

ALDH2 in stroke: from genetic susceptibility to therapeutic target: a narrative review

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Abstract

Stroke, a devastating neurological disorder resulting from acute cerebrovascular injury, represents the second most common cause of global mortality and a predominant contributor to long-term disability. Aldehyde dehydrogenase 2 (ALDH2) is a critical mitochondrial enzyme that plays a pivotal role in the metabolism of toxic reactive aldehydes, including 4-hydroxynonenal and acetaldehyde. The rs671 (Glu504Lys) polymorphism of ALDH2, which exhibits remarkably high prevalence in East Asian populations, has emerged as a genetic determinant of stroke susceptibility and recovery. This narrative review provides an overview of the multifaceted relationship between ALDH2 genetic variants and stroke. We summarize the reported associations of ALDH2 polymorphisms with stroke incidence and clinical outcomes, describe the neuroprotective mechanisms mediated by ALDH2 enzymatic activity, and discuss the dual role of ALDH2 in Mendelian randomization studies—as an instrumental variable in alcohol-related research and as a mediator of cerebrovascular risk with potential therapeutic relevance. Throughout, we emphasize the areas of uncertainty and the conflicting findings that remain in this field. By integrating epidemiological findings with mechanistic insights, this review offers a translational perspective on ALDH2 as a potential biomarker and a candidate target for stroke prevention and management.

Keywords: Aldehyde dehydrogenase 2, Genetic polymorphism, Mendelian randomization, Stroke

Introduction

Stroke is an acute-onset focal neurological deficit attributable to a cerebrovascular pathology, typically presenting as hemiparesis, dysarthria, sensory disturbances, aphasia, and visual field defects. Stroke is the second leading cause of death globally and the third most prevalent cause of disability worldwide.^[1] Globally, the

number of new incident cases of stroke increased to 11.9 million in 2021, representing a 70% increase from 1990. Concurrently, the number of stroke survivors rose to 93.8 million, marking an 86% increase.^[2] In China, stroke has become a major cause of death, accounting for approximately one-third of global stroke fatalities and imposing a heavy socioeconomic burden.^[3]

Risk factors for stroke are classically divided into modifiable and nonmodifiable categories, with age and sex representing the most significant nonmodifiable determinants. Epidemiological studies demonstrate a consistent doubling of stroke risk per decade beyond age 55.^[4] Sex-specific risk profile follows a triphasic pattern: young women (<30 years) exhibit elevated incidence attributable to pregnancy-related physiology and hormonal influences, middle-aged populations show male predominance, with risk convergence occurring in octogenarians (≥80 years).^[5] Modifiable risk factors, including hypertension, diabetes mellitus, dyslipidemia, smoking, and alcohol, account for most incident cases worldwide.^[6] This underscores the critical importance of early detection and intervention in global stroke prevention strategies. Rapid cerebral reperfusion is recognized as the therapeutic cornerstone of acute ischemic stroke (IS). First-line therapy includes intravenous thrombolysis with agents, such as alteplase or tenecteplase within approved time windows and endovascular thrombectomy.^[1] Emerging therapies, including advanced neuroimaging-guided patient selection, stem cell therapy, activity-based therapies, such as robot-assisted training, home-based telerehabilitation, and computerized language therapy, have provided new advances and directions for improving neurological functional recovery.^[7–10] Beyond conventional risk factors and therapeutic approaches, genetic polymorphisms affecting critical metabolic pathways are now established as pivotal determinants of stroke susceptibility and clinical outcomes. Emerging evidence suggests that genetic factors at the nexus of modifiable and nonmodifiable risk elements reflect a

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paradigm shift in our understanding that genetic risk itself exhibits plasticity—amenable to direct genetic modulation or through modification of gene-environment interactions.^[11] Within this conceptual framework, aldehyde dehydrogenase 2 (ALDH2), a mitochondrial enzyme crucial for detoxifying reactive aldehydes, has emerged as a key therapeutic target in stroke research.

