REVIEW ARTICLE

The role of ALDH2 and its substrates in central nervous system disorders

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ABSTRACT

Background: Aldehyde Dehydrogenase 2 (ALDH2) is a mitochondrial dehydrogenase enzyme primarily tasked with the detoxification of acetaldehyde produced from alcohol metabolism and endogenous aldehydes. These aldehyde compounds, such as 4-Hydroxynonenal (4-HNE) and 3,4-dihydroxyphenylacetaldehyde (DOPAL), are predominantly generated through lipid peroxidation and are known to form adducts with proteins, DNA, and lipids, thereby inducing neurotoxicity.

Methods: This review examines the role of ALDH2 in central nervous system (CNS) diseases by analyzing epidemiological studies and disease models. The focus is on understanding the impact of the ALDH2 rs671 G>A polymorphism, which reduces or eliminates enzyme activity.

Results: This genetic polymorphism of ALDH2 is closely associated with the onset of various central nervous system (CNS) diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), schizophrenia, and stroke potentially linked to the accumulation of aldehyde compounds within the CNS.

Conclusions: A deeper understanding of the mechanisms by which ALDH2 influences these diseases will enhance therapeutic strategies for patients carrying the ALDH2 rs671 polymorphism and also offer new insights for the prevention and diagnosis of these conditions.

Keywords: ALDH2; Alzheimer's disease; Parkinson's disease; Schizophrenia; Stroke; 4-HNE.

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1. INTRODUCTION

The central nervous system (CNS) serves as the core regulator for maintaining complex physiological and cognitive functions, playing a crucial role in overall health. In recent years, scientific research has delved into the regulatory mechanisms governing CNS homeostasis and the intricate molecular mechanisms underlying the onset of neurological disorders. The brain, serving as the 'command center' of the CNS, comprises only 2% of total body mass, yet accounts for a substantial 20% of the body's total energy consumption (1), making it the organ with the highest energy expenditure (2). This high energy demand is primarily met through the generation of reactive oxygen species (ROS), byproducts of oxidative phosphorylation in the abundant mitochondria within neurons(3). Healthy mitochondria counteract ROS-induced damage by providing effective antioxidant capabilities and metabolizing excessive ROS-induced α,β-unsaturated carbonyls.

However, at times, the production of ROS may surpass the compensatory capacity of mitochondria, leading to mitochondrial damage, subsequent initiation of mitochondrial dysfunction, apoptosis, and cell death(4, 5).

In the realm of neurobiology, the dysregulation of ROS and the resultant augmented oxidative stress, specifically manifesting as lipid peroxidation in mitochondria, lead to the formation of various aldehyde species that exhibit reactivity and toxicity(6). These aldehydes are prevalent not only in external environments, such as automobile emissions, chemical manufacturing processes, cosmetics, and food and beverages(7), but also originate within the body through the metabolic processes of neurotransmitters, amino acids, and lipids. Among them, 4-hydroxynonenal (4-HNE), acetaldehyde, acrolein, formaldehyde, 3,4-dihydroxyphenylacetaldehyde (DOPAL), and 3,4-dihydroxyphenylglycolaldehyde (PDPEGAL) are particularly crucial high-reactivity aldehyde species. The overabundance of 4-HNE, which has been the subject of extensive research, can disrupt cellular operations and precipitate apoptosis. These aldehydes are known to form conjugates with vital biomolecules, including DNA, proteins, and enzymes(8, 9), including mitochondrial electron transport chain proteins, proteasome proteins, and cytoskeletal proteins, leading to their functional impairment(6). The aggregation of these aldehydes, coupled with mitochondrial dysfunction, is implicated in the etiology of numerous neurological conditions such as Huntington's disease (HD), Alzheimer's disease (AD), Parkinson's disease (PD), various forms of dementia, ataxia, seizures, cerebral pathologies associated with hypertension, and ischemic stroke(10-12).

Mitochondrial aldehyde dehydrogenase 2 (ALDH2), as a critical detoxifying enzyme, is primarily responsible for metabolizing endogenous and exogenous aldehyde species. It not only functions in alcohol metabolism but also plays a crucial role in processes associated with oxidative stress(10, 13, 14). ALDH2 deficiency arises from a polymorphism in the 487th amino acid structure, where the substitution of glutamate with lysine results in an allelic gene change from G (wild-type allele *1) to A (mutant allele *2), significantly reducing the enzyme's catalytic activity, leading to the accumulation of toxic aldehyde species. However, the association between ALDH2 enzyme activity deficiency and the risk assessment of CNS disorders has not been extensively studied, and research models are lacking. Therefore, gaining a deeper understanding of the function and molecular regulatory mechanisms of ALDH2 in the CNS is crucial for unraveling the complexity of neurological disorders. This review aims to amalgamate existing studies, specifically concentrating on the involvement of ALDH2 in conditions such as AD, PD, schizophrenia, and stroke.

2. ALDH2 AND ENDOGENOUS ALDEHYDE METABOLISM

The ALDH2 enzyme, localized in mitochondria, is encoded by a gene situated on the 12q24 chromosome region. This gene is structured into 13 exons and translates into a 517 amino acid long polypeptide(15). The enzyme is targeted to the mitochondrial matrix by a mitochondrial targeting sequence at its N-terminus, comprising 17 amino acids. Upon arrival, this sequence is cleaved by mitochondrial proteases, a step critical for the enzyme's maturation(16). Within the genetic structure of ALDH2, researchers have identified a total of 535 single nucleotide polymorphisms (SNPs), with the rs671 SNP in exon 12 receiving significant scientific focus. The rs671 SNP encompasses a G to A nucleotide transition, resulting in an amino acid change from glutamate to lysine at the 487th position (E487K or E504K, accounting for the cleavage of the N-terminal sequence). This specific mutation leads to an alteration in hydrogen bonding, which adversely affects the binding site for NAD^+, a cofactor essential for aldehyde oxidation. Consequently, the rs671 variant is associated with reduced enzymatic activity of the dehydrogenase(17).

ALDH2 plays a pivotal role in metabolizing toxic aldehydes generated directly or indirectly from ethanol metabolism. Ethanol can be oxidized to acetaldehyde via the following pathways: in most cases, ethanol is oxidized to acetaldehyde by alcohol dehydrogenases (ADHs) in the cytoplasm; ethanol is oxidized through the microsomal ethanol-oxidizing system (MEOS); in the presence of catalase (CAT), ethanol is converted to acetaldehyde(18). ALDH2 further metabolizes acetaldehyde into acetate, which can either exit the cell through a carrier or undergo enzymatic transformation into acetyl-coenzyme A (acetyl-CoA) by cytosolic acetyl-CoA synthetase 2 (ACSS2)(19). Acetyl-CoA subsequently participates in several metabolic pathways, including the tricarboxylic acid (TCA) cycle and the oxidative phosphorylation (OXPHOS)

pathway(20), eventually being metabolized into water and carbon dioxide. Moreover, malondialdehyde (MDA), generated through lipid peroxidation, undergoes conversion to malonic semialdehyde facilitated by ALDH2. Subsequently, malonic semialdehyde further metabolizes into malonic acid (MOA). Alternatively, MDA can undergo a process where a carboxyl group is removed, resulting in its conversion into acetaldehyde. Under the influence of ALDH2, a portion of the 4-NHE generated during lipid peroxidation converts into 4-hydroxy-2-nonenoic acid (HNA). Concurrently, the remaining portion is catalyzed by other reductase enzymes, like glutathione-S-transferase (GST) and aldo-keto reductases (AKRs)/ADHs(21). The reduction or functional impairment of ALDH2 activity disrupts its protective role against aldehydes, resulting in escalated production of ROS and enhanced oxidative cellular damage, which may culminate in various human pathologies.

