Published in final edited form as:
Expert Opin Drug Metab Toxicol. 2008 June ; 4(6): 697–720. doi:10.1517/17425250802102627.

Non-P450 aldehyde oxidizing enzymes: the aldehyde dehydrogenase superfamily

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Abstract

Background—Aldehydes are highly reactive molecules. While several non-P450 enzyme systems participate in their metabolism, one of the most important is the aldehyde dehydrogenase (ALDH) superfamily, composed of $NAD(P)^+$-dependent enzymes that catalyze aldehyde oxidation.

Objective—This article presents a review of what is currently known about each member of the human ALDH superfamily including the pathophysiological significance of these enzymes.

Methods—Relevant literature involving all members of the human ALDH family was extensively reviewed, with the primary focus on recent and novel findings.

Conclusion—To date, 19 ALDH genes have been identified in the human genome and mutations in these genes and subsequent inborn errors in aldehyde metabolism are the molecular basis of several diseases, including Sjögren-Larsson syndrome, type II hyperprolinemia, γ-hydroxybutyric aciduria and pyridoxine-dependent seizures. ALDH enzymes also play important roles in embryogenesis and development, neurotransmission, oxidative stress and cancer. Finally, ALDH enzymes display multiple catalytic and non-catalytic functions including ester hydrolysis, antioxidant properties, xenobiotic bioactivation and UV light absorption.

Keywords

aldehyde dehydrogenase; aldehyde metabolism; ALDH

1. Introduction

Aldehydes are generated from a wide variety of endogenous and exogenous precursors during numerous physiological processes, including the biotransformation of endogenous compounds such as amino acids, neurotransmitters, carbohydrates, and lipids [1–3]. More than 200 aldehyde species arise from the oxidative degradation of cellular membrane lipids, also known as lipid peroxidation (LPO), including 4-hydroxy-2-nonenal (4-HNE) and malondialdehyde (MDA) [4]. Amino acid catabolism generates several aldehyde intermediates, including glutamate γ-semialdehyde, while neurotransmitters, such as gamma-aminobutyric acid (GABA), serotonin, noradrenaline, adrenaline, and dopamine, also give rise to aldehyde metabolites [2,5]. Xenobiotics and drugs – including ethanol, which generates acetaldehyde,

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Declaration of interest
The authors state no conflict of interest and have received no payment in preparation of this manuscript.

and the anticancer drugs cyclophosphamide (CP) and ifosfamide, which generate acrolein – are important aldehyde precursors. Various aldehydes, including formaldehyde, acetaldehyde and acrolein, are also ubiquitous in the environment and are present in smog, cigarette smoke and motor vehicle exhaust. Aldehydes are also used or generated in a wide variety of industrial applications including in the production of resins, polyurethane and polyester plastics. In addition, numerous dietary aldehydes, including citral and benzaldehyde, naturally exist or are approved additives in various foods where they impart flavor and odor.

While some aldehydes play vital roles in normal physiological processes, including vision, embryonic development, and neurotransmission, many are cytotoxic and carcinogenic [6]. Aldehydes are strong electrophilic compounds with terminal carbonyl groups, making them highly reactive, and α,β-unsaturated aldehydes, such as 4-HNE and acrolein, also contain a second electrophile at the β-carbon. Unlike free radicals, aldehydes are relatively long-lived and not only react with cellular components in the vicinity of their formation but, through diffusion or transportation, also affect targets some distance away [4]. Aldehydes form adducts, believed to be the primary mechanism underlying their toxicity, with various cellular targets including glutathione (GSH), nucleic acids, and protein amino acids leading to impaired cellular homeostasis, enzyme inactivation, DNA damage, and cell death [7,8].

