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Causal relationship between mitochondrial proteins and risks of aortic aneurysms and aortic dissection: a Mendelian randomization study

Lei Wang[1,4†], Yuzuo Lin[3†], Ziyan Lin[3], Qingtong Wu[3], Guodong Zhong[2*†] and Liangwan Chen[1,4,5*†]

Abstract

Background Mitochondrial dysfunction may be linked to the development of aortic aneurysm (AA) and aortic dissection (AD). This study aimed to evaluate the potential associations between proteins related to mitochondrial function and the risks of AA/AD using Mendelian randomization (MR).

Methods Large-scale publicly available genome-wide association studies (GWAS) and FinnGen summary data were utilized for MR analysis. The causal relationship between mitochondrial proteins and AA/AD was assessed using inverse-variance weighted (IVW) as the primary method. Sensitivity analyses were conducted to detect heterogeneity and pleiotropy by Cochran's Q test, MR-Egger test, MR-PRESSO global test, and "leave-one-out" analysis.

Results There were potential causal relationships between several mitochondrial proteins and AA/AD. Specifically, the iron-sulfur cluster assembly enzyme ISCU (OR = 1.165, 95% CI: 1.051–1.291, $P = 0.004$) and NFU1 iron-sulfur cluster scaffold homolog (OR = 1.184, 95% CI: 1.056–1.329, $P = 0.004$) were identified as potential risk factors for AA; whereas the 39 S ribosomal protein L14 (OR = 0.868, 95% CI: 0.764–0.987, $P = 0.031$) was found to be a protective factor for AA. Furthermore, 39 S ribosomal protein L33 (OR = 1.134, 95% CI: 1.010–1.274, $P = 0.033$) and cytochrome C oxidase subunit 5B (OR = 1.330, 95% CI: 1.037–1.706, $P = 0.025$) were associated with increased risks of AD; whereas the 39 S ribosomal protein L52 (OR = 0.736, 95% CI: 0.550–0.984, $P = 0.038$) and mitochondrial ubiquitin ligase activator of NFKB 1 (OR = 0.806, 95% CI: 0.656–0.989, $P = 0.039$) were identified as potential protective factors for AD. Sensitivity analysis confirmed the stability of the results.

†Lei Wang and Yuzuo Lin are co-first authors with equal contributions.

†Guodong Zhong and Liangwan Chencontributed equally to this work and should be considered co-corresponding authors.

*Correspondence:
Guodong Zhong
18459111686@163.com
Liangwan Chen
clw1259@163.com

Full list of author information is available at the end of the article

Conclusions This study identified potential genetic associations between mitochondrial proteins and AA/AD. Targeting these mitochondrial proteins may help prevent the occurrence of AA/AD.

Keywords Mitochondria, Aortic aneurysm, Aortic dissection, Mendelian randomization

Introduction

Aortic aneurysm (AA) and aortic dissection (AD) are life-threatening diseases with a global incidence of 35 cases per 100,000 people annually [1]. AA is characterized by localized, progressive, and irreversible dilation of the aortic walls, including thoracic aortic aneurysm and abdominal aortic aneurysm (AAA). Acute AD is considered a severe cardiovascular emergency with high mortality and morbidity. It is characterized by tearing in the intima of the aorta, leading to blood entering the middle layer of the arterial wall to form dissection hematoma. This extends along the artery forming true and false lumens. AA and AD are associated with risk factors such as advanced age, male sex, smoking, hypertension, dyslipidemia, and hereditary disorders [2]. The rupture risk significantly increases when the aortic diameter expands beyond 50% of normal [3], with AAA patients experiencing a mortality rate of 60–70%, resulting in approximately 150,000 to 200,000 deaths annually due to AAA rupture [4]. Global mortality rates for aortic diseases are on the rise [4]. Currently, open surgery remains the main treatment for these conditions; however, the high risk of surgery and high postoperative morbidity impose significant burdens on healthcare systems. The pathogenesis of AA/AD is still not fully understood. Given the high risk of mortality associated with AA/AD, it is imperative to delve into the etiology and mechanisms of disease progression, elucidate the risk factors, implement primary prevention measures, and identify new predictive targets and therapeutic strategies. These efforts are essential in order to reduce the incidence of AA/AD.

Mitochondria are crucial organelles present in the majority of cells. They serve as the "power stations" of cells and play a central role in energy metabolism, possessing a distinct mitochondrial genome. Mitochondria produce 90% of adenosine triphosphate (ATP) through oxidative phosphorylation within the respiratory chain, thereby supplying energy to cells and sustaining cellular functions. However, during energy production, mitochondria also act as the primary source of reactive oxygen species (ROS) within cells. The excessive accumulation of ROS, surpassing the scavenging capacity of the mitochondrial antioxidant defense system, can result in oxidative stress, reduced mitochondrial biogenesis, and increased glycolysis [5]. This can lead to inflammation, cellular injury, and apoptosis [6]. When mitochondrial dysfunction arises due to mitochondrial DNA damage, elevated ROS levels, and an imbalance in mitochondrial homeostasis, it can give rise to various disorders such as obesity [7], ischemic heart disease [8], diabetic cardiomyopathy [9], cardiac hypertrophy and heart failure [10], and may also contribute to AA/AD [11].