ALDH2, a vital enzyme in aldehyde detoxification, experiences a reduction in its dehydrogenase function due to the rs671 G>A polymorphism. This genetic variation results in an increased buildup of acetaldehyde and other endogenous aldehydes, often evidenced by the facial flushing observed post-alcohol intake. Intriguingly, this polymorphism is predominantly found in East Asian populations, with a prevalence of 30-50%, in stark contrast to less than 5% in individuals of European ancestry (22). Due to the activation of ALDH2 through multiple pathways and its close association with various pathophysiological processes, including its involvement in and impact on the occurrence and development of diverse diseases and metabolic processes, ALDH2, as a key regulatory enzyme in oxidative stress, has garnered increasing attention. Given its exceptionally high mutation rate in Asian populations, gaining a deeper understanding of the role of ALDH2 in the diseases of the Chinese population holds significant significance.

3. ALDH2 AND NEURODEGENERATIVE DISEASES

The cerebral environment, characterized by an abundance of polyunsaturated fatty acids, engenders a heightened oxygen presence within its lipid membranes. This aspect renders the brain more vulnerable to lipid peroxidation, a consequence of oxidative stress, as well as mitochondrial impairments and subsequent accumulation of aldehyde derivatives. These elements are crucial contributors to the deterioration of memory functions, cognitive deficits, and the pathogenesis of neurodegenerative disorders(23). This section reviews epidemiological evidences and findings from model-based studies related to ALDH2 in AD and PD, both of which are key neurodegenerative conditions, and assesses the implications of aldehyde buildup in these neurodegenerative states.

3.1. ALDH2 and Alzheimer's disease

Currently, Alzheimer's disease (AD) stands as the most widespread neurodegenerative disorder, yet efficacious treatment modalities remain elusive. Data reveals that in the United States alone, over 4.5 million individuals are afflicted with AD, a figure anticipated to escalate to 13.8 million by 2060 owing to increased longevity(24). The development of AD is closely associated with oxidative stress, a phenomenon commonly observed in neurodegenerative events(25). Studies have identified signs of oxidative stress in the blood, cerebrospinal fluid, and brain tissues of AD patients, highlighting its critical role in the disease's pathophysiology(26). ROS facilitate the production of various aldehyde by-products, among which 4-HNE is considered a fundamental signaling molecule in the pathology of AD. Similar to other aldehydes, the detoxification of 4-HNE depends on the enzymatic activity of ALDH2. When ALDH2 activity is inhibited, cells become more susceptible to damage induced by 4-HNE. Therefore, an enhanced comprehension of the role of ALDH2 in AD, especially its impact on oxidative stress and 4-HNE metabolism, could provide crucial insights for developing strategies to prevent or reverse the progression of AD.

The relationship between ALDH2 polymorphism and AD remains inconclusive, as evidenced by varied research outcomes summarized in Table 1. Two separate investigations conducted in South Korea, with participant pools of 690 and 510, respectively, did not establish a significant link between the ALDH2 polymorphism and AD(27, 28). Similarly, research within the Mongolian demographic of China also failed to recognize the ALDH2 gene as a contributing factor for AD(29). Conversely, outcomes from Japanese research present a contrasting picture. One study involving 447 individuals indicated the genotype frequency for the ALDH2*2 allele was significantly higher in the patients with AD than individuals without AD(30).

A cohort study in Japan, encompassing 271 AD patients, echoed these observations(31). Yet, another case-control study from Japan did not find any notable connection between the ALDH2*2 variant and AD(32).

Further investigations in China, particularly a study focusing on individuals over 90 years old, found a link between ALDH2*2 polymorphism and cognitive impairment(33). Additionally, two independent Chinese studies suggested that ALDH2*2 polymorphism is associated with an increased risk of AD(34, 35). A comprehensive meta-analysis, aggregating data from 1824 AD cases and 4300 controls across six Asian case-control studies, inferred that possession of the ALDH2*2 allele might escalate AD risk(29, 32, 34-37). Recently, an analysis of 469 human brain tissue samples from a Chinese brain tissue repository revealed that the ALDH2 rs671 variant increases amyloid-beta pathology, unveiling its molecular mechanism at the chemical bond and organelle levels for the first time. The connection between ALDH2 and AD, therefore, continues to be a topic of debate, underscoring the need for expanded research endeavors involving larger and more heterogeneous cohorts to arrive at more conclusive insights.

In AD research, the use of cellular and animal models has significantly contributed to elucidating the disease's underlying mechanisms. Initial investigations utilizing the PC12 cell line demonstrated that the presence of the ALDH2*2 allele results in diminished mitochondrial ALDH2 enzyme activity. These cells, when subjected to external 4-HNE, displayed an increased susceptibility, highlighting their vulnerability under oxidative stress conditions(38). Furthermore, research conducted on rat primary neuronal cells has shown that an elevation in ALDH2 enzymatic activity serves as a defensive mechanism, countering synaptic damage and oxidative stress triggered by 4-HNE(39).

In terms of animal models, transgenic AD mouse models have been pivotal for investigating the impact of oxidative stress on AD's pathological and behavioral aspects(40). These animal models are engineered to express mutated versions of the human amyloid precursor protein (APP) and harbor a detrimental mutation in mitochondrial ALDH2. Observations from this model include a reduction in lifespan, expedited amyloid plaque formation, enhanced tau protein phosphorylation, and increased gliosis. Furthermore, the DAL101 mouse model, distinguished by its deficient ALDH2 activity, represents an age-related dementia model. It displays progressively worsening pathological characteristics, mirroring chronic oxidative stress exposure(41).