As one of the 19 members of the ALDH family, ALDH2 is an important mitochondrial antioxidant enzyme responsible for metabolizing toxic aldehydes, including exogenous acetaldehyde and endogenous byproducts of lipid peroxidation, such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA).^[12] ALDH2 exerts protective effects in various diseases, such as cardiovascular diseases (CVDs), cancer, neurodegenerative disorders, and liver diseases.^[13–15] ALDH2 gene, located on chromosome 12 (12q24) and consisting 13 exons in humans, exhibits genetic polymorphism in human populations. The most common mutation in ALDH2 is a missense mutation occurring at codon 504 of exon 12, where guanine (G) is replaced by adenine (A), leading to the substitution of glutamic acid (Glu) with lysine (Lys). This mutation is known as Glu504Lys (rs671) and is associated with a marked reduction in the functional activity of ALDH2, which is highly prevalent in East Asian populations.^[16] Population studies have identified three ALDH2 genotypes: wild-type homozygotes (ALDH2*1/*1), heterozygous carriers (ALDH2*1/*2), and mutant homozygotes (ALDH2*2/*2). Because ALDH2 functions as a tetramer, the mutant subunit can exert a dominant-negative effect, so heterozygotes show substantially reduced rather than simply halved enzymatic activity; the residual activity also varies across experimental systems and should be reported from directly measured values. Mutant homozygotes show nearly complete loss of function.^[17] The same substitution is numbered Glu504Lys (precursor, including a 17-residue signal peptide) and Glu487Lys (mature protein); this paper uses the former throughout. In this review, we summarized the role of ALDH2 in stroke, including the association between ALDH2 genetic polymorphism and stroke susceptibility across different subtypes, ALDH2, stroke prognosis, and the neuroprotective mechanisms mediated by ALDH2, highlighting a complex interplay with alcohol. Furthermore, we summarize research utilizing ALDH2 as a genetic instrument in Mendelian randomization (MR) studies. Finally, we explored the translational potential of these findings, outlining how genetic insights into ALDH2 could pave the way for targeted therapeutic strategies and precision medicine for cerebrovascular diseases (Fig. 1).

Methods

Literature search strategy

This narrative review provides an overview of the role of ALDH2 in stroke. PubMed was searched for relevant English-language articles published up to May 2025 using combinations of terms related to “aldehyde dehydrogenase 2”, “stroke”, “cerebrovascular disease”, “reperfusion injury”, and “Mendelian randomization”. Reference lists of relevant articles and key reviews were also examined to identify additional studies.

Study selection and inclusion criteria

Articles were selected on the basis of their relevance to the scope of this narrative review. The review considered basic experimental studies, clinical and epidemiological studies, Mendelian randomization studies, and relevant reviews addressing ALDH2

polymorphisms, stroke risk and outcomes, neuroprotective mechanisms, and translational implications. Duplicate publications, conference abstracts, editorials without substantive evidence, and articles unrelated to ALDH2 or cerebrovascular disease were not considered. As this was a narrative review, no formal systematic study-selection or risk-of-bias assessment was performed.

Narrative structure

Relevant findings were summarized and synthesized narratively according to the major themes of the review. This review is structured to logically present the current evidence, beginning by outlining epidemiological and genetic association studies linking ALDH2 polymorphisms to stroke risk, delving into the molecular and cellular mechanisms underlying ALDH2-mediated neuroprotection, and discussing translational perspectives and the unique utility of ALDH2 in MR research. This structured approach aims to provide a comprehensive overview of ALDH2 as a critical biomarker and therapeutic target for stroke.

Role of ALDH2 polymorphism in stroke risk and outcomes

ALDH2 and risk of ischemic stroke

The rs671 polymorphism in ALDH2, a well-characterized functional variant, has been linked to an elevated risk of IS. In a systematic review, Jiang et al.^[18] demonstrated that the ALDH2 rs671 polymorphism was associated with an increased risk of IS in the Chinese population, suggesting that the rs671 mutation may serve as a risk factor for IS. This finding was further validated by Xu et al. in a meta-analysis involving 9 case-control studies on Chinese populations, which revealed a potential genetic link between the ALDH2 rs671 A allele and an increased risk of IS. They reported a statistically significant association, particularly in homozygotes (ALDH2*2/*2 vs. ALDH2*1/*1: odds ratio [OR]: 1.86; $P < 0.01$). However, these findings should be interpreted with caution. The overall credibility of the evidence exhibits a high degree of heterogeneity ($I^2 = 78.2\%$) in the dominant model (*2 vs. *1), indicating substantial inconsistency among the included studies.^[19] Mechanistically, researchers hypothesized that the ALDH2 rs671 variant impairs ALDH2 enzymatic activity, leading to dysregulated acetaldehyde metabolism and the accumulation of cytotoxic aldehydes, thereby increasing the risk of IS.