The primary pathological characteristics of AA/AD vessel wall include hydrolytic destruction of extracellular matrix proteins and dysfunction and cell death of vascular smooth muscle cells (VSMCs) [12]. Inflammation, ROS, and oxidative stress all play significant roles in the development and progression of AA/AD [13]. High levels of ROS, cyclooxygenase-2, and lipid peroxidation products are present in human AA biopsy tissues, exacerbating apoptosis of VSMCs and promoting protein degradation of the extracellular matrix [14]. Chronic aortic inflammation can also lead to aortic tissue destruction and dysfunction of VSMCs, ultimately resulting in VSMC apoptosis [13]. Mitochondrial biological dysfunction is one of the pathogenic mechanisms underlying AA/AD [11]. All aforementioned aortic pathological characteristics are associated with mitochondrial dysfunction, which is linked to impaired energy metabolism in VSMCs, inflammation, and oxidative stress. This might lead to VSMC contractile dysfunction, phenotypic transformation, and cell death. Mitochondrial proteins (MPs) are a class of proteins primarily localized in mitochondria, playing crucial roles and serving as important markers reflecting the biological functions of mitochondria. MPs are encoded by both nuclear genes and mitochondrial DNA. Approximately 99% of MPs are encoded by nuclear genes, and these nuclear-encoded MPs possess specific targeting signals that guide newly synthesized proteins from the cytoplasm to the mitochondrial surface receptor, and subsequently into the appropriate mitochondrial subcompartment [15].

Current research on the functions of MPs remains limited, with only 10–20% of human MPs having their functions elucidated. This suggests that, beyond their established roles in energy production, storage, and release, mitochondria possess additional functions yet to be uncovered. Studies have indicated that abnormal quantities or dysfunctions of certain MPs are linked to mitochondrial dysfunction. For example, Xie et al. demonstrated that the absence of cell-cycle exit and neuronal differentiation 1 (CEND1) can lead to an increase in dynamin-related protein 1 and enhanced mitochondrial fission, resulting in mitochondrial dysfunction and contributing to the pathogenesis of Alzheimer's disease [16]. Furthermore, mitochondrial fusion protein 2 (Mfn2) not only plays a role in anchoring mitochondria to the endoplasmic reticulum but also facilitates calcium uptake by

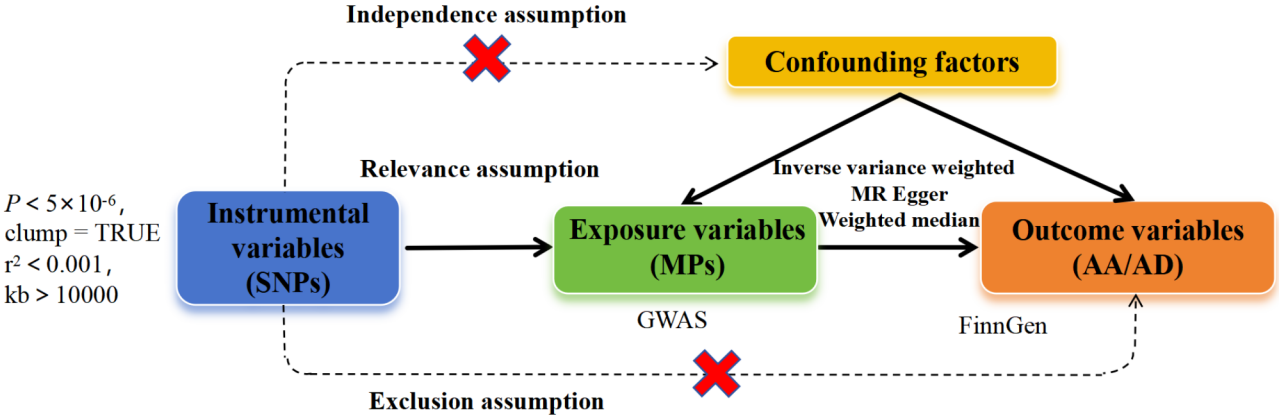

Fig. 1 The thorough design of the current Mendelian randomization analysis. AA: aortic aneurysm; AD: aortic dissection; MPs: mitochondrial proteins; MR: Mendelian randomization; GWAS: genome-wide association studies; SNPs: single nucleotide polymorphisms

Table 1 Baseline characteristics of outcome variable datasets

Outcome variables	Dataset ID	Year of publication	Sample size	Case (*n*)	Control (*n*)	Population	SNPs (*n*)
AA	finngen_R10_I9_AORTANEUR	2023	294,730	6092	288,638	European	19,682,397
AD	finngen_R10_I9_AORTDIS	2023	289,318	680	288,638	European	19,682,294

AA: aortic aneurysm; AD: aortic dissection; SNP: single nucleotide polymorphism

mitochondria, influences the dynamics of mitochondrial fusion/fission processes, and is involved in cellular proliferation, regulation of calcium homeostasis, apoptosis, and oxidative stress responses. Overexpression of Mfn2 has been shown to reduce vascular smooth muscle cell (VSMC) proliferation while promoting apoptosis through modulation of mitochondrial function and related signaling pathways [17]. At present, the specific role of MPs in aortic diseases remains unclear. It is uncertain whether MPs directly contribute to the development of AA/AD, or if there exists a potential causal relationship between these conditions. We hypothesize that abnormal quantities or functionalities of MPs may induce mitochondrial dysfunction which could exacerbate inflammatory responses, oxidative stress levels or VSMC cell death—thereby promoting the occurrence of AA/AD.

Mendelian randomization (MR) is a unique epidemiological research method derived from Mendelian laws of heredity. It utilizes single-nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to infer potential causal relationships between exposures and outcomes, thereby minimizing confounding factors and avoiding reverse causation as much as possible. Since specific SNP alleles are randomly allocated during meiosis of germ cells, genetic variation remains unaffected by potential confounding factors. Consequently, MR analysis effectively reduces confounding factors and avoids reverse causality to the greatest extent possible, greatly enhancing the reliability of results. Clinical epidemiologic studies have not been able to verify the relationship between MPs related to mitochondrial function and risks of AA/AD. Therefore, two-sample MR analysis was employed in this study to assess the potential causal relationship between MPs and AA/AD in order to provide new targets for prevention and treatment of AA/AD.

Materials and methods

Research design

A two-sample MR analysis was conducted to investigate the causal relationship between MPs and AA/AD. The exposure variable was 66 MPs, and the IVs were SNPs significantly associated with MPs. The outcome variables were AA/AD. According to the STROBE-MR guidelines [18], three core assumptions of MR analysis were as follows: (1) Relevance assumption: the IVs have a stable correlation with the exposure variable (MPs). (2) Exclusion assumption: IVs only affect the incidence of AA/AD through MPs and do not involve any other pathways. (3) Independence assumption: IVs and AA/AD do not have any other confounding factors. The flow chart of MR analysis was shown in Fig. 1.

