentially expressed in aorta of subjects with and without aortic dissection.

Results: We found 23 genes that were regulated by hypertension GWAS loci and were altered in aorta of dissection patients. In particular, the *DCAF16* gene could be detected in blood, providing a possibility of non-invasive early detection or prediction of hypertensive individuals at risk of aortic dissection.

Conclusions: Our analyses identified effect genes in aorta and provided a possibility of non-invasive early detection of aortic dissection.

Trial registration: Retrospectively registered.

Introduction

The aorta is the largest blood vessel in the body, originating from the left ventricle of the heart [1–4]. It is made up of the intima, media, and adventitia layers, consisting of endothelial cells and connective and muscle tissues. A tear in the intimal layer of the aorta that results in the separation of the layers of the aortic wall will lead to a life-threatening condition called aortic dissection [1–4]. Aortic dissection is a lethal but rare cardiovascular disease [5–9]. Clinically, the symptoms of aortic dissection are sometimes atypical, and the onset are always acute. It can be suddenly fatal and 40% of people die immediately once the aorta dissects [4–6]. Delays in recognition, diagnosis, and treatment are associated with rapid increases in mortality. Therefore, patients with related symptoms or at risk should be thoroughly investigated despite its rare nature. Previous observational studies have analyzed clinical variables for rapid estimation of the individual risk of dissection on arrival in the emergency department [10]. Noninvasive, early prediction or detection of dissection in earlier stage might benefit to improved survival and effective treatment. This relies on a better understanding of the underlying molecular and genetic mechanisms.

While it is not always clear why a tear may occur, quite often it involves uncontrolled hypertension, aging, heart surgery, and genetic disorders that involve the connective tissue, such as Marfan's syndrome. More than 70% of individuals with aortic dissection have a previous history of hypertension. About 18% of individuals with an acute aortic dissection have a history of heart surgery. Aging is also an important risk factor, as there is reduced resistance of arterial walls with age. Indeed, aortic dissection is more prevalent in the elderly. Of these risk factors, hypertension is the most significant and the only modifiable factor.

There is no doubt that a subgroup of individuals with hypertension will develop aortic dissection. Identification of this at-risk subgroup, or assessment of risk of artic dissection in the large hypertension population, might help for potential early intervention. Taking advantage of large scale and reliable genome-wide association study (GWAS) and high throughput transcriptome data, we herein attempted to identify molecular predictor of dissection for at-risk individuals with hypertension.

Methods

Study rationale and design

As it is hard to perform a reliable GWAS of aortic dissection, which requires a large sample size, recognizing at-risk subgroups in hypertensive population before the dissection occurs is a feasible strategy. Hypertension has a heritability around 50% [11-13]. Numerous large-scale GWASs have identified genetic loci that are associated with blood pressure or hypertension [14-20]. As hypertension is the most significant risk factor for aortic dissection, it is reasonable to speculate that there are aortic dissection risk genes among those hypertension-associated loci. Since most GWAS locus functions through its biological role in gene expression regulation, we converted the hypertension GWAS signals to transcriptomic profiles in aorta using the Functional Summary-based Imputation (FUSION) algorithm [21]. The FUSION derived genes represent genetically driven gene expression in the target organ. Those hypertension GWAS loci regulated genes in aorta were thus defined as effect genes underlying the genetics factors for at-risk hypertension individuals. These effect genes were then checked whether they were differentially expressed in aorta and blood of patients, to explore the possibility of non-invasive detection. The rationale and workflow were shown in **Figure 1**.

GWAS of hypertension and GWAS-based transcriptome wide analysis

GWAS summary statistics of UK Biobank (https://www.ukbiobank.ac.uk/) [22] traits “Hypertension (Self-reported) (n = 337,159)”, “High blood pressure (n = 336,683)”, “Systolic blood pressure, automated reading (n = 317,754)”, and “Diastolic blood pressure, automated reading (n = 317,756)” were used in the this study. GWAS data were processed and were made openly available by the Neale lab rapid GWAS release (http://www.nealelab.is/blog/2017/7/19/rapid-gwas-of-thousands-of-phenotypes-for-337000-samples-in-the-uk-biobank). The four GWAS data were subjected to transcriptome-wide association study (TWAS) by using the tool Functional Summary-based Imputation (FUSION, https://github.com/gusevlab/fusion_twas) [23]. FUSION, developed by the Gusev Lab at the Dana-Farber Cancer Institute and Harvard Medical School (http://twas-hub.org/about/) [23], measures the gene expression changes based on GWAS summary-level data, using precomputed eQTL (expression Quantitative Trait Loci) data from GTEx [7,24] as the as weight matrix for gene expression in aorta. More details regarding the methods and data source were available through the TWAS hub (http://twas-hub.org/about/) [23] . To obtain robust and unbiased results, overlapped FUSION-predicted genes from all the four GWASs were subjected to differential expression analysis.