The ALDH2$^{-/-}$ mouse model has proven to be exceptionally valuable in mimicking disease mechanisms and in the exploration of potential therapeutic approaches. In these models, the lack of ALDH2 activity results in an accumulation of 4-HNE, which in turn initiates a series of pathological changes characteristic of AD. These changes include an increase in Aβ and phosphorylated tau, a decline in synaptic proteins, cerebral atrophy, and cognitive deficits(42). Similar findings were also reported by Ohta *et al.* in 18-month-old ALDH2 knockout mice(43). Consequently, ALDH2$^{-/-}$ mice are increasingly recognized as an accurate animal model for sporadic AD, effectively replicating the oxidative stress-induced cognitive impairments observed in AD pathology(44-46). Intriguingly, dietary intervention with D-PUFAs in ALDH2$^{-/-}$ mice has shown a reversal in cognitive impairments, highlighting D-PUFAs as a promising approach for countering AD-related cognitive decline(47). Furthermore, the overexpression of ALDH2 in APP/PS1 mice resulted in significant cognitive improvements, emphasizing the critical importance of ALDH2 activity in AD pathology(48). These models have not only facilitated a more profound understanding of AD pathology but also opened avenues for the development of novel therapeutic strategies.

3.2. ALDH2 and Parkinson's disease

Parkinson's disease (PD) is a degenerative neurological condition marked by the progressive loss of dopaminergic neurons in the substantia nigra, resulting in involuntary movements and varying degrees of dementia. Epidemiologically, PD affects approximately 1% of the population aged over 65, with rates increasing to 4-5% in individuals aged over 85(49) . Given the increasing life expectancy in Asia, projections suggest that by 2030, the number of PD patients might reach approximately 5 million, accounting for nearly 60% of PD cases worldwide(50). The etiology of PD involves familial genetic defects, including mutations in α-synuclein, PARKIN, PINK1, DJ-1, and LRRK2 genes, as well as hereditary and environmental toxins(51). Additionally, oxidative stress in mitochondria is considered a significant influencing factor in

PD(52). Research has observed a decline in mitochondrial numbers in the dopaminergic neurons of the substantia nigra in PD patients, emphasizing the crucial role of mitochondrial integrity in these neurons and their vulnerability to the detrimental effects of aldehydes.

As previously mentioned, the mutation rate of ALDH2 rs671 can reach up to 50% in the East Asian population, making it crucial to understand the impact of rs671 polymorphism on the Asian PD population. Epidemiological studies, including one by Zhao *et al.* using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) analysis, have shown that the risk of PD in the Chinese population carrying the ALDH2 gene GA and AA genotypes is significantly higher than those with the GG genotype(34). However, a cohort study based on the Chinese population indicated no correlation between ALDH2 rs671 polymorphism and PD(53). A comprehensive meta-analysis encompassing 5315 samples and 9 case-control studies concluded that there is no notable correlation observed between the ALDH2 rs671 polymorphism and the risk of PD(54).A case-control study comparing 93 Parkinson's disease patients with different genotypes to 297 healthy controls found no association between the ALDH2 genotype and PD. Nonetheless, the patients with PD carrying ALDH2*2 allele are more likely to develop heightened daytime sleepiness and have difficulty in maintaining asleep. These results support the hypothesis that the accumulation of neurotoxic monoamine neurotransmitter aldehyde metabolites, resulting from decreased ALDH2 enzyme activity, could contribute to more severe loss of monoaminergic neurons, thus exhibiting more severe symptoms in wakefulness and sleep regulation(55). Moreover, PD patients with the ALDH2*1 allele genotype are more prone to depressive moods(56).

In the context of animal model research, α-synuclein has been identified as highly susceptible to modification by reactive aldehydes, potentially leading to the formation of neurotoxic oligomers. Specifically, in rat PD models, the administration of 6-hydroxydopamine (6-OHDA) has shown to significantly reduce ALDH activity in the striatum(57). Furthering this, Stott's research also found that 6-OHDA-induced striatal damage in mice led to a decrease in the number of dopaminergic neurons in the substantia nigra, accompanied by an increase in 4-HNE and DOPAL. Similarly, the ratio of DOPAL to dopamine significantly increased in the striatum of double gene knockout mice, indicating increased neurotoxicity, which mirrors the situation in the striatum of PD patients' post-mortem. The neurotoxin 1-methyl-4-phenylpyridinium ion (MPP^+) is commonly used to establish PD models, and in PC12 cells, treatment with MPP^+ increased the aldehyde load of MDA and 4-HNE. The specific inhibitor of ALDH2, daidzin, prevented the reduction in cell viability and the increase in apoptosis, oxidative stress, and aldehyde stress induced by MPP^+, indicating a protective role of ALDH2 against neurotoxicity and PD(58). Through the study of these models, we not only deepen our understanding of the pathophysiological mechanisms of PD but also provide possible directions for developing new therapeutic methods.

4. ALDH2 AND SCHIZOPHRENIA

Schizophrenia, a complex psychiatric condition manifesting in behavioral, emotional, and cognitive impairments, often follows a chronic trajectory(59). Since the 1930s, when Roy Hoskins first posited the influence of oxidative stress in the genesis and progression of schizophrenia, substantial attention has been focused on patients, whether untreated, in the early stages of the disease, or in its chronic phases(60-62). In the research conducted by Wang *et al.* immunohistochemical techniques were employed to measure HNE-protein adducts, revealing a 47% increase in HNE levels in the anterior cingulate cortex of post-mortem schizophrenic patients compared to healthy controls, thereby suggesting a correlation between schizophrenia and oxidative stress(63). Additionally, a tight association between ALDH2 and oxidative stress was observed; research involving 1316 schizophrenic patients and 1349 healthy controls indicated a positive correlation between the ALDH2 rs671 G A mutation and schizophrenia(64). Mounting evidence underscores the significant role of inflammation in schizophrenia. For instance, a study demonstrated that treatments with risperidone and amisulpride alleviated negative symptoms such as affective flattening and social withdrawal in schizophrenic patients with ALDH2 polymorphism(65). Proteome-wide association studies (PWAS), combined with MR and genetic colocalization analysis, further confirmed that an increase in ALDH2 protein abundance helps reduce feelings of loneliness in schizophrenic patients(66).

Current studies demonstrate significant differences between male and female schizophrenia patients in terms of disease onset, progression, treatment response, and brain structural abnormalities(67). In the study by Ramos-Loy *et al.*, a gender-based analysis of serum HNE levels in patients suffering from paranoid schizophrenia was performed. The findings revealed elevated 4-HNE concentrations in male patients compared to their female counterparts. This disparity could potentially be ascribed to the neuroprotective role of estrogens against oxidative stress, which are more prevalent in females(68). Additionally, the incidence of schizophrenia in women has been observed to rise during menopause, a phase characterized by a reduction in estrogen's protective influence(69). However, contrary results were reported by Wang *et al.* (63), whose immunohistochemical study did not identify any significant gender-based differences in HNE levels among schizophrenia patients. Thus, the existence of gender-specific variations in 4-HNE levels within schizophrenia remains an open question, highlighting the need for further focused investigations to clarify this important dimension.