Beyond the well-characterized rs671, a spectrum of other ALDH2 polymorphisms contributes to IS susceptibility. Substantially elevated risks of IS were observed for rare homozygous mutations at loci such as rs886205 and rs7296651 under recessive inheritance models, with ORs of 5.99 and 8.93, respectively. Notably, the clinical significance of these associations exhibits exceptionally wide confidence intervals (CIs), indicating considerable imprecision in the effect estimates, and necessitates confirmation in larger cohorts.^[20] In male-dominant cohorts, polymorphisms, such as rs10744777, at chromosome 12q24 are established as independent risk factors, with variant genotypes conferring a nearly 2-fold increased risk (OR: 1.99). This risk appears to be further stratified by IS subtype, being most pronounced in large artery atherosclerosis (OR: 2.27).^[21]

This sex-specific risk pattern was further exemplified by the *2/*2 genotype. It is reproducibly identified as a significant risk factor for IS in males, with ORs consistently around

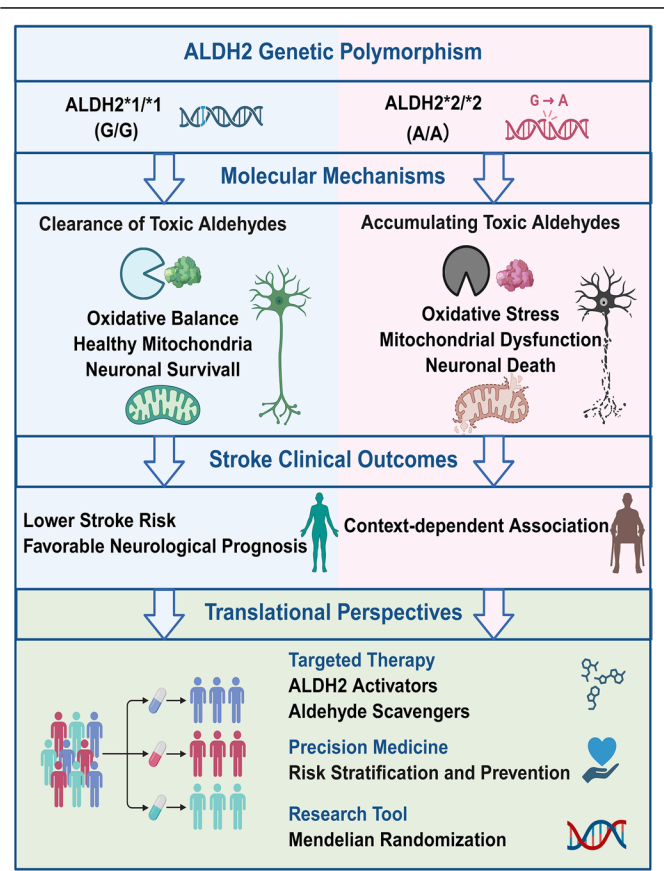


Figure 1. Schematic overview of the impact of ALDH2 on stroke. Image created using BioRender.com. The wild-type ALDH2*1/*1 (G/G) genotype promotes efficient clearance of toxic aldehydes, thereby maintaining oxidative balance, preserving mitochondrial integrity, and supporting neuronal survival, which is generally associated with lower stroke risk and a favorable neurological prognosis. In contrast, the inactive ALDH2*2/*2 (A/A) variant leads to accumulation of toxic aldehydes, oxidative stress, mitochondrial dysfunction, and neuronal death. However, the association between ALDH2 rs671 and stroke is heterogeneous and may be modified by sex, alcohol exposure, ancestry, vascular risk profile, and stroke subtype. The lower panel highlights translational perspectives, including targeted therapies with ALDH2 activators and aldehyde scavengers, precision medicine strategies for risk stratification and prevention, and the use of ALDH2 variants as genetic instruments in Mendelian randomization studies. ALDH2, aldehyde dehydrogenase 2; ALDH2*1/*1, wild-type homozygous genotype; ALDH2*2/*2, variant homozygous genotype.

1.9–2.0. In contrast, the same genotype appears to be neutral or even protective in females, as evidenced by a 55% risk reduction in a Hakka population study. The collective evidence thus highlights ALDH2 not as a monolithic risk factor, but as one whose effect is critically modified by sex.^[22–24] The proposed mechanisms, ranging from estrogen-mediated regulation to dimorphic oxidative stress responses, provide a plausible biological framework for these disparities, although definitive mechanistic proof remains an area for future investigation.^[25–29]