Data sources

The dataset for 66 MPs were obtained from the integrative epidemiology unit open genome-wide association study (GWAS) database with a total sample size of 3301 European participants [19], while datasets for AA and AD were retrieved from the FinnGen database [20]. The baseline characteristics of the exposure variables and outcome variables were presented in Supplementary Table S1 and Table 1. Both the GWAS and FinnGen datasets are publicly available and have been approved by

the appropriate ethical committee. As a result, additional ethical approval was not required for the analyses conducted in this study.

Selection of IVs

SNPs significantly associated with MPs ($P < 5 \times 10^{-6}$) were selected as IVs. $R^2 < 0.001$ and kb > 10,000 were set to remove SNPs with linkage disequilibrium. Additionally, palindromic SNPs were excluded to ensure that the effects of these SNPs on the exposure variable corresponded to the same allele as their effect on the outcome variables. Furthermore, F statistics were utilized to assess potential weak IV bias. The F statistic was calculated using the formula $F = R^2\ (N - K - 1)\ /\ [K\ (1 - R^2)]$, where R^2 represents the cumulative explained variance attributed to the SNPs during exposure, N denotes the sample size of the exposure dataset, and K represents the count of SNPs included in the final analysis. A strong predictive power for SNPs on the exposure variable was indicated by F-statistics > 10; therefore, SNPs with an F statistic < 10 were excluded from further analyses.

Two-sample MR analysis

The causal relationship between MPs and AA/AD was assessed using three MR analysis methods: IVW as the primary method, with MR Egger and weighted median methods as supplementary ones. The MR results were visualized using the "TwoSampleMR" R package, including scatter plots, forest plots, and funnel plots, focusing mainly on the IVW results. Scatter plots with a small intercept indicate little influence of confounding factors on the reliability of the results. A positive slope of the line indicates that the exposure variable is a risk factor, while a negative slope indicates a protective factor. The forest plots were used to assess the predictive efficacy of each SNP on the outcome variables, with solid dots on the left representing protective factors of SNPs and solid dots on the right representing risk factors. Funnel plots were used to assess randomization; if the IVs were symmetrically distributed along both sides of the IVW line, it indicated compliance with Mendel's second law of random grouping. A P value < 0.05 indicated a statistically significant causal relationship between exposure and outcomes.

Sensitivity analysis

Sensitivity analyses were conducted to assess the reliability of MR results. Heterogeneity of SNPs in IVW and MR Egger methods was assessed using Cochran's Q test, with a P value > 0.05 indicating no significant heterogeneity among the selected IVs. The presence of horizontal pleiotropy in SNPs was examined using the MR Egger intercept and MR-PRESSO methods, with the P value > 0.05 indicating no horizontal pleiotropy and thus probably no confounding factors in the study. Additionally, the "leave-one-out" method was employed to re-evaluate the effect values of remaining SNPs after individually removing each SNP; any significant changes in effect values indicated potential significant effects on causal relationships, prompting removal from analyses.

Statistical analysis

The data were analyzed using the "twoSampleMR" and "MR-PRESSO" packages within R software version 4.3.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Selection of SNPs

After excluding SNPs with linkage disequilibrium, palindromic SNPs, and SNPs with F-statistics < 10, a total of 830 SNPs associated with MPs were included in the MR analysis. The number of selected SNPs per MP was shown in Supplemental Table S1.

The causal relationship between MPs and AA and AD

The IVW method demonstrated a potential causal association between certain MPs and AA/AD. The iron-sulfur cluster assembly enzyme ISCU, mitochondrial (ISCU) and NFU1 iron-sulfur cluster scaffold homolog, mitochondrial (NFU1) were identified as risk factors for AA, while 39 S ribosomal protein L14, mitochondrial (MRPL14) was found to be a protective factor for AA. Additionally, 39 S ribosomal protein L33, mitochondrial (MRPL33) and cytochrome C oxidase subunit 5B, mitochondrial (COX5B) were identified as risk factors for AD, whereas 39 S ribosomal protein L52, mitochondrial (MRPL52) and mitochondrial ubiquitin ligase activator of NFKB 1 were found to be protective factors for AD (Table 2; Fig. 2). The figures in Figs. 3 and 4, and Fig. 5 present scatter plots, forest plots, and funnel plots illustrating the MR analysis of MPs and AA/AD. Among the seven potential causal associations mentioned above, the small intercept of the scatter plot indicated minimal influence from confounding factors on exposure and outcome variables, which might not affect the reliability of the results. Additionally, the negative linear slope indicated that certain MPs act as protective factors for AA/AD, while the positive linear slope indicated that certain MPs act as risk factors for AA/AD (Fig. 3). The total predictive efficacy values of SNPs for outcome variables in the forest plot located on the left side indicated that certain MPs were protective factors, while on the right side indicate that certain MPs were risk factors (Fig. 4). The symmetry of SNPs distribution shown in funnel plots suggested relative stability of the results (Fig. 5).