5. ALDH2 AND STROKE

Stroke stands as a predominant contributor to chronic disability and mortality worldwide, a statement corroborated by robust evidence(70). Remarkably, China experiences the highest incidence and fatality rates associated with stroke globally, with staggering figures exceeding 2.4 million new cases and 1.1 million deaths each year. Significantly, ischemic stroke constitutes approximately 87% of these cases(71). This alarming prevalence underscores the imperative need for comprehensive genetic research in stroke susceptibility. Such studies are pivotal for the identification of high-risk demographics and the elucidation of the intricate etiological pathways of stroke. Additionally, these researches are instrumental in advancing predictive methodologies for stroke progression, thereby facilitating the development and application of efficacious preventative strategies within clinical paradigms(72, 73).

Ischemic stroke, characterized as a life-threatening cerebrovascular condition, has been the focus of recent scientific inquiry. Two groundbreaking genome-wide association studies (GWAS) have shed light on the genetic underpinnings of this ailment. These studies have pinpointed a correlation between genetic markers near the ALDH2 gene located on chromosome 12q24 and the onset of stroke(74). Intriguingly, the ALDH2 rs671 polymorphism has been identified as a genetic determinant in East Asian populations, primarily linked to the phenomenon of facial flushing post-alcohol consumption(75). An expansive study involving a cohort of over half a million participants further explored this link, indicating a heightened risk of stroke associated with alcohol consumption, especially in individuals with the ALDH2 rs671 G>A variant(10, 76, 77). Concurrently, dedicated research within the Han Chinese demographic, coupled with comprehensive meta-analyses focusing on the broader Chinese population, unanimously echoes these findings. They affirm the ALDH2 rs671 variant as a significant risk factor for ischemic stroke(78-80).

Expanding the scope of this research, a distinct study targeting the Hakka population in China, involving 329 hemorrhagic stroke patients alongside 515 control subjects, meticulously analyzed the ALDH2 rs671 genotypes. The study unveiled notable statistical disparities in the genotype and allele distributions between the patient cohort and control group. Crucially, it revealed a markedly amplified risk of hemorrhagic stroke in individuals carrying the ALDH2*2 allele. This revelation propels the hypothesis that the ALDH2 rs671 polymorphism might serve as a salient risk factor for hemorrhagic stroke, further enriching our understanding of stroke pathophysiology(81).

The role of chronic inflammation, tissue hypoxia, and oxidative stress in cerebrovascular diseases is substantial(82). ALDH2 emerges as a pivotal biological agent in this context, exerting protective effects against oxidative damage. It achieves this function by metabolizing aldehydes, compounds known for their toxicity, thereby mitigating oxidative stress. This function of ALDH2 is particularly pronounced in the case of ischemic stroke, where its impact is most palpable(83, 84). Additionally, research focusing on hemorrhagic stroke has unveiled a correlation between ALDH2 activity and key cardiovascular markers, namely systolic and diastolic blood pressure, as well as its association with serum levels of HDL and LDL cholesterol(85, 86). These findings collectively offer a more profound insight into the complex interplay between genetic factors and stroke, paving the way for targeted therapeutic interventions and preventive measures.

Cellular and animal model studies have indicated a potential link between ALDH2 and stroke. Through an unbiased proteomic search, the study revealed ALDH2 deficiency in stroke-prone spontaneously hypertensive rats (SHR-SP) compared to spontaneously hypertensive rats. It was concluded that the deficiency of ALDH2 plays a causative role in neuronal injury, as evidenced by in vitro studies showing that overexpression or activation of ALDH2 provides neuroprotection by clearing 4-HNE(87). Some studies suggest that ROS may act as potential activators of the JNK signaling pathway, triggering neuronal apoptosis during cerebral ischemia. Overexpression of ALDH2, by inhibiting JNK-induced caspase 3 activation and transcription, has been shown to reduce mitochondrial apoptosis in both in vivo rat focal cerebral ischemic model and in vitro neuronal cell oxygen-glucose deprivation/re-oxygenation (OGD/R) models of cerebral ischemia(88). These experimental findings suggest that ALDH2 might play a significant role in the development of ischemic stroke.

6. CONCLUSION

ALDH2 plays a key role not only in preventing and managing alcohol addiction but also in the intricate regulatory pathways of neurodegenerative ailments and cerebrovascular disorders (Figure 1) Diminished ALDH2 enzymatic activity leads to the accumulation of aldehydes, which are inherently volatile and strong electrophilic reagents. These toxic

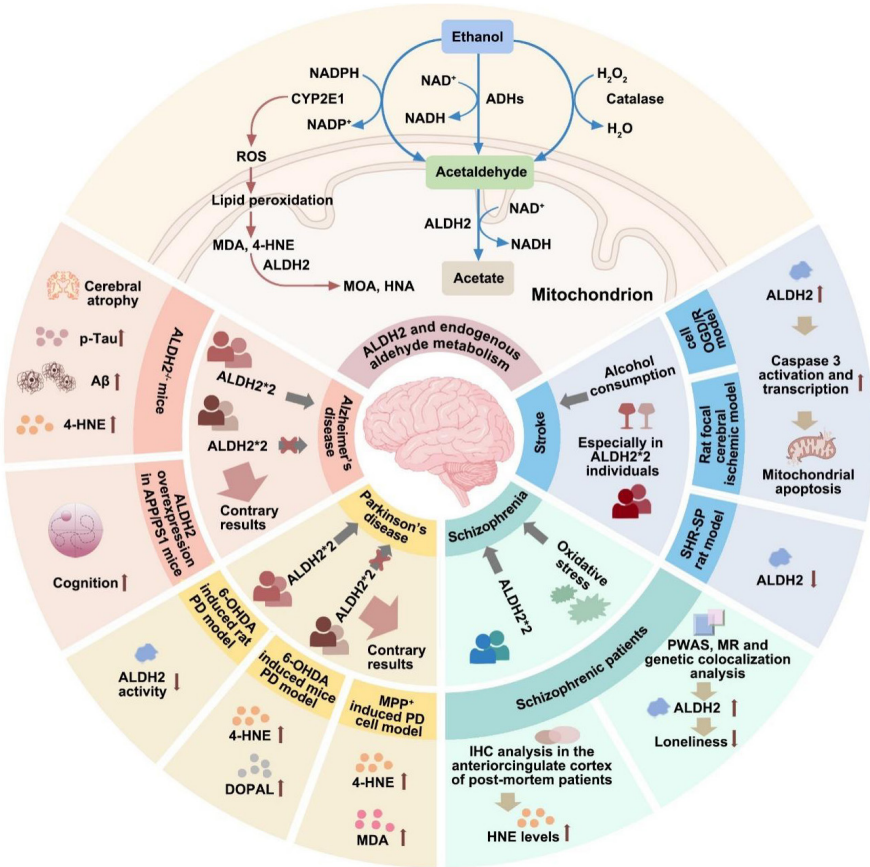

Figure 1. The effect of reduced ALDH2 enzyme activity and the role of ALDH2 in central nervous system diseases. 4-HNE, 4-Hydroxynonenal; 6-OHDA, 6-Hydroxydopamine; ADHs, Alcohol dehydrogenases; ALDH2, Aldehyde dehydrogenase 2; APP, Amyloid precursor protein; Aβ, Amyloid-beta peptides; CYP2E1, Cytochrome P450 2E1; DOPAL, 3,4-Dihydroxyphenylacetaldehyde; HNA, 4-Hydroxy-2-nonenoic acid; MDA, Malondialdehyde; MOA, Malonic acid; MPP^+, 1-Methyl-4-phenylpyridinium ion; OGD/R, Oxygen-glucose deprivation/re-oxygenation; MR, Magnetic resonance; PS1, Presenilin-1; p-Tau, Phosphorylated-tau protein; PWAS, Proteome-wide association studies; ROS, Reactive oxygen species; SHR-SP, Stroke-prone spontaneously hypertensive rats.