ALDH2 and susceptibility to other stroke subtypes

Beyond IS, growing evidence implicates ALDH2 genetic variants in susceptibility to other stroke subtypes, including hemorrhagic stroke and cerebral small vessel diseases (CSVDs), such as lacunar infarcts. In a case–control study of 329 patients with

hemorrhagic stroke and 515 controls, Zhang et al.^[30] demonstrated significantly increased risk associated with both the ALDH2*1/*2 (OR: 1.68; 95% CI: 1.15–2.45; *P* = 0.007) and ALDH2*2/*2 (OR: 2.52; 95% CI: 1.13–5.59; *P* = 0.024) genotypes. However, in a cross-sectional study of Japanese residents, Nagasawa et al.^[31] demonstrated that men carrying the ALDH2*1/*1 genotype had a significantly higher prevalence of multiple cerebral lacunar infarcts (OR: 3.73; 95% CI: 1.43–9.74). A possible explanation is that patients with the ALDH2*1/*1 genotype generate more nitric oxide than those with the ALDH2*1/*2 or *2/*2 genotypes. Consequently, increased nitric oxide production may elevate free radical generation, leading to greater microvascular damage.

ALDH2, alcohol, and stroke risk: a complex interplay

The interaction between ALDH2 genotype and alcohol metabolism significantly influences stroke risk through drinking behavioral modification. ALDH2 polymorphism is closely associated with drinking behavior. Because of reduced ability to metabolize alcohol, individuals carrying ALDH2 rs671 mutation experience adverse reactions after alcohol consumption, such as facial flushing, nausea, and tachycardia, known as “alcohol flush reaction,” which reduces the likelihood of habitual drinking. In contrast, individuals with the wild-type ALDH2 genotype are more tolerant to alcohol and potentially more likely to consume larger amounts of alcohol. Several studies have demonstrated that ALDH2 genotype influences the drinking behavior of patients with stroke. Yao et al.^[32] found that the ALDH2*2 allele served as a strong independent protective factor against heavy drinking history in Han Chinese men with stroke (OR: 0.072; 95% CI: 0.02–0.26). Higuchi et al.^[33] investigated 1300 Japanese patients with alcohol dependence and found that none of them were identified as ALDH2*2/*2 homozygotes, suggesting that this genotype may prevent against alcoholism development. Therefore, alcohol consumption may represent both a significant confounding variable and mediating factor in the relationship between ALDH2 polymorphisms and alcohol-related health outcomes, including stroke susceptibility. In a prospective cohort study conducted by Shin et al., the unadjusted risk of stroke among men carrying the wild-type ALDH2 allele was 2.02 times higher (95% CI: 1.03–3.99) compared with men carrying the mutant allele. However, after adjusting for alcohol consumption, this association was attenuated (hazard ratio: 1.99; 95% CI: 0.96–4.13), suggesting that alcohol acts as a confounding factor in the relationship between ALDH2 polymorphism and stroke risk.^[34] Qu et al. reported that ALDH2 mutant genotypes were negatively associated with severe intracranial vascular stenosis (OR: 0.44; 95% CI: 0.21–0.91; *P* = 0.03), and the heavy drinking rate in the ALDH2 mutant group was significantly lower than that in the wild-type group (18.6% vs. 38.0%, *P* = 0.01). Researchers have hypothesized that the ALDH2*2 allele confers protection against severe intracranial vascular stenosis by reducing alcohol intake.^[35] These findings reveal a gene–lifestyle interplay in which the interaction between ALDH2 genotype and alcohol consumption creates divergent risk profiles for cerebrovascular diseases.

ALDH2 and stroke prognosis

Existing evidence indicates that ALDH2 genetic variations significantly affect poststroke recovery and long-term prognosis. Qu et al.^[36] found that ALDH2*1/*2 and ALDH2*2/*2 genotypes independently predicted worse 90-day functional recovery

in 394 patients with acute IS (OR: 2.39; 95% CI: 1.05–5.46; $P = 0.039$), potentially mediated by impaired collateral circulation and compromised neuronal repair mechanisms. Additionally, Cheng et al.^[21] observed a borderline association between the rs886205*1/*2 genotypes and poststroke functional impairment in male patients (OR: 1.76; 95% CI: 1.03–3.00; $P = 0.057$). Yu et al. studied the association between ALDH2 genotype and neurocognitive assessment. They found that patients carrying the ALDH2 wild-type genotype exhibited significantly superior performance on the Montreal Cognitive Assessment compared with both mutant-type and heterozygous carriers ($P = 0.034$). The authors propose that this cognitive advantage may be mediated by ALDH2 in mitigating 4-HNE accumulation, thereby reducing oxidative stress-induced neurotoxicity.^[37] Yang et al. revealed that individuals carrying the ALDH2*2 allele exhibited significantly elevated levels of plasma 4-HNE and increased susceptibility to poststroke epilepsy. Through in vitro experiments, they found that ALDH2 overexpression partially reversed the 4-HNE-induced elevations in MDA, reactive oxygen species (ROS), and cellular apoptosis.^[38] These findings suggest that the modulation of ALDH2 activity may provide a promising neuroprotective strategy for stroke prognosis.