Transcriptome profiles of aorta and blood of patients with aortic dissection

The cross-validated, hypertension-GWAS-based, FUSION-predicted genes were investigated in expression dataset of aorta biopsies from individuals with and without aortic dissection. By searching the term “aortic dissection” through the NCBI GEO (Gene Expression Omnibus) browser (https://www.ncbi.nlm.nih.gov/geo/browse/), we got the dataset GSE52093. In GSE52093, gene expression profiles of ascending aorta were measured by the Illumina HumanHT-12 V4.0 expression beadchip. Differentially expressed genes were identified by comparing the gene expression profiling of dissected ascending aorta (n = 7) with that of control (n = 5) using the *limma* R package. Those differentially expressed FUSION-derived genes were genetically regulated effect genes for aortic dissection in hypertension population.

To explore the clinical potential of the identified effect genes in aorta, we investigated the gene expression of these genes in expression dataset of blood from aortic dissection patients (GSE9106) [25]. GSE9106 contains gene expression profiles of 61 peripheral blood RNA samples (training set) collected from 25 controls and 36 patients with thoracic aortic aneurysm [25], which usually leads to aortic dissection [26,27,28,29]. The testing set of GSE9106 that contains 22 TAA samples and 11 controls was also used for validating the expression change of *DCAF16* [25].The transcriptomes were analyzed by the Applied Biosystems Human Genome Survey Microarrays that include 29,098 human genes [25]. Detection of those effect aortic genes in blood of patients might provide a way to identify individuals at risk for aortic dissection.

Results

Genome-wide significant genes implicated by Hypertension-GWAS based TWAS analysis

We integrated the eQTL matrix of GTEx aorta and GWAS summary statistics of UK Biobank (https://www.ukbiobank.ac.uk/) [22] traits “Hypertension (Self-reported)”, “High blood pressure”, “Systolic blood pressure, automated reading”, and “Diastolic blood pressure, automated reading” through used the FUSION-based TWAS analysis [21]. At the canonically genome-wide significant level (TWAS *P-value* < 5.0×10^{-8}), we observed 28 genes for “Hypertension (Self-reported)” (Supplementary Table S1), 28 genes for “High blood pressure” (Supplementary Table S2), 39 genes for “Systolic blood pressure, automated reading” (Supplementary Table S3), and 45 genes for “Diastolic blood pressure, automated reading” (Supplementary Table S4). Among these genes, 32 genes were overlapped by at least two GWAS, representing the most significant and robust genes that are regulated by hypertension-risk loci and function in aorta (**Table 1**). To explore whether these predicted genes were truly involved in aortic dissection, we investigated their expression changes in aorta from dissection patients. Eight (*NOV*, *OPRL1*, *ERI1*, *HAUS8*, *UBE2D3*, *SPATA33*, *DCAF16*, *ARHGAP42*) out of these cross-validated 32 genes were differentially expressed in aorta of patients with marginal significance (GSE52093, **Table 1**).

Suggestively significant genes cross-validated by four hypertension-related GWASs

In addition to the genome-wide significant hits, genes showing suggestively significant TWAS *P*-values in all four GWASs might also be relevant in aorta. We then extended the gene list with a nominally significant threshold of TWAS-*P*-value < 0.01 (**Supplementary Table 1**). There were 113 such cross validated genes with a TWAS *P-value* < 0.01 in all the four GWASs “Hypertension (Self-reported)” (n = 385), “High blood pressure” (n = 381), “Systolic blood pressure, automated reading” (n = 402), and “Diastolic blood pressure, automated reading” (n = 423) (**Figure 2**). These 113 suggestively significant genes might be hypertension-risk-loci regulated genes that contribute to aortic dissection and were subjected to differential expression analysis. 19 genes were differentially (*P-value* < 0.05) expressed in aorta of patients in GSE52093, including four genome-wide significant genes mentioned above. This added 15 additional targets (*ALDH2, AGTRAP, SF3B3, CTSW, SPNS1, CCNT2, PRADC1, ACADVL, TUFM, SLC26A1, TPD52L2, MRAS, SMOC1, OIP5-AS1, and TOP3A*) in the effect gene list (**Table 1**). These 23 genes were genetically-regulated and were differentially expressed in aorta of patients, thus acting as the underlying effect genes for aortic dissection in at-risk individuals with hypertension.

