

## DAB2IP Expression in Abdominal Aortic Aneurysm: EZH2 and mir-363-3p as Potential Mediators

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**Abstract.** *Background/Aim:* Nine genetic loci have been associated with abdominal aortic aneurysm (AAA) susceptibility, including DAB2IP. This gene is playing a role in apoptosis, cell proliferation and epithelial-to-mesenchymal transition in cancers. This study aimed to elucidate the differential expression levels of DAB2IP in AAA tissues and investigate whether mir-363-3p and EZH2 can be considered as potential mediators of its expression. *Materials and Methods:* 18 AAA samples and 15 non-aneurysmatic controls were collected. Relative mRNA expression levels of DAB2IP, EZH2 and mir-363-3p were measured using qPCR. *Results:* DAB2IP was significant up-regulated (~2.29 fold) in AAA tissues, while EZH2 and mir-363-3p were down-regulated (3.28 and 3.62-fold, respectively). A limited negative correlation was found between the DAB2IP and EZH2 expression and between DAB2IP and the mir-363-3p. *Conclusion:* An increased expression of DAB2IP in AAA tissues was shown. We suggest 2 potential mediators of DAB2IP expression in abdominal aortic aneurysm, EZH2 and mir-363-3p.

Abdominal aortic aneurysm (AAA) is a degenerative condition defined as a permanent localized pathological dilation of the aorta more than 50% compared to another site along the aorta, or an aortic diameter exceeding 30 mm.

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*Key Words:* Abdominal aortic aneurysm (AAA), Disabled homolog 2-interacting protein (DAB2IP), miR-363-3p, EZH2.

AAA is a common disease, often asymptomatic and it was discovered accidentally in imaging studies. If left untreated, AAA can rupture at advanced stages leading to high morbidity and mortality rates (1-3).

Nowadays, the prevalence of AAA ranges between 1.7-4.5% in men versus 0.5-1.3% in women, showing the highest prevalence in ages of 65-74 years (4-6). It is a complex, multifactorial disease influenced by genetic and environmental risk factors, with smoking, coronary artery disease and family history being the main contributors (7, 8). The pathogenesis of AAA is a result of several biological processes and involves all vascular cell subtypes. From the histological perspective, inflammation, extracellular matrix degradation, vascular smooth muscle cells (SMCs) apoptosis and increased oxidative stress are key mechanisms involved in the development of AAA (3, 9). To date, pharmacological treatment cannot prevent further progression of the disease or rupture without significant side-effects (3). The only available treatment option is the endovascular or open repair of the lesion; however, patients still face the operative risk. Candidates for this operation are patients with AAA  $\geq 55$  mm, while smaller ones cannot benefit from any treatment (3, 10). Therefore, a better understanding of the genetic mechanisms contributing to the disease could open the way for novel, nonsurgical approaches.

Evidence suggests that genetics contribute to the development of AAA (10, 11). Previous genome-wide associations studies (GWAS) have indicated six highly implicated chromosomal regions for high AAA risk: i) Disabled homolog 2-interacting protein interactive protein (DAB2IP), ii) low density lipoprotein receptor-related protein 1 (LRP1), iii) CDKN2BAS, iv) low-density lipoprotein receptor (LDLR), v) sortilin 1 (SORT1) and vi) interleukin 6 (IL-6) (12-15). Recently, a meta-analysis added 4 disease specific loci: i) matrix Metalloproteinase-9 (MMP9), ii) long intergenic non-protein coding RNA 540 (LINC00540), iii) ETS-related gene (ERG), and iv) SET and MYND domain-containing 2 (SMYD2) (14).

Gretarsdottir *et al.*, have identified an association between the rs7025486 in DAB2IP and abdominal aortic aneurysm, a single nuclear polymorphism (SNP), which is also associated with coronary artery disease, peripheral arterial disease, venous thromboembolism, and pulmonary embolism (16). DAB2IP is a member of the RAS-GTPase activating protein family located on human chromosome 9q33.1–q33.3. DAB2IP has been implicated in various biological processes including proliferation, apoptosis, epithelial-to-mesenchymal transition (EMT), cancer stem cell (CSC) and autophagy (17). The role of DAB2IP has been extensively described in different cancers; however its exact role in abdominal aortic aneurysm still remains unknown. DAB2IP implication in promoting apoptosis and suppressing cell survival and proliferation *via* PI3-Akt and ASK1-JNK-MAPK pathways make it as a plausible candidate gene for AAA pathobiology (7, 18). DAB2IP has also been referred as an endogenous inhibitor of VEGFR2-mediated signaling, an important regulator of angio-genesis (19).