Mechanistic insights into ALDH2 in neuroprotection

Mitigation of reactive aldehydes accumulation and oxidative stress

ALDH2 demonstrates neuroprotective efficacy through the clearance of toxic aldehydes (eg, 4-HNE and MDA) and attenuation of oxidative stress. Both 4-HNE and MDA, the major end products of lipid peroxidation, not only reflect the intensity of oxidative stress but also participate in the regulation of various pathological processes. They can exacerbate cellular damage via the covalent conjugation of proteins, DNA, and lipids. Clinical data revealed that plasma 4-HNE levels were significantly higher in stroke patients than in individuals with no history of stroke, and this elevation persisted for ≥ 6 months poststroke, suggesting its potential utility as a diagnostic biomarker for stroke and prognosis assessment.^[39] Guo et al.^[39] found that serum 4-HNE levels were persistently elevated and negatively correlated with lifespan in stroke-prone spontaneously hypertensive rats. Similarly, Lee et al. reported that plasma 4-HNE levels were elevated in rats following middle cerebral artery occlusion, an experimental model of stroke. Moreover, exogenous 4-HNE administration aggravated cerebral ischemic injury and oxidative stress.^[40] Additionally, Wang et al. showed that rats subjected to 6 weeks of high-dose ethanol consumption before middle cerebral artery occlusion exhibited suppressed ALDH2 activity due to an altered isoelectric point. This results in elevated cerebral acetaldehyde and serum levels of reactive aldehydes, including 4-HNE and MDA, which worsen ischemic brain injury. These findings underscore the critical relationship between aldehyde accumulation and brain damage.^[41]

Enhancement of ALDH2 activity, such as using the ALDH2 activator Alda-1, significantly enhances ALDH2 catalytic efficiency, reduces 4-HNE and MDA accumulation, and consequently decreases cerebral infarct volume, while improving neurological outcomes.^[42, 43] Fu et al. showed that in a rat model of focal cerebral ischemia/reperfusion (I/R), treatment with Alda-1 markedly decreases cerebral 4-HNE and MDA levels. These changes were associated with reduced cerebral infarct volume,

decreased neuronal apoptosis and mortality, and improved neurological outcomes.^[42] Mao et al. reported that miR-193 overexpression in a rat cerebral I/R model suppressed ALDH2 activity, leading to the accumulation of toxic aldehydes, such as 4-HNE and MDA. This subsequently induces the dysfunction of tyrosine hydroxylase, causing tyrosine accumulation and insufficient dopamine synthesis, ultimately exacerbating brain damage. Thus, targeted inhibition of miR-193 to relieve its suppression of ALDH2 represents a potential novel therapeutic strategy for IS.^[44] Together, these findings highlight the critical protective role of ALDH2 in alleviating neuronal injury after stroke, at least in part, by clearing toxic aldehydes.^[39, 40]

Preservation of mitochondrial function

ALDH2 plays a pivotal role in maintaining mitochondrial integrity and function under ischemic conditions. In models of chronic cerebral hypoperfusion, ALDH2 overexpression significantly improved mitochondrial morphology and enhanced key bioenergetic parameters, including increased mitochondrial membrane potential, adenosine triphosphate production, and oxygen consumption rate. Mechanistically, these benefits are mediated through the SIRT1/ROS axis, as demonstrated by their abolition upon SIRT1 inhibition.^[45] In cerebral ischemia-reperfusion injury, ALDH2 also exerts protective effects by directly stabilizing mitochondrial function, suppressing harmful signaling, such as c-Jun N-terminal kinase activation, and thereby preventing downstream mitochondrial dysfunction.^[46] This establishes ALDH2 as a crucial upstream regulator in preserving mitochondrial homeostasis during ischemic stress.