Table 2 MR analysis of exposure and outcome variables using IVW method and the sensitivity analysis

Exposure variables (GWAS ID)	Outcome variables	Selected SNPs (*n*)	*P* value, IVW	OR (95% CI), IVW	Heterogeneity test. *P*		Horizontal pleiotropy test. *P*	
					IVW	MR-Egger	MR-Egger.intercept	MR.PRESSO.Global.Test
ISCU (prot-a-1572)	AA	11	0.004	1.165 (1.051–1.291)	0.209	0.151	0.944	0.212
NFU1 (prot-a-2041)	AA	8	0.004	1.184 (1.056–1.329)	0.660	0.545	0.958	0.667
MRPL14 (prot-a-1940)	AA	5	0.031	0.868 (0.764–0.987)	0.451	0.393	0.468	0.536
MRPL33 (prot-a-1942)	AD	11	0.033	1.134 (1.010–1.274)	0.365	0.295	0.709	0.377
COX5B (prot-a-638)	AD	12	0.025	1.330 (1.037–1.706)	0.323	0.287	0.497	0.338
MRPL52 (prot-a-1944)	AD	7	0.038	0.736 (0.550–0.984)	0.871	0.792	0.783	0.882
Mitochondrial ubiquitin ligase activator of NFKB 1 (prot-a-1970)	AD	11	0.039	0.806 (0.656–0.989)	0.751	0.710	0.530	0.781

CI: confidence interval; COX5B: cytochrome C oxidase subunit 5B, mitochondrial; GWAS: genome-wide association study; ISCU: iron-sulfur cluster assembly enzyme ISCU, mitochondrial; IVW: inverse-variance weighted; MR: Mendelian randomization; MRPL14: 39 S ribosomal protein L14, mitochondrial; MRPL33: 39 S ribosomal protein L33, mitochondrial; MRPL52: 39 S ribosomal protein L52, mitochondrial; NFU1: NFU1 iron-sulfur cluster scaffold homolog, mitochondrial; OR: odds ratios

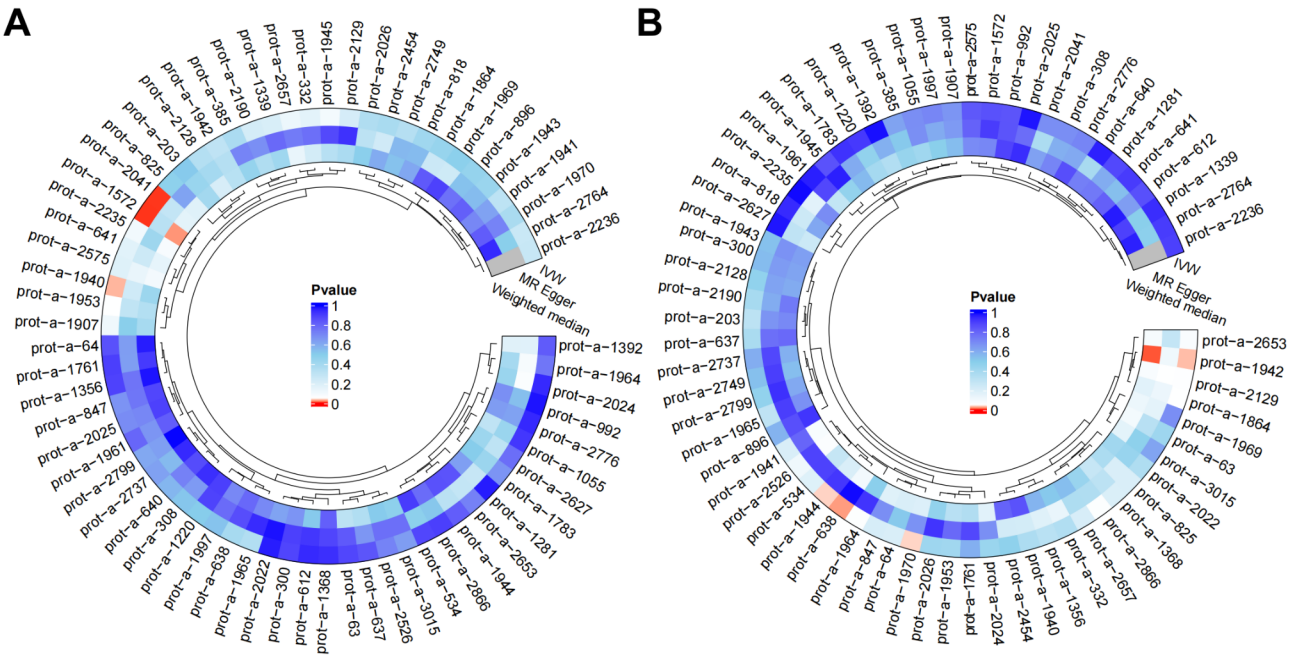

Fig. 2 MR analysis of mitochondrial proteins and aortic aneurysm/dissection using IVW, MR Egger and weighted median methods. (**A**) MR analysis of mitochondrial proteins and aortic aneurysm using IVW, MR Egger and weighted median methods. (**B**) MR analysis of mitochondrial proteins and aortic dissection using IVW, MR Egger and weighted median methods. IVW: inverse-variance weighted

Sensitivity analysis

Heterogeneity was assessed using the IVW and MR Egger methods, and the *P* values of the selected SNPs were all > 0.05, indicating the absence of heterogeneity. MR Egger intercept and MR-PRESSO analyses were employed to detect the presence of horizontal pleiotropy in the SNPs, and the results indicated that all *P* values were > 0.05, suggesting no evidence of pleiotropy in the SNPs (Table 2). The "leave-one-out" analysis demonstrated that when a SNP was removed, the entire error bar was situated only on one side of the IVW line, indicating that each SNP had an equal effect on the results with no strong interference from any individual SNP (Fig. 6). These findings contribute to enhancing the reliability of our study results.