Detection of genetically dysregulated aortic gene DCAF16 in blood of dissection patients

We then asked whether the dysregulated genes in aorta could be observed in blood of patients with thoracic aortic aneurysm [25], which usually leads to aortic dissection [26-29]. In the gene expression dataset GSE9106 which contains 36 cases and 25 controls [25], we found that three (*OPRL1*, *HAUS8*, *DCAF16*) out of the 23 effect genes were significantly altered in blood of patients compared with controls. However, the directions of differential expression of *OPRL1* and *HAUS8* were opposite between aorta (GSE52093) and blood (GSE9106). *DCAF16* was the only hit that shows consistent decrease in both aorta and blood (*P* = 0.00948 in the training set, 36 cases and 25 controls) of patients (**Figure 3**). Notably, expression change of *DCAF16* was well-validated by the testing set (*P* = 0.0002 in 22 cases and 11 controls) of GSE9106.

Discussion

Aortic dissection is a life-threatening vascular disease caused by a tear in the intimal layer of the aorta [4]. It is most prevalent in the elderly with an incidence of 35 cases per 100,000 old people per year [4,5,6,22]. Since most cases happen with an acute onset and bad prognosis, development of methods regarding risk prediction and early diagnosis will be the key for better management of the condition [30]. Because of the difficulty of sample collection of aortic dissection,

patient-based studies, such as genetic study and longitudinal study, is limited in the field [31]. Hypertension is the most common risk factor for the dissection. Recognition of patients at substantial risk for aortic dissection in the large hypertensive population before the dissection occurs is essential for early intervention. In the current study, we performed a data-mining aiming at identify effect genes and potential biomarkers based on genomic and transcriptomic data.

Note that there is currently few large-scale genetic studies of aortic dissection and the number of risk genes was limited [26,32-35]. By converting hypertension GWAS signal to transcriptome in aorta, we obtained 113 genes regulated by hypertension-related genetic variants. These 113 genes might function in the aorta, underlying the contribution of hypertension to aortic dissection. Expression of 23 out of the 113 genes indeed altered in aorta of patients, providing a list for further functional mechanistic studies. Compared with classical genetic studies, it seemed more fruitful by taking advantage of recent advances on GWAS of hypertension related traits and bioinformatic approaches. Note that expression of *FBN1*, one of the recognized top hits for aortic dissection [26,32-35], is also altered in aorta of patients (P = 0.0074, logFold_Change = 0.865 in GSE52093), supporting the reliability of the current strategy.

In addition to the implications for mechanistic studies, we identified a gene *DCAF16* altered in both aorta and blood of patients. Our results suggest that decreased *DCAF16* expression in blood of hypertensive individuals might predict the risk of thoracic aortic aneurysm and aortic dissection. Clinically, people with chest pain or back pain were subjected to history taking and physical examination on arrival in the emergency department [1,2,3,5,10]. Clinical prediction of aortic dissection mainly relies on clinical variables such as back pain and blood pressure. However, in most cases the dissection is acute. Noninvasive and rapid prediction or diagnosis of dissection in early stage using biomarkers might benefit to improved survival and effective treatment. For those people assessed as at high risk, early intervention such as adrenergic blocking and surgical avoiding could be suggested. Knowledge of molecular sign of dissection might help for early prediction of dissection.

There are several limitations of the current study. Firstly, it is not sure whether we can use this predictor to separate acute dissection from other aortic disorders such as penetrating aortic ulcer. Secondly, datasets used for aorta and blood were from different individuals, longitudinal study is needed confirm the results. Also, there is gaps between the list of effect genes and the mechanism of the disease. Further functional investigation of these genes might benefit from the current study.

