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ORIGINAL RESEARCH

The Role of Mitochondrial DNA Copy Number in Neurodevelopmental Disorders: A Bidirectional Two-Sample Mendelian Randomization Study

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Background: Recent studies have indicated a possible connection between impaired mitochondrial bioenergetics and neurodevelopmental disorders (NDDs) such autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and Tourette's syndrome (TS). The precise causal relationship between them is yet uncertain. This study utilized bidirectional dual-sample Mendelian randomization (MR) analysis to investigate the causal relationship between Mitochondrial DNA (mtDNA) copy quantity, an indicator of mitochondrial malfunction, and NDDs.

Methods: The study utilized data from the Psychiatric Genomics Consortium (PGC) and IEU OpenGWAS Project database to investigate the relationship between mtDNA copy number and NDDs using MR method. The accuracy and confidence of our results were evaluated using the inverse-variance weighted (IVW) method along with sensitivity analyses such as weighted median, MR-Egger, and MR-PRESSO. Additionally, we conducted the same procedure in the reverse manner with instruments for NDDs.

Results: A notable correlation was discovered between mtDNA copy number and ASD (OR=0.78, 95% CI: 0.65–0.94, P=0.0077). Furthermore, confirmatory GWAS data analysis yielded similar results, which were even more significant (OR=0.80, 95% CI: 0.68–0.93, P=0.0047). However, bidirectional two-sample MR analysis did not reveal significant correlations between mtDNA copy number and ADHD or TS.

Conclusion: This study has uncovered a significant genetic causal relationship between mtDNA copy number and ASD. No associations were discovered between ADHD and TS during the investigation. Due to the inherent constraints of MR investigations, additional study is needed to definitively clarify these genetic causal links.

Keywords: neurodevelopmental disorders, mitochondrial DNA copy number, mendelian randomization, attention-deficit /hyperactivity disorder, autism spectrum disorder, Tourette syndrome

Introduction

Mitochondria are crucial organelles found in almost all human cells, responsible for important processes such signaling apoptosis, maintaining cellular homeostasis, creating metabolic chemicals, and generating energy.[1] Mitochondrial DNA (mtDNA) comprises the mitochondrial genome, which contains 2 ribosomal RNAs, 22 transfer RNAs, and 13 respiratory chain polypeptides.[2] One cell can hold as many as 7000 mitochondria, each with several copies of mtDNA.[3] The mtDNA copy number reflects the proportion of mitochondrial to nuclear DNA copies, acting as an indicator of mitochondrial quantity and malfunction, indirectly implying mtDNA damage.[4,5] Thus, mtDNA copy number can function as a readily available biomarker for mitochondrial function and general health.

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Neurodevelopmental disorders (NDDs) are a diverse set of illnesses that impact brain function and neural development, resulting in difficulties with cognition, communication, behavior, and motor skills.[6,7] These problems usually appear throughout childhood and continue into age.[8] NDDs in childhood, like autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and Tourette's syndrome (TS), play a significant role in disability-adjusted life years, ranging from 15% to 30%, and are key factors in health-related disabilities among young people.[9,10] Research has demonstrated various changes in mtDNA copy number in NDDs, suggesting a potential role of mtDNA in these disorders.[11–13] The precise relationship between mtDNA copy number and NDDs, such as a potential causal link or reverse causality, is yet unclear.

Mendelian randomization (MR) is an innovative genetic epidemiology research method that seeks to uncover causal connections between modifiable exposures and illness outcomes through the use of Single Nucleotide Polymorphisms (SNPs) as instrumental variables. MR operates like to a randomized controlled trial, assigning genetic variants to children randomly, leading to individuals being distributed randomly throughout various exposure levels.[14] MR assigns genotypes before birth to reduce the influence of external factors, allowing for the discovery of accurate causal relationships between adjustable exposures and particular illness outcomes being studied.[15]

Currently, there is no research that has used MR analysis to study the connection between mtDNA copy number and NDDs. This study addresses the gap by utilizing bidirectional two-sample MR method to investigate the reciprocal causal relationship between mtDNA copy number and vulnerability to neurodevelopmental disorders such ASD, ADHD, and TS.