Inhibition of cell death pathways, neuroinflammation, and cerebral edema

In addition to its canonical role in aldehyde detoxification, ALDH2 regulates multiple cell death pathways, including apoptosis, pyroptosis, ferroptosis, and autophagy, constituting a crucial neuroprotective mechanism. The antiapoptotic role of ALDH2 has been well-documented across multiple experimental systems. In in vitro studies using various neuronal models, including hypoxic PC12 cells with low endogenous ALDH2 expression as well as HT22 cells and mouse cortical neurons subjected to oxygen-glucose deprivation/reoxygenation (OGD/R), ALDH2 knockdown was shown to significantly potentiate apoptotic cell death. Conversely, ALDH2 overexpression significantly improved cell survival and reduced apoptosis.^[47, 48] In vivo, pharmacological activation of ALDH2 with Alda-1 reduced neuronal apoptosis in the cerebral cortex and hippocampal CA1 region and improved neurobehavioral scores in a rat cerebral I/R model.^[47] In a rat spinal cord I/R model, Liu et al.^[49] found that moderate ethanol intake (2.5% ethanol) increased ALDH2 expression and protected the spinal cord from I/R injury by inhibiting apoptosis. Additionally, ALDH2 overexpression attenuates multiple regulated cell death in OGD/R models using HT22 cells and mouse cortical neurons, including pyroptosis through the NOD-like receptor family pyrin domain-containing 3/gasdermin D pathway, ferroptosis via the acyl-CoA synthetase long-chain family member 4/glutathione peroxidase 4 pathway, and excessive autophagy activation mediated by the microtubule-associated protein 1 light chain 3 beta /p62 signaling pathway. Conversely, ALDH2 knockdown exacerbated these processes.^[48] Diao et al. reported that Alda-1 alleviated postresuscitation cardiac and neurological injuries in a porcine cardiac arrest resuscitation model. This protection was mediated, at least in part, through the inhibition of

ROS-induced the NOD-like receptor family pyrin domain-containing 3 inflammasome activation, leading to attenuated pyroptosis, as demonstrated by reduced expression of the pyroptotic executioner protein gasdermin D.^[50]

Furthermore, ALDH2 exerts neuroprotective effects through its anti-inflammatory action and edema attenuation. In a rat model of subarachnoid hemorrhage (SAH), pharmacological activation of ALDH2 using the compound LJ529 effectively inhibited mast cell-mediated release of proinflammatory cytokines (IL-6, TNF- α) through the A3 receptor (A3R)-PKC ϵ -ALDH2 signaling axis. This anti-inflammatory effect is associated with both improved short-term neurological function and long-term functional recovery.^[51] Additionally, ALDH2 plays a pivotal role in cerebral edema attenuation through aquaporin-4 (AQP4) regulation. ALDH2 activation markedly reduces 4-HNE accumulation in infarcted areas while downregulating AQP4 expression, thereby ameliorating cerebral edema severity and improving neurological outcomes.^[43] Collectively, these studies establish ALDH2 as a pivotal regulator of multiple pathological processes in cerebral ischemia, orchestrating cell survival pathways while modulating neuroinflammation and edema.

Mechanisms of ALDH2 regulation in cerebral ischemia/reperfusion

During cerebral ischemia and reperfusion, the activity and expression of mitochondrial ALDH2 are tightly regulated by multiple mechanisms. Although not fully elucidated, recent studies have demonstrated that ALDH2 regulation involves multiple mechanisms, including epigenetic modifications, microRNA-mediated suppression, posttranslational modifications, and pharmacological modulation. Qu et al. found that the low expression of ALDH2 in both HT22 cells and mouse cortical neurons subjected to OGD/R was associated with hypermethylation of its promoter region, while restoring ALDH2 levels by genetic overexpression significantly enhanced cell viability and suppressed multiple cell death pathways.^[48] In a rat cerebral I/R model, bioinformatics analysis identified ALDH2 as a direct target of miR-193, validated through in vitro and in vivo studies. MiR-193 directly targeted ALDH2 mRNA and reduced its expression, which triggered toxic aldehyde accumulation, disrupted tyrosine hydroxylase function, and ultimately worsened brain damage.^[44] Nene et al. investigated the role of protein kinase C- ϵ (PKC ϵ) mediated phosphorylation sites (T185, S279, T412) in regulating ALDH2 activity, employing in vitro enzymatic assays, site-directed mutagenesis, and evolutionary sequence analysis. S279 was identified as the critical PKC phosphorylation site for ALDH2 activation, which may shield the enzyme's catalytic cysteine (C302) from reactive aldehydes.^[52] Moreover, pharmacological activation of ALDH2, such as using Alda-1, moderate ethanol, or PKC activation, has been demonstrated to exert protective effects across different types of brain injury (eg, SAH and IS).^[39, 51] These findings highlight the complex regulatory network governing ALDH2 in cerebral ischemia. Further studies elucidating the underlying mechanisms may provide novel therapeutic strategies for mitigating brain injury.