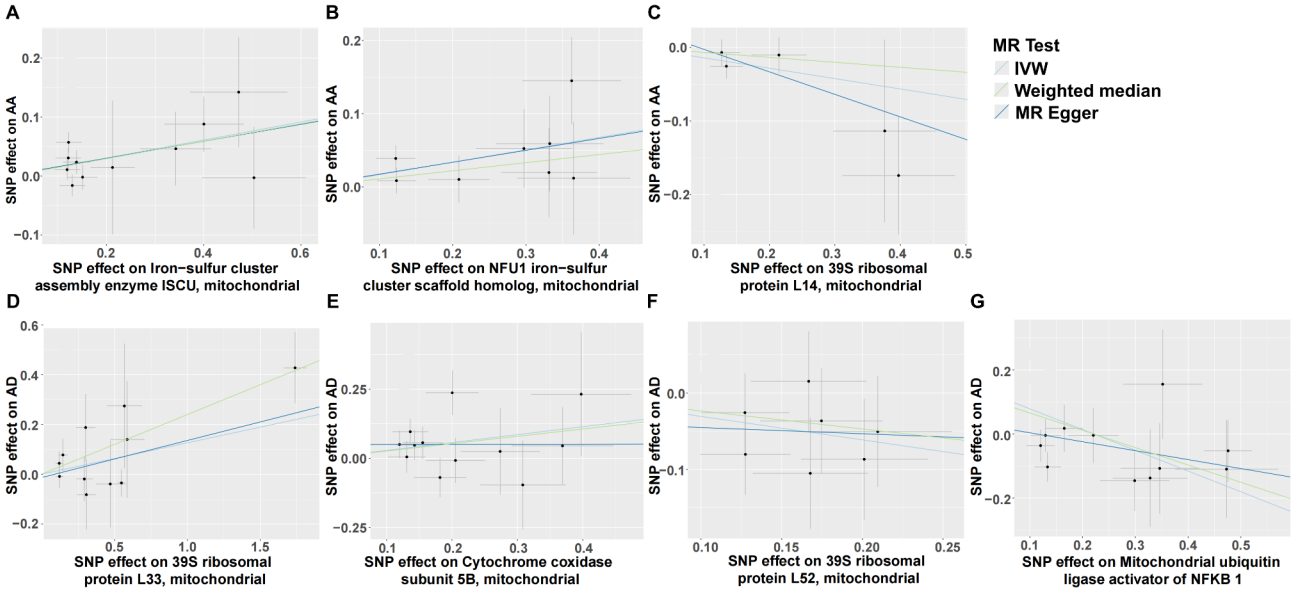

Fig. 3 Scatter plots of MR analysis, primarilyusing the IVW method. (A) Scatterplot of ISCU and AA. (B) Scatterplot ofNFU1 and AA. (C) Scatterplot ofMRPL14 and AA. (D) Scatterplot ofMRPL33 and AD. (E) Scatterplot ofCOX5B and AD. (F) Scatterplot ofMRPL52 and AD. (G) Scatterplot ofmitochondrial ubiquitin ligase activator of NFκB 1 and AD. AA: aortic aneurysm; AD: aortic dissection; COX5B: cytochrome C oxidase subunit 5B, mitochondrial; ISCU: iron-sulfur cluster assembly enzyme ISCU, mitochondrial; IVW: inverse-variance weighted; MRPL14: 39S ribosomal protein L14, mitochondrial; MRPL33: 39S ribosomal protein L33, mitochondrial; MRPL52: 39S ribosomal protein L52, mitochondrial; NFU1: NFU1 iron-sulfur cluster scaffold homolog, mitochondrial

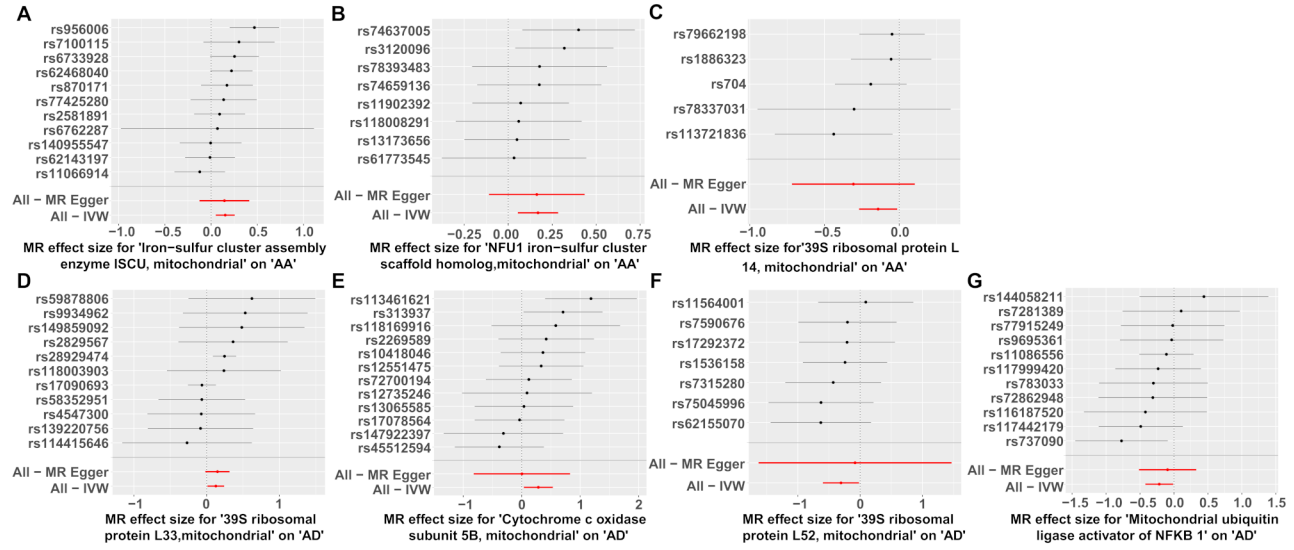

Fig. 4 Forest plots of MR analysis, primarily using the IVW method. (**A**) Forest plot of ISCU and AA. (**B**) Forest plot of NFU1 and AA. (**C**) Forest plot of MRPL14 and AA. (**D**) Forest plot of MRPL33 and AD. (**E**) Forest plot of COX5B and AD. (**F**) Forest plot of MRPL52 and AD. (**G**) Forest plot of mitochondrial ubiquitin ligase activator of NFκB 1 and AD. AA: aortic aneurysm; AD: aortic dissection

Discussion

In this study, we conducted a two-sample MR analysis to investigate the potential causal relationship between MPs related to mitochondrial function and AA/AD. The findings revealed a causal link between certain MPs and the risk of AA/AD. Specifically, it was suggested that ISCU and NFU1 acted as upstream risk factors for AA, while MRPL14 served as an upstream protective factor for AA. Additionally, MRPL33 and COX5B were identified as upstream risk factors for AD, whereas MRPL52 and mitochondrial ubiquitin ligase activator of NFκB 1 were found to be upstream protective factors for AA.