Methods

Overall Study Design

The study design is depicted in Figure 1. We used MR analysis to investigate the causal link between mtDNA copy number and NDDs, and to assess the influence of NDDs on mtDNA copy number. The main idea of MR is to evaluate the causal link between a genetic factor affecting an exposure and a resulting outcome related to that exposure.[16] For a genetic instrument to be effective, it must satisfy three conditions: (i) SNPs are linked to the exposure, (ii) SNPs are not influenced by confounding variables, and (iii) SNPs impact the outcome only through the exposure. This study encompasses ADHD, ASD, and TS. All summary data were publicly accessible and authorized by relevant review bodies, eliminating the necessity for further ethical approval. The study's reporting follows the STROBE-MR criteria.[17]

Data Sources

The study obtained mtDNA copy number data from Chong et al, who developed a new method called "automatic mitochondrial copy (AutoMitoC)" and used it on 383,476 individuals of European descent from the UK Biobank study to identify common and rare genetic factors influencing mtDNA copy number.[18] This study is the most extensive genetic evaluation of mtDNA copy

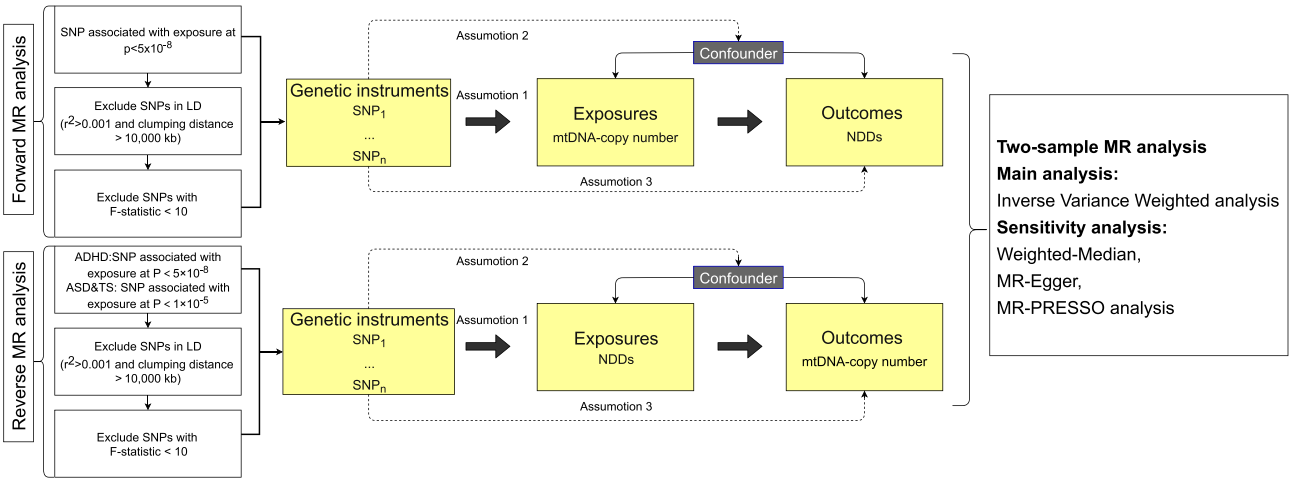

Figure 1 Flowchart of the data collection, processing, and analysis procedures of our study. All genetic instruments were single nucleotide polymorphisms (SNPs).

number to date, exceeding prior studies in scale.[19] Furthermore, mtDNA copy number information was obtained from a study by Longchamps et al, who performed a genome-wide association study (GWAS) on 465,809 Caucasian individuals from the Genome Epidemiology Alliance and the Royal Society of Medicine's Heart and Aging Research cohort.[20]

The Psychiatric Genomics Consortium (PGC) has conducted large-scale GWAS meta-analyses to advance the understanding of the genetic basis of psychiatric disorders.[21] Rigorous and thorough GWAS meta-analyses have been conducted for several psychiatric diseases such as ASD,[22] ADHD,[23] and TS,[24] which are pertinent to our research. The GWAS for ASD and ADHD combined samples from the Integrative Psychiatric Research (iPSYCH) consortium and PGC. iPSYCH samples were collected from a population cohort consisting of all children born in Denmark from 1981 to 2005, whereas PGC samples were gathered from several European cohorts. PGC conducted the GWAS for TS using samples from four European cohorts.