Aldehydes are detoxified primarily through reductive and oxidative Phase I enzyme-catalyzed reactions, including the non-P450 aldehyde reduction enzyme systems alcohol dehydrogenase (ADH), aldo-keto reductase (AKR) and short-chain dehydrogenase/reductase (SDR), and aldehyde oxidation enzyme systems xanthine oxidase (XO), aldehyde oxidase (AOX) and aldehyde dehydrogenase (ALDH) (Figure 1). The ALDH superfamily catalyzes the oxidation of numerous aldehyde substrates and, while other enzymes metabolize aldehydes, these enzymes play a particularly critical role in the cellular protection against these toxic species, as evidenced by the fact that mutations and polymorphisms in *ALDH* genes (leading to perturbations in aldehyde metabolism) are the molecular basis of several disease states and metabolic anomalies [2]. The present paper comprehensively reviews the 19 human ALDH proteins.

2. The ALDH superfamily

The human ALDH superfamily consists of 19 putatively functional genes with distinct chromosomal locations (Figure 2)[9]. A standardized gene nomenclature system based on divergent evolution and amino acid identity was established for the ALDH superfamily in 1998 [10]. The ALDH enzymes catalyze the $NAD(P)^+$-dependent irreversible oxidation of a wide spectrum of endogenous and exogenous aldehydes (Table 1). ALDH proteins are found in all subcellular regions including cytosol, mitochondria, endoplasmic reticulum and nucleus, with several found in more than one compartment. ALDH isozymes found in organelles other than cytosol possess leader or signal sequences that allow their translocation to specific subcellular regions [11]. After translocation or import, mitochondrial sequences may be removed (resulting in shorter mature proteins), while microsomal and nuclear signals remain intact [12,13]. Most of the ALDHs have a wide tissue distribution and display distinct substrate specificity [2,14]. Generally regarded as detoxification enzymes, ALDHs serve to protect cells from the effects of aldehydes by oxidizing them to their respective carboxylic acids (Figure 1). This is evident from several studies in which an ALDH has been shown to protect against aldehyde-induced cytotoxicity [13]. However, the most compelling evidence relies on the observation that mutations and polymorphisms in *ALDH* genes (leading to loss of function) are associated with distinct phenotypes in humans and rodents [2,15], including Sjögren-Larsson syndrome (SLS) [16], type II hyperprolinemia [17], γ-hydroxybutyric aciduria [18], pyridoxine-dependent seizures [19], hyperammonemia [20], alcohol-related diseases [21], cancer [6] and late-onset alzheimer's disease (AD) [22] (Figure 2). In addition to clinical phenotypes associated with

mutations in ALDH genes, transgenic knockout mice have suggested a pivotal role of ALDHs in physiological functions and processes, such as embryogenesis and development [23,24].

Aside from their role in aldehyde detoxification, many ALDH enzymes possess multiple additional catalytic and non-catalytic functions (Table 1). Indeed, several ALDHs are known to catalyze ester hydrolysis [25] and act as binding proteins for various endogenous (e.g., androgen, cholesterol and thyroid hormone) and exogenous (e.g., acetaminophen) compounds [2]. Additionally, ALDH enzymes may have important antioxidant roles including the production of NAD(P)H [26,27], the absorption of UV light [28,29] and the scavenging of hydroxyl radicals via cysteine and methionine sulfhydryl groups [30].

ALDH enzymes share a number of highly conserved residues necessary for catalysis and cofactor binding [31–36]. The invariant catalytic cysteine Cys-302 (numbering based on the mature human ALDH2 protein), Glu-268, Gly-299, and Asn-169 are all essential for catalysis. Gly-245 and Gly-250 are essential residues of the ALDH Rossmann fold (GxxxxG) necessary for cofactor binding. In addition, Lys-192, Glu-399, and Phe-401 are believed to be integral for cofactor binding and may facilitate catalysis. Crystal structures of mammalian ALDH enzymes have revealed that each subunit contains three domains, namely an $NAD(P)^+$ cofactor-binding domain, a catalytic domain, and a bridging domain [31,32]. At the interface of these domains lies a funnel passage leading to the catalytic pocket. The upper portion of the funnel, composed of residues from all three domains, is believed to confer the required ALDH specificity toward particular aldehyde substrates. The lower portion of the funnel, made up of highly conserved residues from both the cofactor and catalytic domains, appears to be the catalytic site where hydride transfer from substrate to cofactor takes place.