DAB2IP expression, which is strongly down-regulated in most types of cancer, is epigenetically suppressed by EZH2, a histone methyltransferase that forms part of the polycomb repressor complex. An inverse correlation between *EZH2* and *hDAB2IP* gene expression has been mentioned in PCa and medulloblastoma cells. The EZH2 appears to be a transcription repressor that is involved with the cellular memory system, X-inactivation, germline development, stem cell pluripotency and cancer metastasis (20, 21).

MiRNAs are also important gene expression regulators. They are small single-stranded molecules, 20-23 nucleotides long, that regulate gene expression by inhibiting translation or by leading their targets (mRNAs) to degradation (22). According to the databases “mirdb.org” and “Target Scan Human 7.2”, *mir-363-3p* is a potential regulator of DAB2IP expression.

To the best of our knowledge there are only few data about DAB2IP expression in abdominal aortic aneurysm. Therefore, this study aims to elucidate the differential expression of *DAB2IP* in abdominal aortic aneurysm tissues and to investigate potential mediators of its expression, such as *mir-363-3p* and *EZH2*.

## Materials and Methods

**Collection of specimens.** Over the period of two years, full-thickness aortic tissue samples were collected from the anterior section of the point of maximum diameter of the intrarenal aorta of patients (n=18) undergoing open AAA repair. The patients who participated in the study (2 females, 16 males) were hospitalized at the First Department of Surgery at Laiko General Hospital of Athens (Greece) and their mean age was 71.8±8.23. AAA specimens were transferred and stored at -80°C at the Biology Laboratory of the Athens School of Medicine. When technically feasible and without jeopardizing the technical success of the procedure and the expected patient outcomes, non-aneurysmatic aortic samples of the aneurysm neck were also collected for use as controls (n=15). All participants provided written informed consent before entering the study. The

Table I. Demographics and clinical characteristics of patients participate in our study.

Parameter	Value (n=18)
Gender (F/M)	2/16
Age (mean±SEM, years)	71.8±8.23
Smoking	16 (88.8%)
Diabetes (%)	3 (16.6%)
Hypertension (%)	15 (83.3%)
Cholesterol (%)	6 (33.3%)
Triglycerides (%)	5 (27.8%)
Coronary artery disease (%)	4 (22.2%)
Chronic obstructive pulmonary disease (%)	7 (38.9%)
Chronic kidney disease (%)	3 (16.7%)
Statin therapy	6 (33.3%)
Antiplatelet drugs (%)	8 (44.4%)

study was conducted in accordance with the Declaration of Helsinki and was approved by our Hospital’s Ethics committee. Table I shows the data concerning the demographic and clinical parameters of our patients.

**RNA Extraction and Quantitative Real Time PCR.** Total RNA was extracted using the TRIzol® (Invitrogen, Waltham, MA, USA) method followed by cDNA synthesis using the PrimeScript RT Reagent Kit -Perfect Real Time (Takara Bio Europe, Saint-Germain-en-Laye, France) in the SC300 SuperCycler- Thermal Cycler (Kyratec, Queensland, Australia). SYBR Green real time PCR (KAPA SYBR FAST qPCR Master Mix - Kapa Biosystems (Wilmington, MA, USA) was performed in a Sa-Cycler 96 Real Time PCR System (Sacace Biotechnologies, Como, Italy) to identify *DAB2IP*, and *mir-363-3p* expression by employing the *glyceraldehyde-3-phosphate-dehydrogenase (GAPDH)* and *U6snRNA* expression levels as internal controls (reference genes). The primers sequences (Forward: F and Reverse: R) were specific for each gene and miRNA as follows: *DAB2IP* F: 5'-CCTGGACGATGTGCTCTATG-3'; *DAB2IP* R: 5'-TCTTCTTCTTCTTGTCCGGTCTC-3'; *EZH2* F: 5'-AATCAG AGTACATGCGACTGAGA-3'; *EZH2* R: 5'-GCTGTATCCTTC GCTGTTTCC-3'; *Mir-363-3p* F: 5'-ACACTCCAGCTGGGGAA TTGCACGGTATCCA-3'; *Mir-363-3p* R: 5'-TGGTGTCGTGG AGTCG-3'; *GAPDH* F: 5'-CATCTCTGCCCC CTCTGCTG-3'; *GAPDH* R: 5'-GCCTGCTTACCACCTTCTTG-3'; *U6snRNA* F: 5'-ATTGCAACGATACAGAGAAGATT-3'; *U6snRNA* R: 5'-GGA ACGCTTACGAATTTG-3'

The experiment was performed in duplicates. Differentiation between gene expression in AAA and control tissues was measured as a fold change.