In this study, we first considered mitochondrial DNA copy number (mtDNA-CN) as the exposure and neurodevelopmental disorders (NDDs; ASD, ADHD, and TS) as the outcomes. Subsequently, we conducted a reverse analysis by treating NDDs as the exposures and mtDNA-CN as the outcome. This bidirectional design allowed us to comprehensively assess potential causal relationships between mtDNA-CN and NDDs, as summarized in the first three columns of Table 1.

Instruments Selection

We used strict selection criteria to find qualified instrumental variables, with a significance threshold for SNPs set at $P < 5\times10^{-8}$. We also performed rigorous linkage disequilibrium (LD) clustering to isolate independent SNPs ($r^2<0.001$ within 10000kb). Due to strict SNP inclusion criterion yielding less than 2 SNPs for ASD and TS in the reverse MR analysis, we decided to reduce the SNP inclusion barrier for ASD and TS to SNP $P<1\times10^{-5}$ to further investigate the association. The instrumental variables' strength related to exposure was assessed using the average SNP-specific F-statistic, obtained by dividing the square of β by the variance of the SNP-exposure association. Weak instrumental variables were identified as having F-statistics below 10 and were subsequently removed.[25]

Statistical Analyses

This study primarily used the inverse-variance weighted (IVW) approach for MR analysis. This approach offers a precise estimate of high performance, assuming the validity of all SNPs as genetic instruments.[26] Weighted median technique and MR-Egger method were used as sensitivity analyses to evaluate the strength of causal links and identify pleiotropy. If less than 50% of SNPs are faulty instruments, the weighted median technique can offer reliable estimations.[27] The MR-Egger approach is beneficial when all SNPs are derived from invalid instruments, up to 100%.[28] The Cochran's Q test was utilized to evaluate heterogeneity in SNP estimations. A significance level of $P < 0.05$ was judged significant in the heterogeneity test, leading to the selection of the IVW random-effects model as the final outcome. We utilized the MR-PRESSO method to identify potential outliers caused by pleiotropy and then conducted MR analysis again by excluding these outliers, using IVW, MR-Egger, and weighted median methods.[29]

The findings were presented as odds ratios (OR) along with their respective 95% confidence intervals (CI) or β (standard error). Statistical studies were conducted in R software (version 4.3.2) utilizing packages such as MR, MR-PRESSO, and Two-Sample MR. We applied Bonferroni correction to adjust for multiple comparisons between mtDNA copy number and neurodevelopmental disorders (and vice versa) ($n=6$ tests), setting a statistical significance threshold of 0.008 (0.05/6). $P \leq 0.05$ but not reaching the Bonferroni corrected significance threshold was suggestive of evidence for a potential causal association.

Table 1 Details From Genome-Wide Association Study in Our Study

Phenotypes	Study/Consortium	Cases/Controls	PubMed ID	Author
Mitochondrial DNA copy number	UK Biobank	383476	35023831	Chong M et al[18]
Mitochondrial DNA copy number	CHARGE and UK Biobank	465809	34859289	Longchamps RJ et al[20]
Attention-Deficit/Hyperactivity Disorder	PGC	30317	36702997	Demontis D et al[21]
Autism Spectrum Disorder	PGC	46351	30804558	Grove J et al[23]
Tourette Syndrome	PGC	14307	30818990	Yu D et al[25]

Results

Association Between mtDNA Copy Number and NDDs Risk

We initially examined the causal links between mtDNA copy number and NDDs such as ADHD, ASD, and TS. Two sets of mitochondrial DNA copy number data were examined, one containing 66 SNPs and the other containing 92 SNPs. Out of these SNPs, 26 were linked to ADHD, 58 to ASD, and 35 to TS. The explained variances were relatively small, and upon analysis using the F statistics for each chosen SNP, all variances exceeded 10, indicating a lack of potential weak instrument bias (see Supplementary Table 1). Table 2 summarizes the findings of MR-PRESSO test, horizontal pleiotropy test, heterogeneity test, and the outcomes of the three MR methods.

Our study revealed a strong connection between mtDNA copy number from Chong's GWAS and NDDs, specifically with ASD (OR=0.78, 95% CI: 0.65–0.94; P=0.0077). Furthermore, examination of Longchamps' GWAS data revealed a comparable and more statistically significant outcome (OR=0.80, 95% CI: 0.68–0.93; P=0.0047), with both P-values satisfying Bonferroni correction. There was no evidence of pleiotropy or heterogeneity seen in either case.