ALDH2 and Mendelian randomization analysis

ALDH2 as a genetic instrument in Mendelian randomization studies

MR is an epidemiological approach that employs genetic polymorphisms as instrumental variables to establish causal

relationships, thereby overcoming the limitations of confounding and reverse causation prevalent in conventional observational studies.^[53] Because of the close relationship between ALDH2 polymorphism and drinking behavior, the ALDH2 rs671 variant (Glu504Lys) has been used as a valuable genetic instrument to investigate the causal effects of alcohol consumption on stroke and CVDs, especially in East Asian populations.^[54] However, because rs671 influences both alcohol consumption and acetaldehyde metabolism, it may violate the exclusion-restriction assumption when used as an instrument for alcohol exposure; estimates derived from rs671 should therefore be interpreted with attention to horizontal pleiotropy and the potential direct biological effects of ALDH2.

Landmark MR studies employing the ALDH2 rs671 variant have revolutionized our understanding of the cerebrovascular effects of alcohol, overturning the long-held belief that moderate alcohol consumption confers cerebrovascular protection. In the large prospective China Kadoorie Biobank Study, conventional epidemiological analyses initially showed a U-shaped association between self-reported alcohol intake and stroke risk in Chinese males. However, MR analysis using ALDH2 and ADH1B genotypes as instrumental variables of alcohol intake revealed a log-linear, dose-dependent association between genetically predicted alcohol consumption and stroke risk, with particularly strong effects on the incidence of intracerebral hemorrhage. Genetically predicted alcohol intake was also strongly and positively associated with systolic blood pressure, providing biological plausibility for the observed stroke risk associations.^[55] Similarly, a prospective cohort study of 40,386 Chinese men yielded discordant results between observational and genetic analyses: while self-reported alcohol consumption demonstrated a J-shaped association with CVD and all-cause mortality, MR analysis utilizing the ALDH2 rs671 variant revealed a linear dose-response relationship between genetically predicted alcohol intake and incident CVD, including both coronary heart disease and stroke. Notably, after excluding heavy drinkers, each standard drink increase in genetically predicted alcohol intake was associated with a striking 27% and 20% higher risk of incident CVD and all-cause mortality, respectively.^[56] Collectively, these genetic epidemiological data demonstrate a consistently harmful effect of alcohol consumption on cardiovascular and cerebrovascular outcomes, challenging the notion of any protective threshold.

Emerging genetic epidemiological evidence has further established ALDH2 as a pivotal tool for elucidating the heterogeneous effects of alcohol on cerebrovascular pathophysiology. A seminal cross-sectional MR study involving 682 Japanese male participants demonstrated that genetically predicted higher alcohol intake was positively associated with imaging markers of CSVD, such as lacunar infarcts, white matter hyperintensities, and microbleeds, but negatively associated with intracranial large artery stenosis.^[57] This divergence suggests distinct pathological mechanisms: the association with SVD may be partly mediated by alcohol-induced hypertension, whereas the association with intracranial large artery stenosis may involve alternative mechanisms.

ALDH2 in stroke pathogenesis: a Mendelian randomization perspective

ALDH2 plays a dual role in MR research—it is not only an instrumental variable for alcohol exposure but has also been examined as a potential risk factor and therapeutic target for

stroke and CVDs in a series of MR studies. Proteome-wide MR analysis reported that genetically predicted plasma ALDH2 protein levels were associated with an increased risk of IS in both East Asian and European populations.^[58] However, genetically predicted circulating protein abundance should not be equated with intracellular enzyme activity, and protein-level MR estimates may be influenced by assay-binding effects, tissue-specific expression, linkage disequilibrium, and pleiotropy. These findings therefore do not by themselves establish that ALDH2 activation increases or reduces stroke risk. Nevertheless, when considered alongside additional lines of evidence, research integrating brain proteomics with genomewide association study data for lacunar stroke indicated that altered ALDH2 protein abundance in the brain was a causal risk factor for lacunar stroke.^[59] Another MR study on CSVD also identified ALDH2 as a key druggable gene, with its causal association with CSVD validated in both blood and brain tissue, providing genetic support for targeting ALDH2 in CSVD therapy.^[60] A recent study integrating MR and bioinformatics analysis further supported the core role of ALDH2 in IS. This study not only confirmed the causal relationships of blood pressure and specific lipids (eg, low-density lipoprotein cholesterol, apoB) with IS but also identified ALDH2 as 1 of 5 key feature genes for constructing an IS risk prediction model through differential expression analysis and machine learning screening.^[61] The latest large-scale proteome MR study further reported a positive association between plasma ALDH2 protein concentration and IS risk, which has been interpreted as additional genetic support for ALDH2 as a candidate therapeutic target for IS.^[62] These findings highlight the role of ALDH2 in stroke pathogenesis, independent of its function in alcohol metabolism, positioning it as a promising druggable target.