**Statistical analysis.** GraphPad Prism software (version 6.0) was used. Results with probability values less than 0.05 ( $p < 0.05$ ) were classified as statistically significant. An independent-samples *t*-test was used to investigate the statistical difference in relative expressions of *DAB2IP*, *EZH2* and *mir-363-3p* between AAA and control groups. A Pearson correlation coefficient was calculated to assess the correlation between a) *DAB2IP* *mir-363-3p* and b) *DAB2IP* and *EZH2*. Chi-square test was used for the comparison of demographic and clinical characteristic in cases and controls, as appropriate.

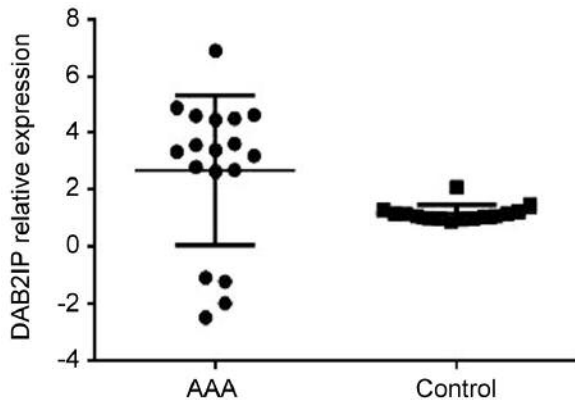


Figure 1. Analysis of the *DAB2IP* mRNA expression in abdominal aortic aneurysm (AAA) and control aortic tissues by real time quantitative RT-PCR. Statistical analysis showed increased mRNA expression level between AAA ( $n=18$ ,  $2.692\pm0.62$ ) and control aortic tissues ( $n=15$ ,  $1.175\pm0.077$ ), with  $p<0.05$ .

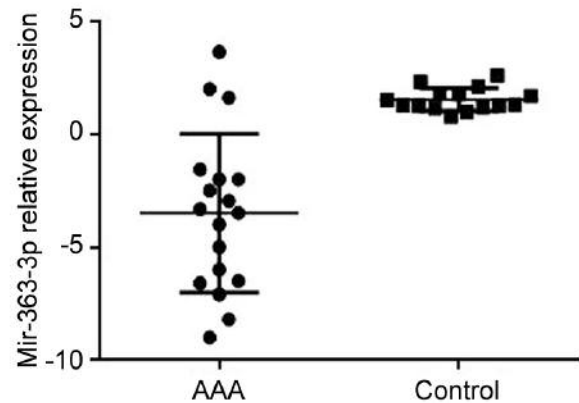


Figure 3. Analysis of the relative expression of *mir-363p* in human abdominal aortic tissues (AAA,  $n=18$ ) and control aortic tissues ( $n=15$ ) by real time quantitative RT-PCR. *mir-363-3p* was significantly down-regulated ( $p<0.0005$ ) in AAA tissues ( $n=18$ ,  $-3.494\pm0.828$ ) compared to controls ( $1.536\pm0.1313$ ).

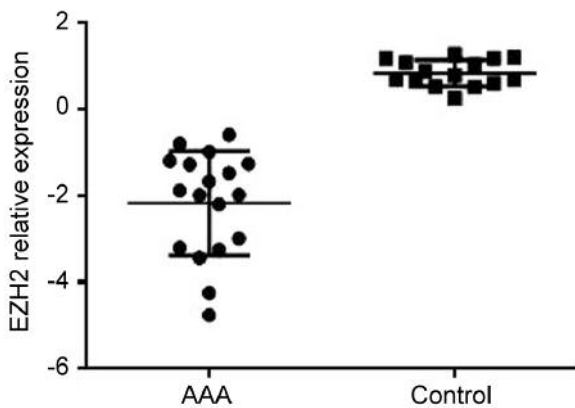


Figure 2. Analysis of the *EZH2* mRNA expression in abdominal aortic aneurysm (AAA) and control aortic tissues by real time quantitative RT-PCR. A lower mRNA expression level was observed between AAA ( $n=18$ ,  $-2.178\pm0.284$ ) and non aneurysmatic aortic tissues ( $n=15$ ,  $0.8307\pm0.079$ ), with  $p<0.0005$ .