Conclusions

Taken together, the present study identified that 23 genes were regulated by hypertension GWAS loci and were altered in aorta of dissection patients. Among the 23 genes, the expression alteration of *DCAF16* could be detected in blood of human patients. Therefore, this potential functional gene is expected to be a biomarker for aortic dissection. Future studies will be necessary to demonstrate whether the *DCAF16* gene has the early diagnostic potential in hypertensive patients at risk of aortic dissection.

Declarations

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Author' contributions

Study design: WZ, HL; data collection, analysis, and interpretation: YC, YL, MZ, JZ, LJ; manuscript preparation: YC, DX, KL, GD; All authors read, revised, and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Ethics approval and consent to participate

Not applicable.

Consent for publication

All the authors have consented for the publication.

Competing interests

The authors declare that they have no competing interests.

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Abbreviations

GWASs, genome-wide association studies

FUSION, functional Summary-based Imputation

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Table

Table 1. Genes implicated by hypertension-GWAS based TWAS analysis

Gene	TWAS					Differential expression (GSE52093)		
	Trait	Best GWAS SNP	eQTL SNP	Model	TWAS *P*-Value	Probe	logFC	P-Value
Genome-wide significant genes								
ARHGAP42	Hypertension	rs604723	rs1216743	enet	3.22E-28	ILMN_1716991	1.38	**0.0773**
TMEM133	Hypertension	rs604723	rs604723	enet	1.94E-22	ILMN_1730516	0.86	0.2440
NMT1	Systolic blood pressure	rs7213273	rs1053733	lasso	2.83E-18	ILMN_1762678	0.21	0.3260
SLC4A7	Hypertension	rs591668	rs820429	enet	2.23E-16	ILMN_2200917	0.34	0.1780
TNNT3	Hypertension	rs4980379	rs7120258	enet	2.06E-13	ILMN_2334080	-0.25	0.7840
FDFT1	Hypertension	rs11250163	rs12680762	lasso	5.09E-12	NA	NA	NA
SPATA33	Hypertension	rs460984	rs459920	enet	8.85E-12	ILMN_1759261	1.35	**0.0295**
ERI1	Hypertension	rs2409096	rs2288671	lasso	2.48E-11	ILMN_3245659	0.88	**0.0049**
NOV	Systolic blood pressure	rs2470002	rs2469996	enet	5.39E-11	ILMN_1787186	-2.82	**0.0004**
OPRL1	Hypertension	rs6062541	rs8121509	lasso	7.89E-11	ILMN_2400926	-2.52	**0.0012**
SPATA2L	Hypertension	rs460984	rs9939542	enet	2.01E-10	ILMN_1691111	0.10	0.6880
MRPL23-AS1	Hypertension	rs4980379	rs7483477	enet	3.05E-10	ILMN_3244224	0.65	0.4020
CISD2	Hypertension	rs223420	rs1080081	lasso	4.20E-10	ILMN_1796397	0.30	0.1790
UBE2D3	Hypertension	rs223420	rs223457	lasso	5.47E-10	ILMN_2241679	2.62	**0.0328**
AC091133.1	Hypertension	rs17637472	rs999475	lasso	9.63E-10	NA	NA	NA
KAT8	Hypertension	rs2032915	rs2855475	lasso	1.55E-09	ILMN_1804679	-0.31	0.1970
TCEA2	Hypertension	rs6062541	rs8121509	lasso	1.94E-09	ILMN_1684742	-0.46	0.5710
AF131215.9	Hypertension	rs1073913	rs7813802	lasso	1.98E-09	NA	NA	NA
AF131215.2	Hypertension	rs1073913	rs13276836	lasso	2.36E-09	NA	NA	NA