aldehydic substances readily interact with macromolecules, perturbing normal biological functions and leading to cellular dysregulation. Epidemiological studies, genetic analyses, and animal model research have pinpointed the excessive buildup of aldehydes as a key molecular mechanism implicated in the pathogenesis of neurodegenerative conditions and cerebrovascular incidents. Considering the crucial role of mitochondrial ALDH2 in the detoxification of aldehydes within the brain, a deeper exploration of its function and impact in neurodegenerative diseases, schizophrenia and stroke becomes imperative, particularly for East Asian populations where ALDH2 deficiency is widespread. The insights provided in this review illuminate the complex relationship among ALDH2, AD, PD, schizophrenia, and stroke, offering a nuanced understanding of these intricate interconnections.

Conflict of Interest Disclosures

The authors declare no conflicts of interest to declare.

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Nonstandard abbreviations and acronyms

Abbreviations	Full name
4-HNE	4-Hydroxynonenal
6-OHDA	6-Hydroxydopamine
Acetyl-CoA	Acetyl-coenzyme A
ACSS2	Acetyl-CoA synthetase 2
AD	Alzheimer's disease
ADHs	Alcohol dehydrogenases
AKRs	Aldo-keto reductases
ALDH2	Aldehyde dehydrogenase 2
APP	Amyloid precursor protein
CAT	Catalase
CNS	Central nervous system
DOPAL	3,4-Dihydroxyphenylacetaldehyde
GST	Glutathione-S-transferase
GWAS	Genome-wide association studies
HD	Huntington's disease
HNA	4-Hydroxy-2-nonenoic acid
MDA	Malondialdehyde
MEOS	Microsomal ethanol-oxidizing system
MOA	Malonic acid
MPP^+	1-Methyl-4-phenylpyridinium ion
OGD/R	Oxygen-glucose deprivation/re-oxygenation
OXPHOS	Oxidative phosphorylation
PCR-RFLP	Polymerase chain reaction-restriction fragment length polymorphism
PD	Parkinson's disease
PDPEGAL	3,4-Dihydroxyphenylglycolaldehyde
PWAS	Proteome-wide association studies
ROS	Reactive oxygen species
SHR-SP	Stroke-prone spontaneously hypertensive rats
SNPs	Single nucleotide polymorphisms
TCA	Tricarboxylic acid

References	Published time	Region	Case	Control	Association between ALDH2 rs671 polymorphism and disease	Disease type
Kim, *et al.* (89)	2004	South Korea	80	229	No association	AD
Shin, *et al.* (27)	2005	South Korea	37	473	No association	AD
Zhou, *et al.* (29)	2010	Mongolia	106	100	No association	AD
Komatsu, *et al.* (32)	2014	Japan	130	201	No association	AD
Kamino, *et al.* (36)	2000	Japan	477	477	Increases AD risk	AD
Ueno, *et al.* (31)	2022	Japan	271	492	Increases AD risk	AD
Wang, *et al.* (35)	2008	China	188	223	Increases AD risk	AD
Ma, *et al.* (34)	2016	China	115	236	Increases AD risk	AD
Jin, *et al.* (33)	2021	China	1114	805	Increases AD risk	AD
Chen, *et al.* (54)	2019	Asia	Meta		Increases AD risk	AD
Yu, *et al.* (56)	2021	China	114	—	Associated with PD non-motor symptoms	PD
Michel, *et al.* (90)	2014	Germany	9	12	ALDH2 activity was significantly increased in the putamen of PD patients	PD
Zhang, *et al.* (53)	2015	China	584	582	No association	PD
Zhao, *et al.* (91)	2016	China	115	214	Increases PD risk	PD
Lin, *et al.* (55)	2019	China	83	—	PD patients carrying allele rs671 (A) are more likely to experience impairment in the regulation of arousal and sleep	PD
Chen, *et al.* (54)	2019	—	Meta		No association	PD
Zheng, *et al.* (64)	2017	China	1316	1349	Related to risk for schizophrenia	Schizophrenia
Lee, *et al.* (65)	2015	China	95	—	The ALDH2*2 genotype predicts that DM drug therapy reduces negative symptoms in schizophrenia patients	Schizophrenia
Zhang, *et al.* (81)	2023	China	329	515	Increases hemorrhagic stroke	Stroke
Shi, *et al.* (80)	2022	China	4727	5029	Increases ischemic stroke	Stroke
Jiang, *et al.* (79)	2020	China	2762	2503	Increases ischemic stroke	Stroke
Xu, *et al.* (78)	2019	China	3236	2893	Increases ischemic stroke	Stroke

AD: Alzheimer's disease, PD: Parkinson's disease, DM: Dextromethorphan

Table 1. Association between ALDH2 rs671 polymorphism and diseases.