VSMCs require a significant amount of energy to maintain vascular tone. Mitochondria serve as the primary energy source for cellular activity, producing ATP through the tricarboxylic acid cycle and oxidative

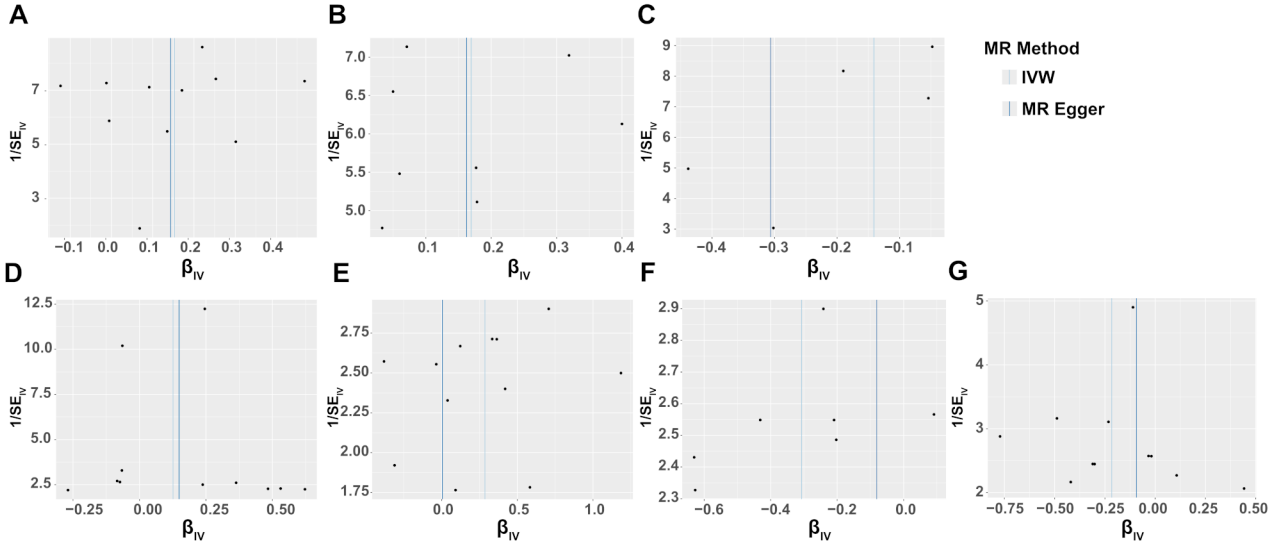

Fig. 5 Forest plots of the "leave-one-out" method for MR analysis. (**A**) Forest plots of the "leave-one-out" method of ISCU and AA. (**B**) Forest plots of the "leave-one-out" method of NFU1 and AA. (**C**) Forest plots of the "leave-one-out" method of MRPL14 and AA. (**D**) Forest plots of the "leave-one-out" method of MRPL33 and AD. (**E**) Forest plots of the "leave-one-out" method of COX5B and AD. (**F**) Forest plots of the "leave-one-out" method of MRPL52 and AD. (**G**) Forest plots of the "leave-one-out" method of mitochondrial ubiquitin ligase activator of NFκB 1 and AD. IV: instrumental variable; IVW: inverse-variance weighted; SE: standard error

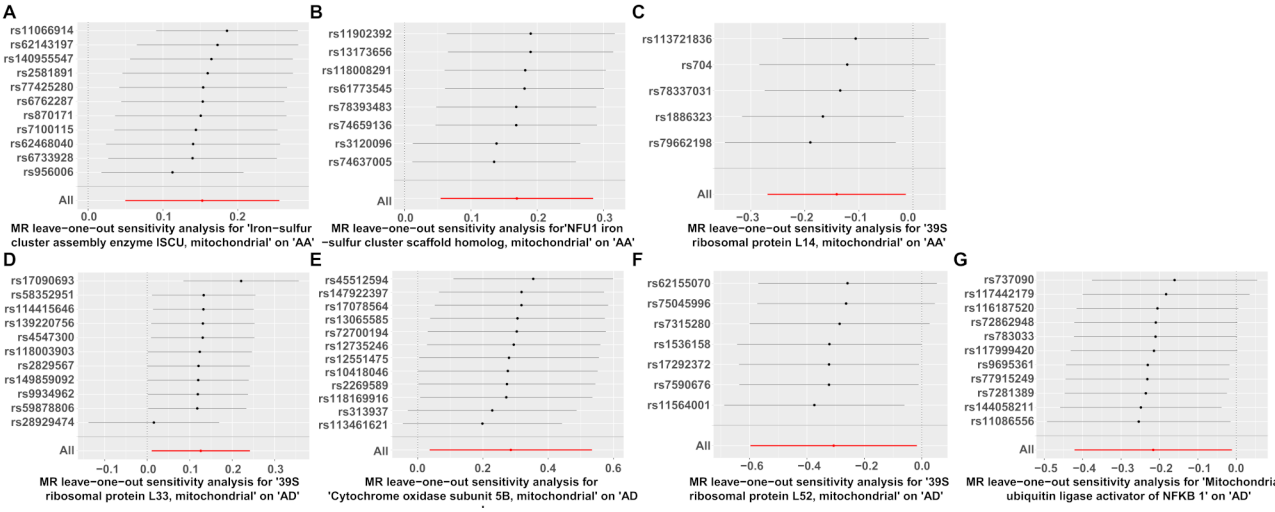

Fig. 6 Funnel plots of MR analyses, primarily using the IVW method. (**A**) Funnel plot of ISCU and AA. (**B**) Funnel plot of NFU1 and AA. (**C**) Funnel plot of MRPL14 and AA. (**D**) Funnel plot of MRPL33 and AD. (**E**) Funnel plot of COX5B and AD. (**F**) Funnel plot of MRPL52 and AD. (**G**) Funnel plot of mitochondrial ubiquitin ligase activator of NFκB 1 and AD. AA: aortic aneurysm; AD: aortic dissection