Based on crystallographic structures of ALDH enzymes, a catalytic mechanism has been proposed involving acylation, followed by deacylation (Figure 3)[31,32,37–39]. Briefly, cofactor binding results in a conformational change and activation of the catalytic Cys-302 nucleophile, which is positioned by Gly-299 [32]. Cys-302 then attacks the aldehydic function of the substrate and forms an oxyanion thiohemiacetal intermediate, stabilized in part by Asn-169 [31]. The negatively-charged oxygen of the oxyanion intermediate then facilitates hydride transfer to the cofactor, resulting in the formation of a thioacylenzyme intermediate. Hydrolysis of the thioaceylenzyme and release of carboxylic acid product takes place via Glu-268, which acts as a general base by activating the hydrolytic water after hydride transfer. For most ALDHs, the reduced cofactor is believed to dissociate from the enzyme last. However, one human ALDH, namely ALDH6A1, is CoA-dependent and has a slightly different catalysis mechanism in which the reduced cofactor is released prior to the deacylation step and yields a CoA ester product instead of a free acid [40].

3. ALDH1A1

ALDH1A1 encodes a homotetramer ubiquitously distributed in the adult epithelium of various organs including testis, brain, eye lens, liver, kidney, lung and retina [41,42]. ALDH1A1 is one of three highly conserved cytosolic isozymes (see ALDH1A2 and ALDH1A3) that catalyze the oxidation of the retinol metabolite, retinal (retinaldehyde), to retinoic acid (RA) [43,44]. ALDH1A1 has high affinity for the oxidation of both all-*trans*-(K_m < 0.1 μM) and 9-*cis*-retinal [45].

RA regulates gene expression by serving as a ligand for nuclear RA receptors (RAR) and retinoid X receptors (RXR). Its synthesis is critical for normal growth, differentiation, development and maintenance of adult epithelia in vertebrate animals [46]. In retinoid-dependent tissues (including the retina), retinal-oxidizing ALDHs have been shown to exhibit differential expression patterns during rodent organogenesis [47–49], indicating that RA signaling is necessary for embryogenesis [50,51]. The *in vivo* role of ALDH1A1 in RA

synthesis is evidenced by the fact that, while *Aldh1a1*$^{-/-}$ mice are viable and have normal morphology of the retina, the livers of *Aldh1a1*$^{-/-}$ mice display reduced RA synthesis and increased serum retinal levels after retinol treatment [52,53]. Interestingly, *Aldh1a1*$^{-/-}$ mice are protected against both diet-induced obesity and insulin resistance, suggesting that retinal may transcriptionally regulate the metabolic response to high-fat diets and that *ALDH1A1* may be a candidate gene for therapeutic targeting [54]. In cultured hepatocytes, supression of *ALDH1A1* reduces both the omega oxidation of free fatty acids and the production of reactive oxygen species (ROS) [55]. *RXR*α$^{-/-}$ mice display decreased liver ALDH1A1 levels, suggesting that RA binding is an activating factor in *ALDH1A1* gene expression [56]. The androgen receptor may also be involved in regulating levels of ALDH1A1 [57], which is known to be an androgen binding protein [58]. RA is required for testicular development and *ALDH1A1* is absent in genital tissues of humans with androgen receptor-negative testicular feminization [57,59].