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REFERENCES

1. Mergenthaler P, Lindauer U, Dienel GA, Meisel A. Sugar for the brain: the role of glucose in physiological and pathological brain function. Trends in neurosciences. 2013;36(10):587-97.
2. Nunnari J, Suomalainen A. Mitochondria: in sickness and in health. Cell. 2012;148(6):1145-59.
3. Rios L, Pokhrel S, Li SJ, Heo G, Haileselassie B, Mochly-Rosen D. Targeting an allosteric site in dynamin-related protein 1 to inhibit Fis1-mediated mitochondrial dysfunction. Nature communications. 2023;14(1):4356.
4. Kumar S, Chhabra V, Shenoy S, Daksh R, Ravichandiran V, Swamy R, Kumar N. Role of Flavonoids in Modulation of Mitochondria Dynamics during Oxidative Stress. Mini reviews in medicinal chemistry. 2023.
5. Borbolis F, Mytilinaiou E, Palikaras K. The Crosstalk between Microbiome and Mitochondrial Homeostasis in Neurodegeneration. Cells. 2023;12(3).
6. Schneider C, Porter NA, Brash AR. Routes to 4-hydroxynonenal: fundamental issues in the mechanisms of lipid peroxidation. The Journal of biological chemistry. 2008; 283(23):15539-43.
7. Lachenmeier DW, Kanteres F, Rehm J. Carcinogenicity of acetaldehyde in alcoholic beverages: risk assessment outside ethanol metabolism. Addiction (Abingdon, England). 2009;104(4):533-50.
8. Di Domenico F, Tramutola A, Butterfield DA. Role of 4-hydroxy-2-nonenal (HNE) in the pathogenesis of alzheimer disease and other selected age-related neurodegenerative disorders. Free radical biology & medicine. 2017;111:253-61.
9. Milkovic L, Zarkovic N, Marusic Z, Zarkovic K, Jaganjac M. The 4-Hydroxynonenal-Protein Adducts and Their Biological Relevance: Are Some Proteins Preferred Targets? Antioxidants (Basel, Switzerland). 2023;12(4).
10. Im PK, Wright N, Yang L, Chan KH, Chen Y, Guo Y, *et al.* Alcohol consumption and risks of more than 200 diseases in Chinese men. Nature medicine. 2023;29(6):1476-86.
11. Deng L, Ding L, Duan X, Peng Y. Shared molecular signatures between coronavirus infection and neurodegenerative diseases provide targets for broad-spectrum drug development. Scientific reports. 2023;13(1):5457.
12. Cronin-Furman EN, Borland MK, Bergquist KE, Bennett JP, Jr., Trimmer PA. Mitochondrial quality, dynamics and functional capacity in Parkinson's disease cybrid cell lines selected for Lewy body expression. Mol Neurodegener. 2013;8:6.
13. Murphy TC, Amarnath V, Gibson KM, Picklo MJ, Sr. Oxidation of 4-hydroxy-2-nonenal by succinic semialdehyde dehydrogenase (ALDH5A). Journal of neurochemistry. 2003;86(2):298-305.
14. Seike T, Chen CH, Mochly-Rosen D. Impact of common ALDH2 inactivating mutation and alcohol consumption on Alzheimer's disease. Front Aging Neurosci. 2023;15:1223977.
15. Raghunathan L, Hsu LC, Klisak I, Sparkes RS, Yoshida A, Mohandas T. Regional localization of the human genes for aldehyde dehydrogenase-1 and aldehyde dehydrogenase-2. Genomics. 1988;2(3):267-9.
16. Braun T, Bober E, Singh S, Agarwal DP, Goedde HW. Evidence for a signal peptide at the amino-terminal end of human mitochondrial aldehyde dehydrogenase. FEBS letters. 1987;215(2):233-6.
17. Yoshida A, Huang IY, Ikawa M. Molecular abnormality of an inactive aldehyde dehydrogenase variant commonly found in Orientals. Proc Natl Acad Sci U S A. 1984;81(1):258-61.
18. Gao J, Hao Y, Piao X, Gu X. Aldehyde Dehydrogenase 2 as a Therapeutic Target in Oxidative Stress-Related Diseases: Post-Translational Modifications Deserve More Attention. International journal of molecular sciences. 2022;23(5).
19. Serio RN, Lu C, Gross SS, Gudas LJ. Different Effects of Knockouts in ALDH2 and ACSS2 on Embryonic Stem Cell Differentiation. Alcoholism, clinical and experimental research. 2019;43(9):1859-71.
20. Shi L, Tu BP. Acetyl-CoA and the regulation of metabolism: mechanisms and consequences. Current opinion in cell biology. 2015;33:125-31.
21. Zhong H, Yin H. Role of lipid peroxidation derived 4-hydroxynonenal (4-HNE) in cancer: focusing on mitochondria. Redox biology. 2015;4:193-9.
22. Zambelli VO, Gross ER, Chen CH, Gutierrez VP, Cury Y, Mochly-Rosen D. Aldehyde dehydrogenase-2 regulates nociception in rodent models of acute inflammatory pain. Science translational medicine. 2014;6(251):251ra118.
23. Haigis MC, Yankner BA. The aging stress response. Molecular cell. 2010;40(2):333-44.

24. 2022 Alzheimer's disease facts and figures. Alzheimer's & Dementia: The Journal of the Alzheimer's Association. 2022;18(4):700-89.
25. Yi L, Luo M, Wang M, Dong Z, Du Y. Fangchinoline alleviates cognitive impairments through enhancing autophagy and mitigating oxidative stress in Alzheimer's disease models. Frontiers in Cell and Developmental Biology. 2023;11:1288506.
26. Aquilani R, Cotta Ramusino M, Maestri R, Iadarola P, Boselli M, Perini G, *et al*. Several dementia subtypes and mild cognitive impairment share brain reduction of neurotransmitter precursor amino acids, impaired energy metabolism, and lipid hyperoxidation. Front Aging Neurosci. 2023;15:1237469.
27. Shin IS, Stewart R, Kim JM, Kim SW, Yang SJ, Shin HY, *et al*. Mitochondrial aldehyde dehydrogenase polymorphism is not associated with incidence of Alzheimer's disease. International Journal of Geriatric Psychiatry. 2005;20(11):1075-80.
28. Kim JM, Stewart R, Shin IS, Jung JS, Yoon JS. Assessment of association between mitochondrial aldehyde dehydrogenase polymorphism and Alzheimer's disease in an older Korean population. Neurobiology of Aging. 2004;25(3):295-301.
29. Zhou S, Huriletemuer, Wang J, Zhang C, Zhao S, Wang de S, *et al*. Absence of association on aldehyde dehydrogenase 2 (ALDH2) polymorphism with Mongolian Alzheimer patients. Neuroscience Letters. 2010;468(3):312-5.
30. Ohta S, Ohsawa I, Kamino K, Ando F, Shimokata H. Mitochondrial ALDH2 deficiency as an oxidative stress. Annals of the New York Academy of Sciences. 2004;1011:36-44.
31. Ueno M, Yoshino Y, Mori H, Funahashi Y, Kumon H, Ochi S, *et al*. Association Study and Meta-Analysis of Polymorphisms and Blood mRNA Expression of the ALDH2 Gene in Patients with Alzheimer's Disease. Journal of Alzheimer's Disease : JAD. 2022;87(2):863-71.
32. Komatsu M, Shibata N, Ohnuma T, Kuerban B, Tomson K, Toda A, *et al*. Polymorphisms in the aldehyde dehydrogenase 2 and dopamine β hydroxylase genes are not associated with Alzheimer's disease. Journal of Neural Transmission (Vienna, Austria : 1996). 2014;121(4):427-32.
33. Jin X, Long T, Chen H, Zeng Y, Zhang X, Yan L, Wu C. Associations of Alcohol Dehydrogenase and Aldehyde Dehydrogenase Polymorphism With Cognitive Impairment Among the Oldest-Old in China. Front Aging Neurosci. 2021;13:710966.
34. Ma L, Lu ZN. Role of ADH1B rs1229984 and ALDH2 rs671 gene polymorphisms in the development of Alzheimer's disease. Genetics and Molecular Research : GMR. 2016;15(4).
35. Wang B, Wang J, Zhou S, Tan S, He X, Yang Z, *et al*. The association of mitochondrial aldehyde dehydrogenase gene (ALDH2) polymorphism with susceptibility to late-onset Alzheimer's disease in Chinese. Journal of the Neurological Sciences. 2008;268(1-2):172-5.
36. Kamino K, Nagasaka K, Imagawa M, Yamamoto H, Yoneda H, Ueki A, *et al*. Deficiency in mitochondrial aldehyde dehydrogenase increases the risk for late-onset Alzheimer's disease in the Japanese population. Biochemical and Biophysical Research Communications. 2000;273(1):192-6.
37. Wu YY, Lee YS, Liu YL, Hsu WC, Ho WM, Huang YH, *et al*. Association Study of Alcohol Dehydrogenase and Aldehyde Dehydrogenase Polymorphism With Alzheimer Disease in the Taiwanese Population. Frontiers in Neuroscience. 2021;15:625885.
38. Ohsawa I, Kamino K, Nagasaka K, Ando F, Niino N, Shimokata H, Ohta S. Genetic deficiency of a mitochondrial aldehyde dehydrogenase increases serum lipid peroxides in community-dwelling females. Journal of Human Genetics. 2003;48(8):404-9.
39. Bai J, Mei Y. Overexpression of aldehyde dehydrogenase-2 attenuates neurotoxicity induced by 4-hydroxynonenal in cultured primary hippocampal neurons. Neurotoxicity Research. 2011;19(3):412-22.
40. Kanamaru T, Kamimura N, Yokota T, Iuchi K, Nishimaki K, Takami S, *et al*. Oxidative stress accelerates amyloid deposition and memory impairment in a double-transgenic mouse model of Alzheimer's disease. Neuroscience Letters. 2015;587:126-31.
41. Nakashima Y, Ohsawa I, Konishi F, Hasegawa T, Kumamoto S, Suzuki Y, Ohta S. Preventive effects of Chlorella on cognitive decline in age-dependent dementia model mice. Neuroscience Letters. 2009;464(3):193-8.
42. D'Souza Y, Elharram A, Soon-Shiong R, Andrew RD, Bennett BM. Characterization of Aldh2 (-/-) mice as an age-related model of cognitive impairment and Alzheimer's disease. Molecular Brain. 2015;8:27.