ULK4	Systolic blood pressure	rs2128834	rs17284313	enet	4.67E-09	ILMN_3236866	0.47	0.2310
HAUS8	Hypertension	rs7246865	rs7254154	lasso	5.42E-09	ILMN_3253579	0.86	**0.0086**
WNT2B	Hypertension	rs3790604	rs12401734	enet	5.43E-09	ILMN_1651492	1.06	0.1100
DCAF16	Hypertension	rs16895971	rs6817306	enet	6.40E-09	ILMN_1753440	-0.69	**0.0424**
YEATS4	Hypertension	rs41324046	rs11615124	enet	1.19E-08	ILMN_1801387	-0.02	0.9510
ZNF589	Hypertension	rs6442106	rs13059037	lasso	1.23E-08	ILMN_1654612	-0.16	0.6200
NEIL2	Hypertension	rs11250163	rs4639	lasso	1.30E-08	ILMN_1715680	0.18	0.4650
SRR	Systolic blood pressure	rs8076897	rs12450028	lasso	1.40E-08	ILMN_1753515	0.17	0.6180
RP11-588K22.2	High blood pressure	rs12643599	rs17033041	lasso	2.22E-08	NA	NA	NA
AC003029.1	Hypertension	rs653178	rs739496	lasso	2.61E-08	NA	NA	NA
IRAK1BP1	Hypertension	rs1567168	rs9443621	lasso	2.84E-08	ILMN_2228538	0.42	0.2960
FBF1	Hypertension	rs17581728	rs1135889	lasso	2.88E-08	ILMN_2144088	-0.03	0.8820
MRPS18AP1	Hypertension	rs6442106	rs13059037	lasso	4.56E-08	NA	NA	NA
Suggestively significant genes								
ACADVL	Hypertension	rs3933469	rs222857	lasso	1.17E-06	ILMN_1806408	0.61	**0.0101**
AGTRAP	Hypertension	rs12567136	rs6676319	lasso	2.86E-04	ILMN_1802458	1.48	**0.0013**
ALDH2	Hypertension	rs653178	rs12315146	enet	7.28E-06	ILMN_1793859	-1.19	**0.0003**
CCNT2	Hypertension	rs6757855	rs3769028	lasso	2.68E-03	ILMN_1787877	1.64	**0.0063**
CTSW	Hypertension	rs642803	rs658938	lasso	6.30E-03	ILMN_1794364	-1.76	**0.0021**
MRAS	Hypertension	rs2293251	rs13324341	lasso	7.66E-08	ILMN_1748881	-0.52	**0.0388**
OIP5-AS1	Hypertension	rs11858678	rs8036498	enet	2.63E-07	ILMN_3297455	0.71	**0.0477**
PRADC1	Hypertension	rs7593084	rs10207625	enet	2.27E-03	ILMN_2229940	0.67	**0.0100**
SF3B3	Hypertension	rs8062183	rs8062183	enet	2.70E-	ILMN_1803110	1.00	**0.0018**

					07			
SLC26A1	Hypertension	rs6843423	rs3796622	lasso	2.77E-03	ILMN_1700379	-4.31	**0.0456**
SMOC1	Hypertension	rs8003166	rs227425	enet	5.56E-04	ILMN_2410938	-1.61	**0.0397**
SPNS1	Hypertension	rs6565300	rs181209	lasso	2.09E-03	ILMN_1681016	0.80	**0.0037**
TOP3A	Hypertension	rs4925159	rs12945597	enet	2.46E-04	ILMN_2072973	0.52	**0.0492**
TPD52L2	Hypertension	rs6062541	rs3795149	enet	1.16E-07	ILMN_1699570	0.46	**0.0316**
TUFM	Hypertension	rs6565300	rs8049439	enet	1.85E-03	ILMN_1738369	0.67	**0.0209**

Note: For cross-validated genes, TWAS *P-value* was shown in one out of the four traits “Hypertension (Self-reported)”, “High blood pressure”, “Systolic blood pressure, automated reading”, and “Diastolic blood pressure, automated reading”. GWAS data were processed and were made openly available by the Neale lab rapid GWAS release (http://www.nealelab.is/blog/2017/7/19/rapid-gwas-of-thousands-of-phenotypes-for-337000-samples-in-the-uk-biobank). The four GWAS data were subjected to transcriptome-wide association study (TWAS) by using the tool Functional Summary-based Imputation (FUSION, https://github.com/gusevlab/fusion_twas) [23]. Suggestively significant *P*-values for genes differentially expressed in aorta of patients in GSE52093 were marked in bold.