phosphorylation. These processes play a crucial role in regulating the resting contractile phenotype of VSMCs [21]. However, mitochondrial dysfunction can lead to impaired energy metabolism in VSMCs [22]. This manifests as decreased ATP production, elevated lactate levels, and increased glycolysis in VSMCs, ultimately resulting in impaired contractile function and a transformation of VSMCs from a contractile phenotype into anabolic, secretory, proliferative, and highly migratory phenotypes [23]. VSMCs with a secretory phenotype secrete large amounts of extracellular matrix and inflammatory factors. This leads to enhanced protein hydrolases, extracellular matrix degradation, and the release of apoptosis-signaling-related molecules [24].

Meanwhile, the opening of the permeability-transition pore in the outer mitochondrial membrane causes a loss of selective permeability and releases redox substances. This results in a large influx of intracellular calcium ions into the mitochondria, leading to mitochondrial calcium overload. Consequently, this triggers the apoptotic pathway and ultimately leads to apoptosis of VSMCs [25, 26]. These processes collectively contribute to the onset and

progression of AA and AD [10]. Additionally, single-cell sequencing studies have revealed that extensive mitochondrial dysfunction is a distinguishing feature of AA in the aorta [27]. Furthermore, restoration of mitochondrial function in VSMCs has been shown to prompt their transition from a synthetic phenotype back to a contractile phenotype [28].

MPs play crucial roles in mitochondrial biological functions. However, they are susceptible to errors during folding and assembly due to oxidative stress and post-translational modifications, which can result in mitochondrial dysfunction [29]. To maintain the quality and quantity of MPs, multiple pathways and regulatory factors are involved in quality control. It is important to note that MPs do not function independently but rather as protein complexes with interconnected structural and functional roles. Any increase or decrease in the expression levels of MPs may contribute to mitochondrial dysfunction and mitochondria-related diseases [16, 17]. Nevertheless, there is still limited research on the mechanism of how MPs contribute to disease.

ISCU is a scaffolding protein associated with the assembly of iron-sulfur clusters, which serves as cofactors for a variety of enzymes involved in regulating metabolism, iron homeostasis, and oxidative stress responses. Ren et al. demonstrated that ISCU promotes tumor growth by facilitating the metabolism of α-ketoglutarate catabolism and an increase in DNA 5mC [30], while Chan et al. found that MicroRNA-210 improves mitochondrial metabolism during hypoxia by inhibiting ISCU1/2 [31]. NFU1 encodes a protein that localizes to mitochondria and plays a crucial role in the synthesis of iron-sulfur clusters. Mutations in this gene are responsible for various mitochondrial dysfunction syndromes [32]. ISCU and NFU1 have been linked to mitochondrial oxidative phosphorylation and oxidative stress. Additionally, there are known interactions between ISCU and NFU1 [33]. However, the specific roles of ISCU and NFU1 in the development of AA/AD remain unclear. The results of the present study suggested that ISCU and NFU1 might be risk factors for the development of AA, possibly due to excessive oxidative stress in mitochondria or alterations in mitochondrial function resulting from interactions between ISCU and NFU1.

Mitochondrial ribosomal proteins are encoded by nuclear genes and they play a role in protein synthesis within mitochondria. The mitochondrial ribosome is composed of a small 28 S subunit and a large 39 S subunit. Current research on mitochondrial ribosomal proteins primarily focuses on their association with tumor-related diseases, with very few studies reported on their connection to AA/AD. MRPL14, MRPL33, and MRPL52 are all protein components of the 39 S subunit of the mitochondrial ribosome. Studies have indicated that selective cleavage of exon 3-containing long isoform of MRPL33 (MRPL33-L) pre-mRNA is regulated by the key splicing regulator hnRNPK to mediate tumorigenesis, and that knockdown of hnRNPK replicates the phenotype of MRPL33-L deletion. The MRPL33-L is upregulated in human colorectal cancer tissues, while deletion of MRPL33-L leads to impaired proliferation and increased apoptosis in cancer cell lines [34]. In gastric tumor tissues, levels of MRPL33-L isoforms are significantly higher than those of MRPL33-S isoforms. The MRPL33-S isoform promoted chemosensitivity to epirubicin in gastric cancer, whereas the presence of MRPL33-L inhibited chemosensitivity to epirubicin [35]. Li et al. discovered that under hypoxic conditions, mitochondrial morphology was more complete in MRPL52 overexpressing breast cancer cells compared to the control cells. It was found that MRPL52 can elevate the level of mitochondrial autophagy in breast cancer cells, thereby stabilizing intracellular oxygen radicals and aiding in the resistance of apoptosis caused by excessive oxidative stress. This enables cancer cells to better survive in a hypoxic microenvironment. Additionally, MRPL52 mediates the activation of the oxygen radical/Notch1-Snail signaling pathway, promoting invasion and metastasis of breast cancer [36]. The relationship between mitochondrial ribosomal proteins and AA/AD is still not well studied. The results from this study suggested that MRPL14 and MRPL52 acted as protective factors for the development of AA/AD, while MRPL33 acted as a risk factor. These findings may be related to altered function of oxidative phosphorylation and production of ROS within mitochondria. Furthermore, they might also be associated with isoform variants and altered biological function of ribosomal proteins.