Chong's GWAS findings revealed that genetically predicted mtDNA copy number did not have a significant correlation with ADHD (OR=0.95, 95% CI: 0.80–1.11; P=0.508) or TS (OR=1.21, 95% CI: 0.84–1.73; P=0.31). Longchamps' GWAS study showed similar findings for ADHD (OR=0.95, 95% CI: 0.82–1.11; P=0.51) and TS (OR=1.16, 95% CI: 0.86–1.56; P=0.34) as presented in Table 2. Given the observed heterogeneity among IVs (Cochrane's Q statistic, $p<0.05$), the multiplicative random effects IVW method was used main method in MR analyses of the causal effect of mtDNA copy number on ADHD. Figure 2 displays scatter plots and leave-one-out analysis plots that demonstrate the forward MR analysis of each SNP-neurodevelopmental disorder connection.

Association Between NDDs and mtDNA Copy Number Risk

We conducted a reverse MR approach to examine the association between NDDs and mitochondrial DNA copy number. We used 26 SNPs as instrumental variables for ADHD, 58 SNPs for ASD, and 35 SNPs for TS. The genetic variants utilized as instrumental variables in the reverse MR analysis for neurodevelopmental disorders can be located in Supplementary Table 2. Our data did not yield substantial evidence to establish a link between ADHD, ASD, and TS with mtDNA copy number. Taking into account the observed heterogeneity among instrumental variables (as indicated by Cochrane's Q statistic, $p<0.05$), the multiplicative random effects inverse variance weighted (IVW) method was employed as the primary approach in the Mendelian randomization (MR) analysis aimed at elucidating the causal influence of ADHD on mitochondrial DNA (mtDNA) copy number. No evidence of horizontal pleiotropy was found in our findings. The sensitivity analysis yielded consistent results, as demonstrated in Table 3. Figure 3 displays scatter plots showing the reverse MR analysis and leave-one-out analysis plots for each SNP's correlation with mtDNA copy number in respect to NDDs.

Discussion

This work is the first to use bidirectional dual-sample MR to explore the relationship between mtDNA copy quantity, a genetic predictive factor, and NDDs. Findings reveal that mitochondrial DNA copy number acts as a safeguard against ASD. The investigation did not definitively indicate a causal relationship between ADHD, TS, and mtDNA copy number.

As the main generators of cellular energy, mitochondria are vulnerable to many internal and external influences, resulting in an accumulation of free radicals and oxidative stress, ultimately resulting in mitochondrial malfunction. Therefore, mitochondria are susceptible to oxidative damage, potentially leading to an increase in mtDNA copy number under oxidative stress conditions.[30,31] Previous research has indicated that mitochondrial dysfunction could play a role in the onset of NDDs.[32,33] Additional research is required to completely comprehend the exact connection between mtDNA copy number and neurodevelopmental disorders such as ASD, ADHD, and TS.

Elevated oxidative stress markers have been found in the brains and blood of individuals with autism.[34–37] However, the connection between mtDNA copy number and ASD is still a subject of controversy. Some studies have shown no link between mtDNA copy number and ASD in children, while others have indicated higher copy numbers of specific mitochondrial genes such as ND1, ND4, and CYTB in the brains of persons with autism.[11–13,32,33,38] The increasing copy