## Results

Samples from 18 patients with abdominal aortic aneurysm were studied. Non-aneurysmatic adjacent regions of 15 samples were used as controls. We first analyzed the levels of *DAB2IP* mRNA and compared them between AAA tissues and controls. An approximately 2.29-fold significant ( $p<0.05$ ) increase was observed in the *DAB2IP* relative expression in AAA ( $n=18$ ,  $2.692\pm0.62$ ) compared to the controls ( $n=15$ ,  $1.175\pm0.077$ ) (Figure 1). In order to investigate possible mediators of *DAB2IP* expression we continued with the *EZH2* expression analysis. Our results presented a highly significant ( $p<0.0001$ ), approximately

3.62 fold reduction in the *EZH2* relative expression in AAA ( $n=18$ ,  $-2.178\pm0.284$ ) compared to the controls ( $n=15$ ,  $0.8307\pm0.079$ ) (Figure 2). *Mir-363-3p* is another possible gene regulator, as it targets *DAB2IP*. We measured *mir-363-3p* relative expression in AAA samples ( $n=18$ ,  $-3.494\pm0.828$ ) and controls ( $n=15$ ,  $1.536\pm0.1313$ ) and we found an extremely significant reduction, approximately 3.28 fold ( $p<0.0001$ ) (Figure 3). The significantly increased *DAB2IP* relative expression and the significantly lower expression of *EZH2* and *mir-363-3p* led us to examine the correlation between *DAB2IP* expression and each mediator through Pearson correlation coefficient (Figure 4). This analysis indicated a limited negative correlation between the *DAB2IP* and *EZH2* expression levels ( $r=-0.45$ ,  $p<0.05$ ). Similar limited negative correlation was observed between the *DAB2IP* and the *mir-363-3p* ( $r=-0.40$ ,  $p<0.05$ ).

## Discussion

AAA is a life threatening, complex, multifactorial disease influenced by genetic and environmental risk factors (7). The pathogenesis of AAA is a result of several biological processes with inflammation, extracellular matrix degradation and vascular smooth muscle cell apoptosis being the majors (23). *DAB2IP* has been widely known to play an important role in many cancers, including prostate, lung, gastrointestinal and breast cancer (25-27).

*DAB2IP* is a tumour suppressor gene involved in cell signalling, survival, migration, maturation, and apoptosis. *In vitro* functional studies have demonstrated that loss of its protein product leads to enhanced cell proliferation and reduced apoptosis *via* the PI3-Akt pathway and ASK1 pathways (18). During the past decade, studies have associated

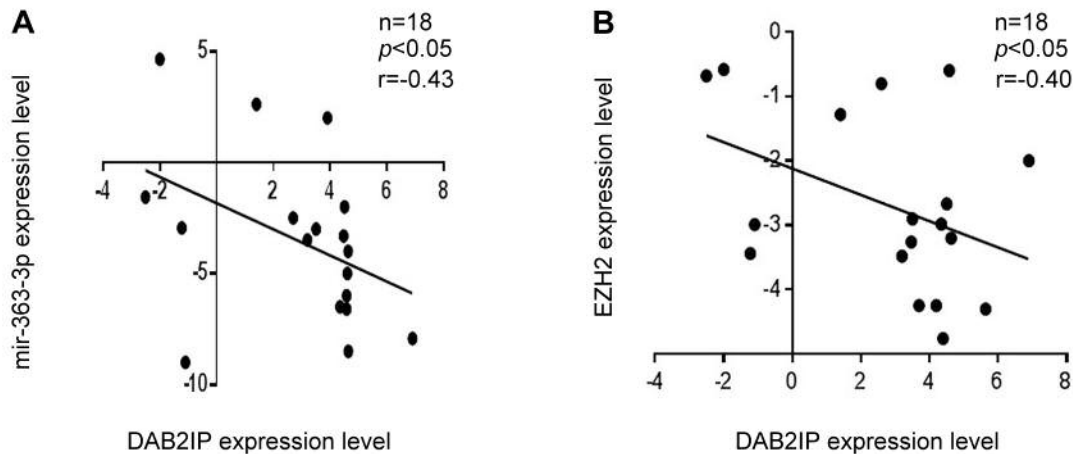


Figure 4. Analysis of the correlation between *DAB2IP* expression and the expression of (A) *miR-363-3p* and (B) *EZH2*, through Pearson correlation coefficient. A limited negative correlation was observed between the *DAB2IP* and both *EZH2* ( $r=-0.45$ ,  $p<0.05$ ) and *miR-363-3p* expression levels ( $r=-0.40$ ,  $p<0.05$ ).