Cytochrome C oxidase (COX) is the terminal enzyme of the mitochondrial respiratory chain. It is a multisubunit enzyme complex that transfers electrons from cytochrome C to oxygen molecules, contributing to the formation of a proton electrochemical gradient across the inner mitochondrial membrane. COX5B serves as the peripheral subunit of the COX complex, maintaining its stability and influencing cell viability. Recent studies have suggested that COX5B may play a role in tumor progression. For example, COX5B has been found to be up-regulated in both breast cancer tissues and cells, and its deficiency inhibits breast cancer cell proliferation. However, it is important to note that COX5B deletion may have different effects on target cells and their surrounding environments [37]. Consistent with the tumorigenic action of COX5B, this study suggested that COX5B might be a risk factor for AD development. The tumorigenic properties of COX5B are thought to be related to its enhanced biological function leading to increased tumor cell proliferation [37]. Similarly, it was proposed

that the pathogenic mechanism in AD might also involve an enhanced function of COX5B resulting in increased phenotypic transformation of VSMCs. However, further research is needed to fully explore these potential associations.

Variations in proteins related to mitochondrial function can lead to mitochondrial dysfunction, which in turn can promote inflammation and phenotypic transformation of VSMCs and may promote the occurrence of AA/AD. The identification of these MPs may serve as potential biomarkers for AA/AD, offering valuable insights for the early prevention and treatment of these conditions. Furthermore, targeted therapies aimed at these MPs, as well as pharmacological strategies aimed at alleviating mitochondrial dysfunction have the potential to reverse the phenotypic transformation of VSMCs and offer options for the prevention and treatment of AA and AD [38]. One promising approach is "mitochondrial transplantation" which involves using exogenous mitochondria with normal function to replace dysfunctional mitochondria in damaged tissues, thereby restoring normal cellular function [39]. These effects could probably inhibit the onset and progression of AA/AD. Further research could be conducted on the following aspects in the future: (1) Investigating the levels of these MPs in the peripheral circulation of AA/AD patients to assess their potential as biomarkers for diagnosing AA/AD. (2) Examining the specific localization of these MPs within cells; Analyzing the interactions and biological effects among these MPs. (3) Exploring the correlations between these MPs and mitochondrial function, oxidative stress, inflammatory responses, and cell death; (4) Assessing the relationship between overexpression, deficiency or gene knockout of these MPs and phenotypic transformation of VSMCs, as well as their role in the occurrence and progression of AA/AD. (5) Additionally, focusing on the relationship between mitochondrial proteomics and AA/AD may provide valuable diagnostic and therapeutic insights into understanding mechanisms, diagnosis, and drug therapy related to AA/AD.

Our study aimed to investigate the potential causal relationship between proteins related to mitochondrial function and AA/AD using a two-sample MR method. The study had several strengths. Firstly, genetic variants, particularly single SNPs, were utilized as IVs in the MR analysis, enhancing the reliability of the causal relationships through Mendel's law of independent assortment. Secondly, potential confounding factors and reverse causation were minimized due to the fact that genetic variants precede disease onset and are not influenced by individual behavior. Thirdly, exploring causality between MPs and AA/AD may offer insights into targeting genes or gene products associated with mitochondrial biological functions, thereby informing strategies for preventing and treating AA/AD. However, there were some limitations in this study. Firstly, it was constrained by a lack of GWAS data on Asian and African populations, with a primary focus on European populations. This limitation may introduce inclusion bias and impact the generalizability of our findings. Secondly, while we employed MR to examine the causal relationship between MPs and AA/AD, we did not extensively explore underlying mechanisms in this study; therefore further investigations into mechanisms are warranted in subsequent studies.

Conclusion

This study employed two-sample MR analysis to unveil a potential causal relationship between MPs and AA/AD. The findings suggest that certain MPs may serve as either risk factors or protective factors for AA/AD, with their overexpression, absence, or functional abnormalities potentially linked to the onset and progression of these conditions. Targeting these MPs might hold promise for preventing both the initiation and advancement of AA/AD.

Abbreviations

AA	Aortic aneurysm
AAA	Abdominal aortic aneurysm
AD	Aortic dissection
ATP	Adenosine triphosphate
CEND1	Cell-cycle exit and neuronal differentiation 1
CI	Confidence interval
COX	Cytochrome C oxidase
COX5B	Cytochrome C oxidase subunit 5B, mitochondrial
GWAS	Genome-wide association study
ISCU	Iron-sulfur cluster assembly enzyme ISCU, mitochondrial
IVs	Instrumental variables
IVW	Inverse-variance weighted
Mfn2	Mitochondrial fusion protein 2
MPs	Mitochondrial proteins
MR	Mendelian randomization
MRPL14	39 S ribosomal protein L14, mitochondrial
MRPL33	39 S ribosomal protein L33, mitochondrial
MRPL52	39 S ribosomal protein L52, mitochondrial
NFU1	NFU1 iron-sulfur cluster scaffold homolog, mitochondrial
OR	Odds ratios
ROS	Reactive oxygen species
SE	Standard error
SNPs	Single-nucleotide polymorphisms
VSMCs	Vascular smooth muscle cells

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13019-025-03389-8.

Supplementary Material 1: **Supplementary table S1**. The baseline characteristics of the exposure variables.

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Author contributions

W L and L Y conceived and wrote the manuscript; L Z and W Q did statistical data analyses; Z G and C L reviewed the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki Declaration. Both the GEO and GWAS datasets are publicly available and have been approved by the appropriate ethical committee. As a result, additional ethical approval was not required for the analyses conducted in this study.

Consent for publication and patient's informed consent
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Cardiovascular Surgery, Fujian Medical University Union Hospital, Fuzhou 350000, Fujian province, China
[2]Department of Pathology, Fujian Province Second People's Hospital, The Second Affiliated Hospital of Fujian University of Traditional Chinese Medicine, Fuzhou 350000, Fujian province, China
[3]Union College of Clinical Medicine, Fujian Medical University Union Hospital, Fuzhou 350000, Fujian province, China
[4]Key Laboratory of Cardio-Thoracic Surgery, Fujian Medical University, Fujian Province University, Fuzhou 350000, Fujian province, China
[5]Engineering Research Center of Tissue and Organ Regeneration, Fujian Province University, Fuzhou 350000, Fujian province, China

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