Table 2 MR Analyses of the Causal Effect of mtDNA Copy Number on NDDs

Exposure	Author	Outcome	SNPs	Methods	OR	Lower 95% CI	Upper 95% CI	Pvalue	MR-Egger Intercept (P value)	Cochran's Q test	P	Outliers from MR-PRESSO
mtDNA copy number	Chong M et al[18]	ADHD	47	Inverse variance weighted (multiplicative random effects)	0.946	0.802	1.116	0.508	0.747	65.947	0.023	NA
				MR Egger	1.002	0.680	1.478	0.991				
				Weighted median	1.093	0.881	1.356	0.418				
				MRPRESSO	0.946	0.922	0.970	0.511				
mtDNA copy number	Longchamps RJ et al[20]	ADHD	67	Inverse variance weighted (multiplicative random effects)	0.950	0.816	1.107	0.510	0.453	116.679	8.835e-05	NA
				MR Egger	1.063	0.764	1.478	0.717				
				Weighted median	1.076	0.888	1.303	0.455				
				MRPRESSO	0.950	0.931	0.969	0.513				
mtDNA copy number	Chong M et al[18]	ASD	56	Inverse variance weighted (fixed effects)	0.779	0.648	0.936	0.008	0.737	52.606	0.528	NA
				MR Egger	0.731	0.483	1.105	0.143				
				Weighted median	0.760	0.572	1.011	0.060				
				MRPRESSO	0.779	0.755	0.803	0.009				
mtDNA copy number	Longchamps RJ et al[20]	ASD	75	Inverse variance weighted (fixed effects)	0.798	0.683	0.933	0.005	0.866	79.672	0.277	NA
				MR Egger	0.819	0.588	1.140	0.240				
				Weighted median	0.799	0.628	1.018	0.069				
				MRPRESSO	0.798	0.780	0.817	0.008				
mtDNA copy number	Chong M et al[18]	TS	52	Inverse variance weighted (fixed effects)	1.206	0.840	1.730	0.310	0.537	50.448	0.456	NA
				MR Egger	0.954	0.418	2.174	0.911				
				Weighted median	1.105	0.634	1.929	0.724				
				MRPRESSO	1.206	1.156	1.256	0.314				
mtDNA copy number	Longchamps RJ et al[20]	TS	75	Inverse variance weighted (fixed effects)	1.157	0.858	1.560	0.340	0.291	68.945	0.613	NA
				MR Egger	1.551	0.836	2.876	0.168				
				Weighted median	1.064	0.665	1.703	0.796				
				MRPRESSO	1.157	1.123	1.190	0.330				

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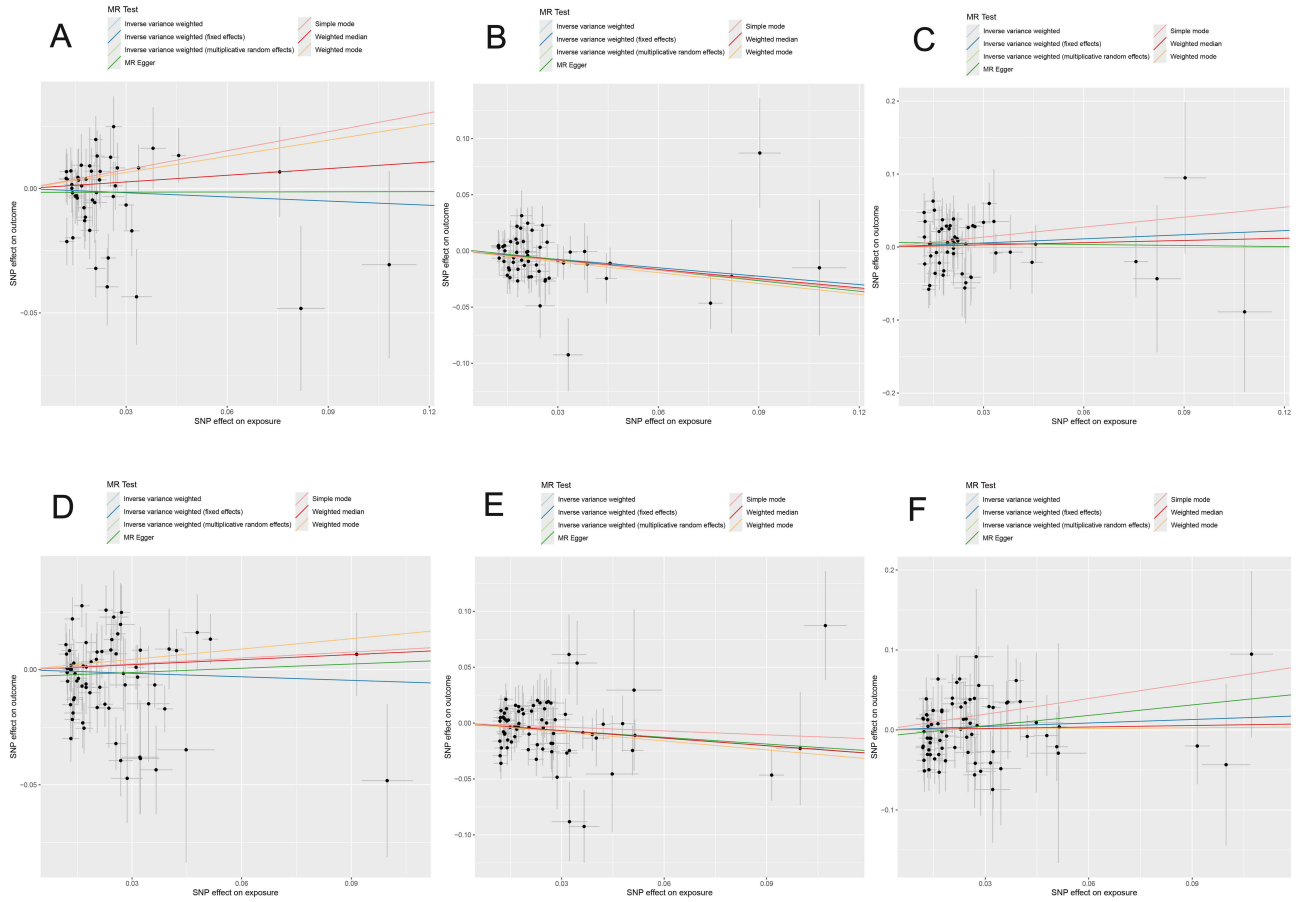