*DAB2IP* with the development of abdominal aortic aneurysm. A GWAS study by Gretarsdottir *et al.*, have identified a sequence variant (rs7025486) within the *DAB2IP* gene, which confers susceptibility to abdominal aortic aneurysm (16). This polymorphism was also confirmed as a risk locus by strong evidence for abdominal aortic aneurysm in a recent meta-analysis (28). A further meta-analysis by Jones *et al.*, has revealed that another SNP, the rs10985349, is also associated with abdominal aortic aneurysm susceptibility (14).

To the best of our knowledge, there is only one study concerning *DAB2IP* expression, despite the strong correlation of these 2 loci to abdominal aortic aneurysm risk. Lenk *et al.*, have concluded that *DAB2IP* expression is significantly reduced in AAA tissues compared to controls, using a whole-genome expression chip on 13 individual RNA samples and 2 pooled RNA samples (29).

Our study examined *DAB2IP* expression in 18 AAA samples and compared it to expression from 15 controls. Contrary to Lenk *et al.*, our results showed a significant increase, approximately 2.75-fold, of *DAB2IP* relative expression in pathological tissues compared to non aneurysmatic. This up-regulation could be associated with abdominal aortic aneurysm as an elevated *DAB2IP* expression may lead to an increase in vascular smooth muscle cells apoptosis (18, 30).

Interestingly, in cancer, *DAB2IP* expression is modulated by *EZH2*, a histone methyltransferase forms part of the polycomb repressor complex (31, 32). A significant negative correlation between overexpressed *EZH2* and down-regulated *DAB2IP* has been reported in prostate and medulloblastoma cancer. *DAB2IP* suppression in medulloblastoma cells can be, at least partly, reversed by *EZH2* inhibition, thus it has been proposed as a potential drug target (20, 21).

In this study, the evaluation of *EZH2* relative expression showed a 2.17-fold down-regulation in aortic tissues compared to controls. A further statistical analysis indicated a limited negative correlation between *EZH2* and *DAB2IP* expression confirming their inverse relationship in abdominal aortic aneurysm in addition to cancer (20, 21).

MiRNAs are a class of RNAs that negatively regulate gene expression (33). Experiments with specific SMCs emphasize the importance of miRNAs for homeostasis of vascular SMCs (34), and it is likely that miRNAs also play a role in aneurysm formation, which is characterized by dysfunction of vascular SMCs (35). Using various miRNA prediction databases and focusing on miRNAs which potentially target *DAB2IP*, we measured the expression of *miR-363-3p* in order to reveal other mediators of *DAB2IP* expression in abdominal aortic aneurysm. *Mir-363-3p* has been associated with prostate cancer and the interaction with *DAB2IP* has been implicated in the suppression of epithelial-to-mesenchymal transition (36). EMT disturbance has been referred to play a role in numerous chronic cardiovascular disease states such as heart failure and pulmonary hypertension and various forms of chronic vasculopathy (37).

According to our findings, *miR-363-3p* was significantly down-regulated in AAA tissues compared to controls, while Pearson's correlation revealed a limited negative correlation between *DAB2IP* expression and this miRNA.

In conclusion, our study reveals an elevated expression of *DAB2IP* which could be modulated *via* the parallel down-regulation of *EZH2* and *miR-363-3p*. Different pathways may be involved, such as increased apoptosis or disturbed EMT. By understanding the pathophysiology of aneurysm formation, treatments targeting certain molecules can be designed to interrupt the growth or prevent the rupture of the

aneurysm. If the link between DAB2IP expression and its mediators is clarified, molecules, such as EZH2 and mir-363-3p could also be potential therapeutic targets which will reduce AAA formation.

### Conflicts of Interest

None.

### Author's Contributions

EL, MG and CK conceived of the presented idea. MG designed the study. EL and AS performed the experiments. EL wrote the article with support from MG, CK, and TL. DA, NP contributed to data and samples collection. EL, AS, MG contributed to the interpretation of the results. MG, CK and TL made the critical revision of the article and the final approval of the version to be published.

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