43. Ohta S, Ohsawa I. Dysfunction of mitochondria and oxidative stress in the pathogenesis of Alzheimer's disease: on defects in the cytochrome c oxidase complex and aldehyde detoxification. Journal of Alzheimer's Disease: JAD. 2006;9(2):155-66.
44. Mehder RH, Bennett BM, Andrew RD. Age-Related Neuronal Deterioration Specifically Within the Dorsal CA1 Region of the Hippocampus in a Mouse Model of Late Onset Alzheimer's Disease. Journal of Alzheimer's Disease : JAD. 2021;79(4):1547-61.
45. Ghoweri AO, Gagolewicz P, Frazier HN, Gant JC, Andrew RD, Bennett BM, Thibault O. Neuronal Calcium Imaging, Excitability, and Plasticity Changes in the Aldh2-/- Mouse Model of Sporadic Alzheimer's Disease. Journal of Alzheimer's Disease : JAD. 2020;77(4):1623-37.
46. Luo J, Lee SH, VandeVrede L, Qin Z, Ben Aissa M, Larson J, *et al*. A multifunctional therapeutic approach to disease modification in multiple familial mouse models and a novel sporadic model of Alzheimer's disease. Mol Neurodegener. 2016;11:35.
47. Elharram A, Czegledy NM, Golod M, Milne GL, Pollock E, Bennett BM, Shchepinov MS. Deuterium-reinforced polyunsaturated fatty acids improve cognition in a mouse model of sporadic Alzheimer's disease. The FEBS Journal. 2017;284(23):4083-95.
48. Yang Y, Chen W, Wang X, Ge W. Impact of mitochondrial aldehyde dehydrogenase 2 on cognitive impairment in the AD model mouse. Acta Biochimica et Biophysica Sinica. 2021;53(7):837-47.
49. Dawson TM, Dawson VL. Neuroprotective and neurorestorative strategies for Parkinson's disease. Nature Neuroscience. 2002;5 Suppl:1058-61.
50. Dorsey ER, Constantinescu R, Thompson JP, Biglan KM, Holloway RG, Kieburtz K, *et al*. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. Neurology. 2007;68(5):384-6.
51. Kalinderi K, Bostantjopoulou S, Fidani L. The genetic background of Parkinson's disease: current progress and future prospects. Acta Neurologica Scandinavica. 2016;134(5):314-26.
52. Pradhan SP, Tejaswani P, Behera A, Sahu PK. Phytomolecules from conventional to nano form: Next-generation approach for Parkinson's disease. Ageing Research Reviews. 2023;93:102136.
53. Zhang X, Ye YL, Wang YN, Liu FF, Liu XX, Hu BL, *et al*. Aldehyde dehydrogenase 2 genetic variations may increase susceptibility to Parkinson's disease in Han Chinese population. Neurobiology of Aging. 2015;36(9):2660.e9-13.
54. Chen J, Huang W, Cheng CH, Zhou L, Jiang GB, Hu YY. Association Between Aldehyde dehydrogenase-2 Polymorphisms and Risk of Alzheimer's Disease and Parkinson's Disease: A Meta-Analysis Based on 5,315 Individuals. Frontiers in Neurology. 2019;10:290.
55. Lin CY, Yu RL, Wu RM, Tan CH. Effect of ALDH2 on Sleep Disturbances in Patients with Parkinson's Disease. Scientific Reports. 2019;9(1):18950.
56. Yu RL, Tu SC, Wu RM, Lu PA, Tan CH. Interactions of COMT and ALDH2 Genetic Polymorphisms on Symptoms of Parkinson's Disease. Brain Sciences. 2021;11(3).
57. Agid Y, Javoy F, Glowinski J. Hyperactivity of remaining dopaminergic neurones after partial destruction of the nigro-striatal dopaminergic system in the rat. Nature: New Biology. 1973;245(144):150-1.
58. Chen AH, Zhang P, Yin WL, Wang L, Zou W, Tang XQ. Role of aldehyde dehydrogenase 2 in 1-methy-4-phenylpyridinium ion-induced aldehyde stress and cytotoxicity in PC12 cells. Neurochemical Research. 2014;39(9):1767-75.
59. Wang Y, Zhang X. The role of immune inflammation in electroconvulsive therapy for schizophrenia: Treatment mechanism, and relationship with clinical efficacy: Immune-inflammation in ECT for schizophrenia. Psychiatry Research. 2023;332:115708.
60. Bošković M, Vovk T, Kores Plesničar B, Grabnar I. Oxidative stress in schizophrenia. Current Neuropharmacology. 2011;9(2):301-12.
61. Emiliani FE, Sedlak TW, Sawa A. Oxidative stress and schizophrenia: recent breakthroughs from an old story. Current Opinion in Psychiatry. 2014;27(3):185-90.
62. Yao JK, Keshavan MS. Antioxidants, redox signaling, and pathophysiology in schizophrenia: an integrative view. Antioxidants & Redox Signaling. 2011;15(7):2011-35.
63. Wang JF, Shao L, Sun X, Young LT. Increased oxidative stress in the anterior cingulate cortex of subjects with bipolar disorder and schizophrenia. Bipolar Disorders. 2009;11(5):523-9.
64. Zheng F, Yan H, Liu B, Yue W, Fan L, Liao J, *et al*. ALDH2 Glu504Lys Confers Susceptibility to