Figure 2 Scatter plot of the association between mtDNA copy number and NDDs. Each point on the scatter plot represents an SNP, and the lines extending from the points represent the 95% CI for the OR value of that SNP. The vertical axis represents the influence of SNPs on mtDNA copy number, with data from Chong et al (**A–C**) and Longchamps et al (**D–F**). The horizontal axis denotes the impact of SNPs on ADHD (**A** and **D**), ASD (**B** and **E**), and TS (**C** and **F**). The slope of the line indicates causality; a positive slope indicates a risk factor, while a negative slope indicates a protective factor.

numbers could be associated with heightened oxidative stress, impaired free radical removal, or reactive oxygen species generation by dysfunctional mitochondria. Chen et al discovered elevated amounts of mtDNA in individuals with autism, suggesting a possible link between mtDNA copy number and the risk of autism.[39] Most studies have focused on using peripheral blood as a substitute indicator for mitochondrial activity in ASD due to the constraints of traditional case-control studies and the difficulty in acquiring brain tissue for research. Peripheral blood mtDNA copy number may mirror brain tissue levels, however it is crucial to account for possible confounding factors when interpreting these results.[40,41] We used an MR technique to investigate the causal link between mtDNA copy number and ASD. Research indicates that increased mtDNA copy numbers may serve as a safeguard against ASD. We suggest that increased mtDNA copy numbers could work as a compensation mechanism to counter mitochondrial oxidative inadequacies, correcting energy deficits and perhaps offering protection against autism, based on a combination of current literature and our MR findings.

Recent findings indicate that mitochondrial dysfunction is at the root of ADHD pathophysiology. Research indicates that individuals with ADHD show multiple irregularities in mitochondrial function, such as decreased mitochondrial respiration, changes in ATP synthase 6/8 transcripts, reduced activity of mitochondrial complex V, disturbed mitochondrial membrane potential, and heightened oxidative stress [58]. A study found a notable connection between a certain mtDNA rs10398 A/G polymorphism and childhood ADHD.[42] Although some research has indicated elevated relative mtDNA copy numbers in individuals with ADHD,[43] our results did not confirm this association. We think this difference may be attributed to the limited sample sizes in earlier research, suggesting inherent limitations. Research on TS is minimal. Our study found no association between TS and mitochondrial DNA copy number similar to our results in ADHD.