Therapeutic translation: from genetic insights to clinical application

The ALDH2*2 allele has been implicated as a risk factor for stroke through genetic and MR evidence. This finding has prompted interest in ALDH2 as a candidate therapeutic target, with translational strategies aimed at restoring metabolic homeostasis in carriers of this loss-of-function allele; however, these strategies remain investigational.

Small-molecule activators and aldehyde scavengers

The development of small-molecule activators that can enhance the catalytic efficiency of ALDH2*2 enzyme or allosterically modulate its stability constitutes a promising therapeutic approach. While no specific ALDH2 activator has been approved for clinical use, compounds such as Alda-1 have provided a compelling proof-of-concept in preclinical models. Alda-1 has been shown to stabilize the active tetrameric form of ALDH2, reduce toxic aldehyde (eg, 4-HNE) accumulation, and mitigate infarct size in models of cerebral ischemia-reperfusion injury.^[42] Beyond direct enzyme activation, a complementary strategy employs aldehyde scavenging agents, such as N-acetylcysteine and hydralazine, to directly neutralize reactive aldehydes or acrolein, thereby reducing the burden on the impaired ALDH2 system.^[63, 64] The primary challenges for this approach include achieving sufficient blood-brain barrier penetration, ensuring long-term safety, and demonstrating clinical efficacy in human trials.

Gene therapy and genome-editing strategies

Gene therapy offers a potential long-term solution to address the genetic risk posed by variants, such as ALDH2*2. In theory, using adeno-associated virus as a delivery vehicle to introduce a functional ALDH2 gene could provide lasting correction of the associated metabolic defect in high-risk individuals.^[65] Another approach involves clustered regularly interspaced short palindromic repeats-based gene editing, which aims to directly repair specific genetic variants in somatic cells.^[66] However, significant hurdles remain, including the development of efficient and safe in vivo delivery vectors to the brain and cardiovascular system, the management of potential immune responses, and the ethical and safety barriers associated with permanent genetic modification. Current research focuses on overcoming these delivery and safety challenges.^[67, 68]

Precision prevention and risk stratification

ALDH2 genotyping could potentially be incorporated into stroke risk assessment to identify individuals with elevated susceptibility to oxidative and metabolic stress and, consequently, a heightened genetic risk of stroke. For such individuals—particularly ALDH2*2 carriers more intensive management of conventional risk factors may be considered, including strict control of blood pressure and lipid levels, smoking cessation, and alcohol avoidance. ALDH2 genotyping nevertheless remains a research strategy rather than an established clinical tool. Before it could be implemented in practice, studies would need to demonstrate incremental predictive value beyond conventional risk scores, clinical utility, safety, cost-effectiveness, and acceptability across relevant populations.

Conclusion

ALDH2 is biologically relevant to stroke through its role in clearing neurotoxic aldehydes and reducing oxidative stress, ameliorating mitochondrial dysfunction, attenuating neuroinflammation, and suppressing cell death and cerebral edema. However, the association between the rs671 polymorphism and stroke is modified by alcohol exposure, sex, ancestry, stroke subtype, and the method of measurement. Although ALDH2 is a candidate therapeutic target, the available evidence is not yet sufficient to recommend routine genotyping or ALDH2-directed therapy for stroke prevention or treatment. Further mechanistic and prospective clinical research is needed to clarify whether enhancing ALDH2 activity can improve stroke outcomes and, ultimately, reduce the global burden of stroke.

Conflict of interest statement

The authors declare no conflict of interest.

Author contributions

Dai T, Xue Y, Wang J, and Zhang R participated in conceptualization. Dai T, Li Y, and Jin C contributed to writing the original draft preparation. Li Y, Jin C, Li J, Wang Y, and Wang J contributed to literature search. Dai T, Li Y, Xue Y, Wang J, and Zhang R contributed to writing, review, and editing. Xue Y, Wang J, and Zhang R contributed to supervision. Jin C, Wang Y, and Zhang R contributed to funding acquisition. Jin C, Li J, Wang Y, and Zhang R participated in language corrections. All authors have read and agreed to the published version of the manuscript.

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