Figures

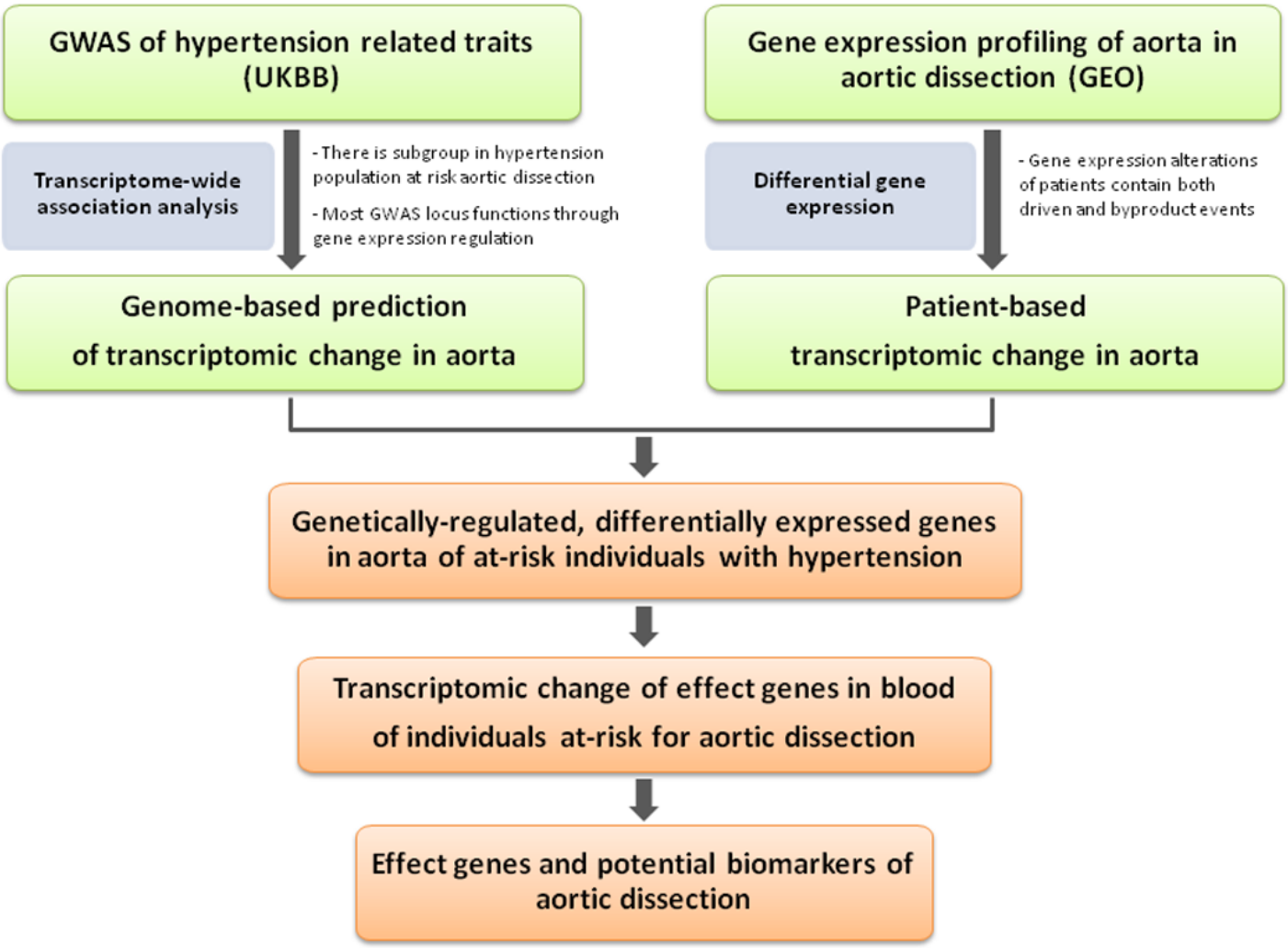

Figure 1

Workflow of the current study. Numerous large-scale GWASs have identified genetic loci that are associated with blood pressure or hypertension [14,15,16,17,18,19,20]. As hypertension is the most significant risk factor for aortic dissection, it is reasonable to speculate that there are aortic dissection risk genes among those hypertension-associated loci. Since most GWAS locus functions through its biological role in gene expression regulation, we converted the hypertension GWAS signals to transcriptomic profiles in aorta using the Functional Summary-based Imputation (FUSION) algorithm [21]. The FUSION derived genes represent genetically driven gene expression in the target organ. Those hypertension GWAS loci regulated genes in aorta were thus defined as effect genes underlying the genetics factors for at-risk hypertension individuals. These effect genes were then checked whether they were differentially expressed in aorta and blood of patients, to explore the possibility of non-invasive detection.