Table 3 MR Analyses of the Causal Effect of NDDs on mtDNA Copy Number

Exposure	Outcome	Author	SNPs	Methods	OR	Lower 95% CI	Upper 95% CI	Pvalue	MR-Egger Intercept (P value)	Cochran's Q test	P	Outliers from MR-PRESSO
ADHD	mtDNA copy number	Chong M et al[18]	23	Inverse variance weighted (multiplicative random effects)	1.013	0.995	1.032	0.163	0.527	34.584	0.031	NA
				MR Egger	1.046	0.947	1.157	0.386				
				Weighted median	1.004	0.983	1.025	0.731				
				MRPRESSO	1.013	1.009	1.017	0.177				
ADHD	mtDNA copy number	Longchamps RJ et al[20]	23	Inverse variance weighted (multiplicative random effects)	1.015	0.993	1.038	0.187	0.591	51.968	1.930E-04	NA
				MR Egger	1.049	0.929	1.186	0.446				
				Weighted median	1.012	0.990	1.035	0.279				
				MRPRESSO	1.015	1.010	1.020	0.201				
ASD	mtDNA copy number	Chong M et al[18]	52	Inverse variance weighted (fixed effects)	1.002	0.994	1.011	0.592	0.111	44.221	0.703	NA
				MR Egger	1.019	0.997	1.041	0.095				
				Weighted median	1.002	0.990	1.014	0.796				
				MRPRESSO	1.002	1.001	1.003	0.578				
ASD	mtDNA copy number	Longchamps RJ et al[20]	52	Inverse variance weighted (fixed effects)	0.997	0.989	1.006	0.508	0.622	44.727	0.684	NA
				MR Egger	1.002	0.981	1.024	0.848				
				Weighted median	0.997	0.985	1.008	0.571				
				MRPRESSO	0.997	0.996	0.998	0.484				
TS	mtDNA copy number	Chong M et al[18]	24	Inverse variance weighted (fixed effects)	1.003	0.997	1.010	0.307	0.256	19.511	0.614	NA
				MR Egger	0.997	0.984	1.009	0.623				
				Weighted median	1.006	0.996	1.015	0.241				
				MRPRESSO	1.003	1.002	1.005	0.295				
TS	mtDNA copy number	Longchamps RJ et al[20]	24	Inverse variance weighted (fixed effects)	1.004	0.998	1.011	0.164	0.421	20.186	0.571	NA
				MR Egger	1.000	0.988	1.013	0.992				
				Weighted median	1.007	0.998	1.016	0.145				
				MRPRESSO	1.004	1.003	1.006	0.157				