Schizophrenia and Impacts Hippocampal-Prefrontal Functional Connectivity. Cerebral Cortex (New York, NY : 1991). 2017;27(3):2034-40.
65. Lee SY, Chen SL, Chang YH, Chen PS, Huang SY, Tzeng NS, *et al*. ALDH2 polymorphism, associated with attenuating negative symptoms in patients with schizophrenia treated with add-on dextromethorphan. Journal of Psychiatric Research. 2015;69:50-6.
66. Gu X, Dou M, Yuan M, Zhang W. Identifying novel proteins underlying loneliness by integrating GWAS summary data with human brain proteomes. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2023;48(7):1087-97.
67. Ramos-Loyo J, Medina-Hernández V, Estarrón-Espinosa M, Canales-Aguirre A, Gómez-Pinedo U, Cerdán-Sánchez LF. Sex differences in lipid peroxidation and fatty acid levels in recent onset schizophrenia. Progress in Neuro-psychopharmacology & Biological Psychiatry. 2013;44:154-61.
68. Cook RL, Parker HM, Donges CE, O'Dwyer NJ, Cheng HL, Steinbeck KS, *et al*. Omega-3 polyunsaturated fatty acids status and cognitive function in young women. Lipids in Health and Disease. 2019;18(1):194.
69. Halbreich U, Kahn LS. Hormonal aspects of schizophrenias: an overview. Psychoneuroendocrinology. 2003;28 Suppl 2:1-16.
70. The burden of diseases and risk factors in Bangladesh, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet Global health. 2023;11(12):e1931-e42.
71. Marsh JD, Keyrouz SG. Stroke prevention and treatment. Journal of the American College of Cardiology. 2010;56(9):683-91.
72. Seshadri S, Wolf PA. Lifetime risk of stroke and dementia: current concepts, and estimates from the Framingham Study. The Lancet Neurology. 2007;6(12):1106-14.
73. Falcone GJ, Malik R, Dichgans M, Rosand J. Current concepts and clinical applications of stroke genetics. The Lancet Neurology. 2014;13(4):405-18.
74. Kilarski LL, Achterberg S, Devan WJ, Traylor M, Malik R, Lindgren A, *et al*. Meta-analysis in more than 17,900 cases of ischemic stroke reveals a novel association at 12q24.12. Neurology. 2014;83(8):678-85.
75. Cho Y, Lin K, Lee SH, Yu C, Valle DS, Avery D, *et al*. Genetic influences on alcohol flushing in East Asian populations. BMC genomics. 2023;24(1):638.
76. Millwood IY, Walters RG, Mei XW, Guo Y, Yang L, Bian Z, *et al*. Conventional and genetic evidence on alcohol and vascular disease aetiology: a prospective study of 500 000 men and women in China. Lancet (London, England). 2019;393(10183):1831-42.
77. Millwood IY, Im PK, Bennett D, Hariri P, Yang L, Du H, *et al*. Alcohol intake and cause-specific mortality: conventional and genetic evidence in a prospective cohort study of 512 000 adults in China. The Lancet Public Health. 2023;8(12):e956-e67.
78. Xu YL, Hu YY, Li JW, Zhou L, Li L, Niu YM. Aldehyde dehydrogenase 2 rs671G>A polymorphism and ischemic stroke risk in Chinese population: a meta-analysis. Neuropsychiatric Disease and Treatment. 2019;15:1015-29.
79. Jiang Y, He J, Liu H, Xu Z. Association between ALDH2 rs671 polymorphism and risk of ischemic stroke: A protocol for systematic review and meta analysis. Medicine. 2020;99(21):e20206.
80. Shi M, Kelly TN, Zhu Z, Li C, Shen C, Sun Y, *et al*. Large-Scale Targeted Sequencing Study of Ischemic Stroke in the Han Chinese Population. Journal of the American Heart Association. 2022;11(19):e025245.
81. Zhang S, Luo W, Pan T, Xie J, Xu Z, Fang Y. ALDH2 rs671 Polymorphism Likely a Risk Factor for Hemorrhagic Stroke: A Hospital-Based Study. International Journal of General Medicine. 2023;16:1471-8.
82. Geltser BI, Kurpatov IG, Kotelnikov VN, Zayats YV. Chronic obstructive pulmonary disease and cerebrovascular diseases: functional and clinical aspect of comorbidity. Terapevticheskii Arkhiv. 2018;90(3):81-8.
83. Sun A, Ren J. ALDH2, a novel protector against stroke? Cell Res. 2013;23(7):874-5.
84. Zhang R, Liu B, Fan X, Wang W, Xu T, Wei S, *et al*. Aldehyde Dehydrogenase 2 Protects Against Post-Cardiac Arrest Myocardial Dysfunction Through a Novel Mechanism of Suppressing Mitochondrial Reactive Oxygen Species Production. Frontiers in Pharmacology. 2020;11:373.
85. Ehret GB, Munroe PB, Rice KM, Bochud M, Johnson AD, Chasman DI, *et al*. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. Nature. 2011;478(7367):103-9.

86. Kato N, Takeuchi F, Tabara Y, Kelly TN, Go MJ, Sim X, *et al*. Meta-analysis of genome-wide association studies identifies common variants associated with blood pressure variation in east Asians. Nature Genetics. 2011;43(6):531-8.
87. Guo JM, Liu AJ, Zang P, Dong WZ, Ying L, Wang W, *et al*. ALDH2 protects against stroke by clearing 4-HNE. Cell Res. 2013; 23(7):915-30.
88. Xia P, Zhang F, Yuan Y, Chen C, Huang Y, Li L, *et al*. ALDH 2 conferred neuroprotection on cerebral ischemic injury by alleviating mitochondria-related apoptosis through JNK/caspase-3 signing pathway. International Journal of Biological Sciences. 2020;16(8):1303-23.
89. Assessment of association between mitochondrial aldehyde dehydrogenase polymorphism and Alzheimer's disease in an older Korean population. Neurobiology of Aging. 2004;25(3):295-301.
90. Michel TM, Käsbauer L, Gsell W, Jecel J, Sheldrick AJ, Cortese M, *et al*. Aldehyde dehydrogenase 2 in sporadic Parkinson's disease. Parkinsonism & Related Disorders. 2014;20 Suppl 1:S68-72.
91. Zhao CC, Cai HB, Wang H, Pan SY. Role of ADH2 and ALDH2 gene polymorphisms in the development of Parkinson's disease in a Chinese population. Genetics and Molecular Research : GMR. 2016;15(3).