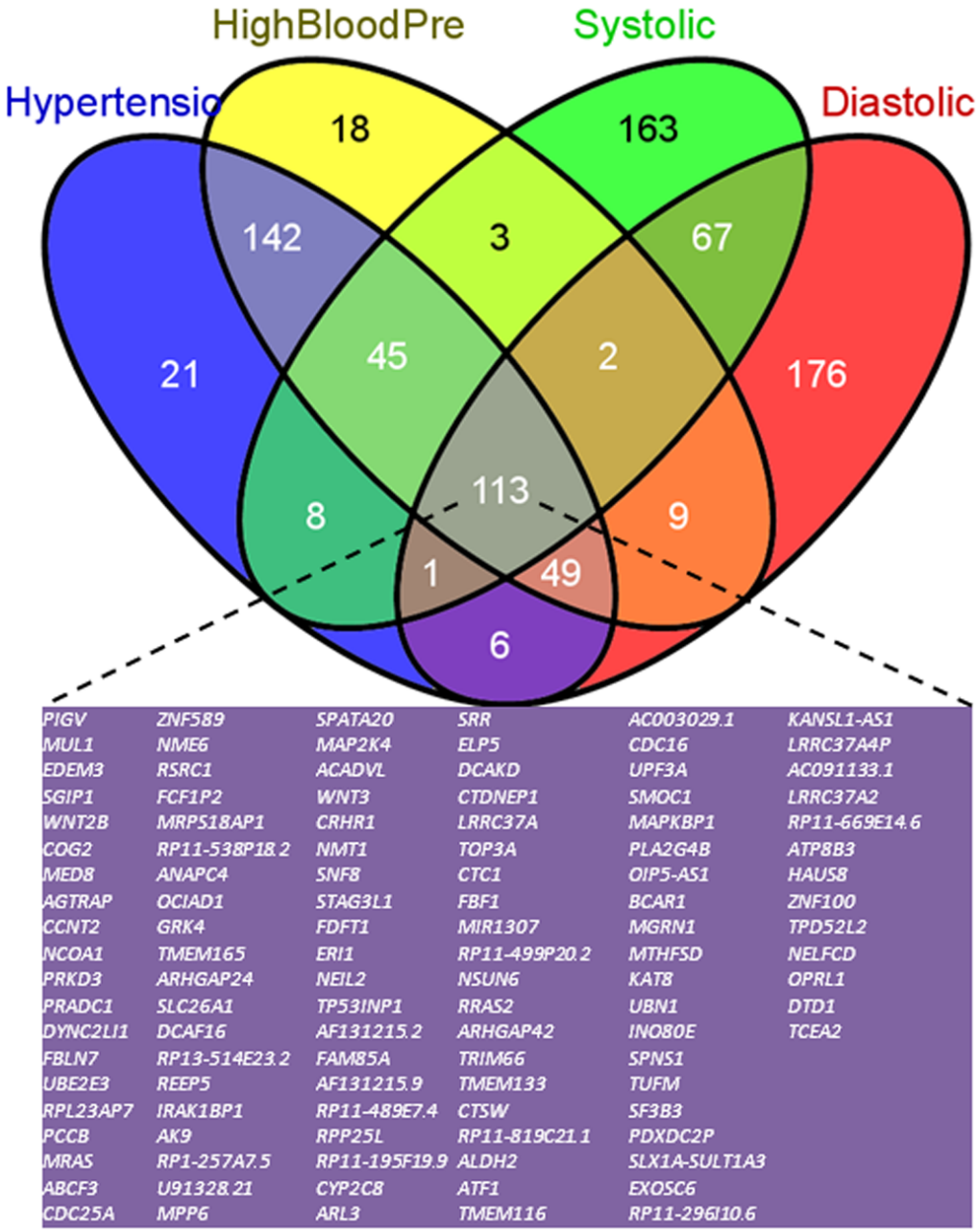

Figure 2

113 cross-validated genes were regulated by hypertension-related loci in aorta. Gene with a nominally significant threshold of TWAS-P-value < 0.01 from the four GWASs were used for cross-validation (Supplementary Table S1-S4). There were 113 such cross validated genes with a TWAS P-value < 0.01 in all the four GWASs “Hypertension (Self-reported)” (marked as “Hypertensio”, n = 385), “High blood pressure” (marked as “HighBloodPre”, n = 381), “Systolic blood pressure, automated reading” (Systolic, n = 402), and “Diastolic blood pressure, automated reading” (marked as “Diastolic”, n = 423). GWAS data were processed and were made openly available by the Neale lab rapid GWAS release (http://www.nealelab.is/blog/2017/7/19/rapid-gwas-of-thousands-of-phenotypes-for-337000-samples-in-the-uk-biobank). The four GWAS data were subjected to transcriptome-wide association study (TWAS) by using the tool Functional Summary-based Imputation (FUSION, https://github.com/gusevlab/fusion_twas) [23].

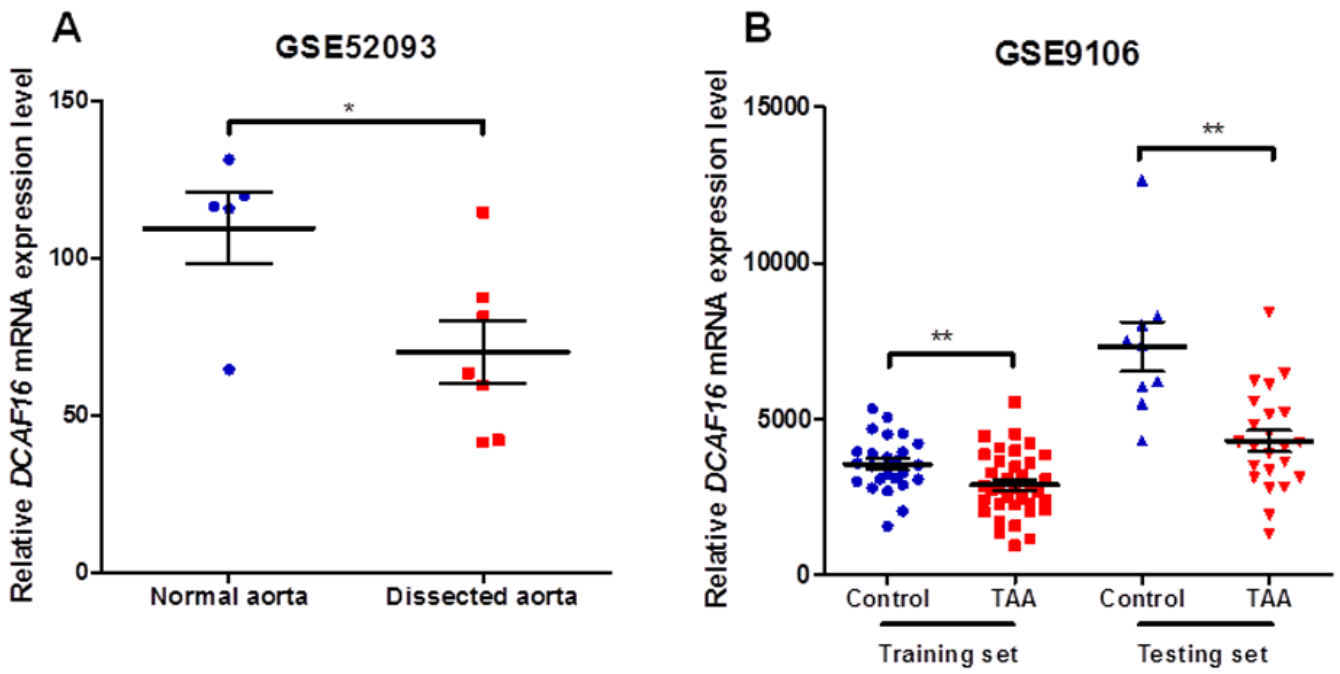

Figure 3

mRNA expression level of DCAF16 was decreased in aorta and blood of dissection patients. DCAF16 shows consistent decrease in both aorta (GSE52093 A) and blood (GSE9106, B) of patients. The training set of GSE9106 contains 36 TAA (Thoracic Aortic Aneurysm) patients and 25 controls, and the testing set contains 22 TAA samples and 11 controls [25].

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TableS1.docx
- TableS2.docx
- TableS3.docx
- TableS4.docx