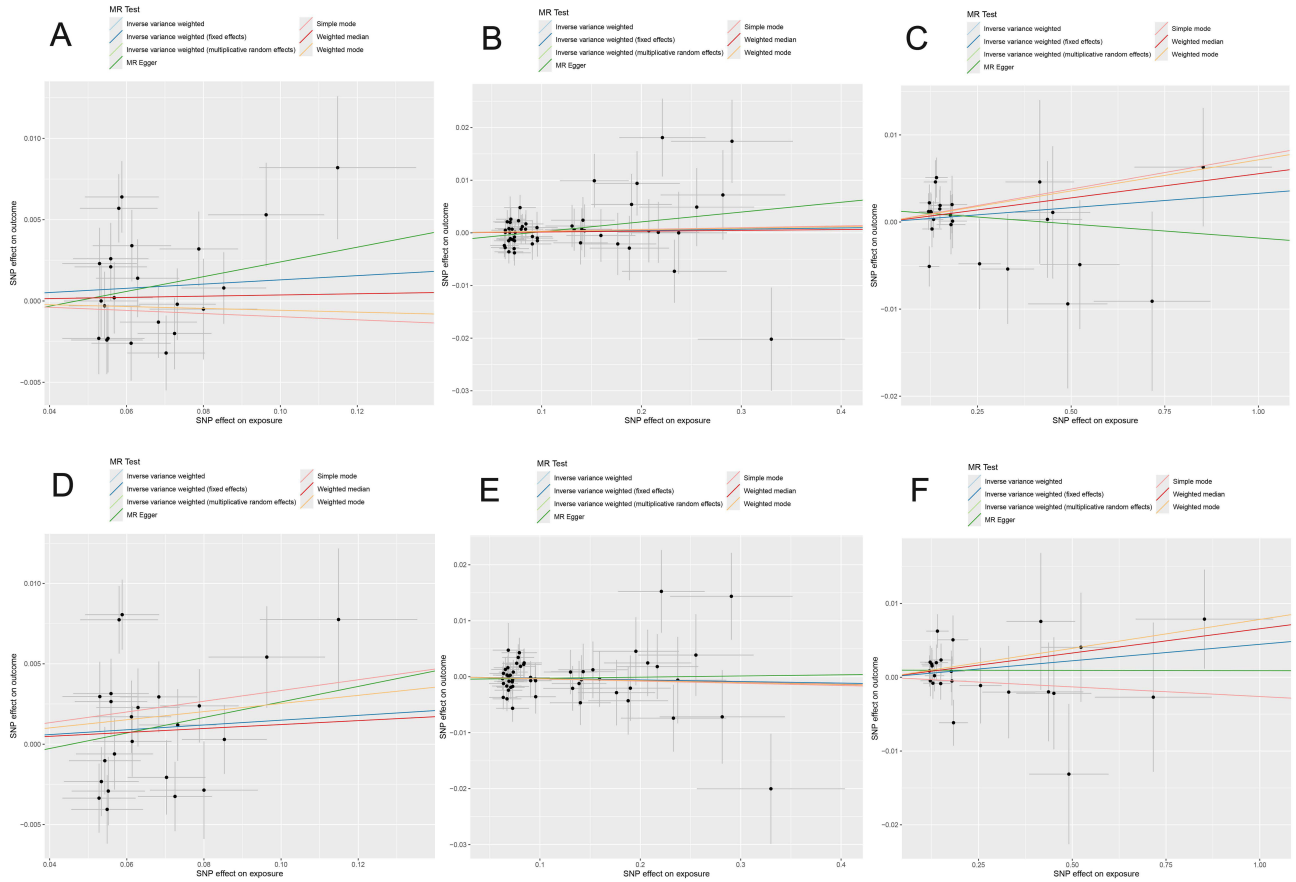

Figure 3 Scatter plot of the association between NDDs and mtDNA copy number. Each point on the scatter plot represents an SNP, and the lines extending from the points represent the 95% CI for the OR value of that SNP. The vertical axis denotes the impact of SNPs on ADHD (**A** and **D**), ASD (**B** and **E**), and TS (**C** and **F**). The horizontal axis represents the influence of SNPs on mtDNA copy number, with data from Chong et al (**A–C**) and Longchamps et al (**D–F**). The slope of the line represents causality; a positive slope represents a risk factor, and a negative slope represents a protective factor.

The study showcases multiple qualities. We performed a bidirectional two-sample MR approach, utilizing SNPs as instrumental variables to explore the causal relationship between mtDNA copy number and NDDs. This approach decreases residual confounding and minimizes the risk of reverse causality by utilizing the random allocation of alleles during gamete development. Our MR methodology utilized extensive genome-wide association study datasets, enhancing statistical efficiency in investigating the association between mitochondrial DNA copy number and neurodevelopmental disorders. Our research offers vital insights into the significance of mtDNA copy number in NDDs. This comprehension improves our understanding of the particular pathogenic pathways implicated in various disorders and their association with mitochondria, potentially resulting in the identification of more efficient biomarkers for clinical diagnosis.

Limitations

While our study offered helpful insights, it is crucial to recognize specific limits. Most of our study participants were from European populations, so it may not be suitable to apply conclusions from MR analysis to other ethnicities, particularly in places such as China where the incidence of NDDs is rising. Using findings from cross-ethnic analysis may lead to biases. Additional sample collection is required for a comprehensive GWAS on mitochondrial DNA copy number in Asian populations. The genetic tools for measuring mtDNA copy number may only account for a small amount of variance in physical characteristics, thus reducing the accuracy of our calculated relationships.

Conclusions

This study provides novel evidence supporting a potential causal association between mitochondrial DNA copy number and ASD, as assessed using a Mendelian randomization approach. Our findings highlight the possible role of mitochondrial function in the etiology of ASD, which may open new avenues for mechanistic research and potential therapeutic strategies. Nevertheless, further studies in diverse populations and functional experiments are warranted to validate and extend our results.

Abbreviations

NDDs, Neurodevelopmental disorders; ASD, Autism spectrum disorder; ADHD, Attention-deficit/hyperactivity disorder; TS, Tourette's syndrome; MR, Mendelian randomization; mtDNA, Mitochondrial DNA; PGC, Psychiatric Genomics Consortium; IVW, Inverse-variance weighted; iPSYCH, Integrative Psychiatric Research; LD, linkage disequilibrium; OR, Odds ratios; CI, Confidence intervals; GWAS, Genome-wide association study.

Ethical Approval Statement

This study was exempt from ethical review in accordance with Article 32, Sections 1 and 2 of the "Ethical Review Measures for Life Sciences and Medical Research Involving Human Subjects" issued by the Chinese government on February 18, 2023, as it utilized only [publicly available and/or anonymized data].

Disclosure

The authors declare that they have no competing interests.

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