In the human brain, ALDH1A1 is highly expressed in dopaminergic neurons [60], which are known to require RA for their differentiation and development [61]. In these neurons, *ALDH1A1* is under the control of Pitx3, a homeodomain transcription factor [61] that may regulate the specification and maintenance of distinct populations of dopaminergic neurons through *ALDH1A1* upregulation [62]. Decreased levels of ALDH1A1 occur in dopaminergic neurons of the substantia nigra in Parkinson's disease (PD) patients [63] and in those of the ventral tegmental area in schizophrenic patients [60]. In the central nervous system (CNS), monoamine oxidase (MAO) metabolizes dopamine to its aldehyde metabolite, 3,4-dihydroxyphenylacetaldehyde (DOPAL). Increasing evidence suggests that DOPAL may be neurotoxic, and its accumulation may lead to cell death associated with neurological pathologies [5]. ALDH1A1 may play a critical role in maintaining low intraneuronal levels of DOPAL by catalyzing its metabolism to 3,4-dihydroxyphenylacetic acid (DOPAC) [5,60].

ALDH1A1 is one of 139 genes that are differentially expressed in primary human hematopoietic stem cells (HSCs) and, through the production of RA, ALDH1A1 has been shown to promote their differentiation [64,65]. These data suggest that ALDH1A1 inhibition could potentially be used for the therapeutic amplification of HSCs.

ALDH1A1 is one of the major enzymes involved in the metabolism of the ethanol metabolite, acetaldehyde (K_m 50 – 180 μM), to which many of the deleterious effects of ethanol are attributed [66]. Indeed, low ALDH1A1 activity may account for alcohol sensitivity in some Caucasian populations [67,68]. Decreased levels of ALDH1A1 are reported in *RXR*α$^{-/-}$ mice, which are more susceptible to alcoholic liver injury [56], while increased ALDH1A1 expression occurs in brains of DBA/2 mice, a mouse strain exhibiting alcohol avoidance [69]. These data in rodents have led to the suggestion that acetaldehyde accumulation in peripheral organs is aversive, while acetaldehyde produced in the brain may be reinforcing.

ALDH1A1 also plays a key role in the cellular defense against oxidative stress. Human ALDH1A1 efficiently oxidizes LPO-derived aldehydes, including 4-HNE (K_m 17.9 μM), hexanal (K_m 13.4 μM), and MDA (K_m 114.4 μM) (Figure 4)[41,70]. Using various *Aldh1a1*$^{-/-}$mouse models, ALDH1A1 has been demonstrated to play a key role in protecting the mouse eye lens and cornea by detoxifying LPO-derived aldehydes and preventing cataract formation induced by oxidative stresses, including ageing and UV radiation [29].

Similar to other ALDHs, ALDH1A1 may also play an important role in cancer therapeutics (Table 2). ALDH1A1 activity has been reported to decrease the effectiveness of some oxazaphosphorine anticancer drugs, such as CP and ifosfamide, by detoxifying their major active aldehyde metabolites [71]. Indeed, inhibition of ALDH1A1 activity leads to increased toxicity of the major metabolite of CP, 4-hydroperoxycyclophosphamide [72]. Accordingly,

patients with low breast tumor ALDH1A1 levels have been reported to respond to CP-based treatment significantly more often than those with high levels, indicating that ALDH1A1 may be a predictor of the drug's therapeutic effectiveness [73]. Various noncancerous cells, such as hematopoietic progenitor cells, express relatively high ALDH1A1 levels and thus are relatively resistant to oxazaphosphorine-induced toxicity [74]. ALDH1A1 has also been shown to bind to certain anticancer drugs, including daunorubicin [75] and flavopiridol [76], and is downregulated in certain carcinomas [77].

Recently, ALDH1A1 was found to be downregulated in cell cultures and whole-skin tissue samples from patients with atopic dermatitis, suggesting its use as a potential dermal biomarker of this disease [78].

Aside from aldehyde metabolism, ALDH1A1 possesses esterase activity [79] and has been proposed to be the major enzyme catalyzing the oxidation of 3-deoxyglucosome, a potent glycating agent [80]. In addition, ALDH1A1 binds thyroid hormone [81] and is induced by estrogens [82], suggesting it may be regulated by or involved in hormone signaling.

4. ALDH1A2

ALDH1A2 is a cytosolic homotetramer expressed in various embryonic and adult tissues including intestine, testis, lung, kidney, liver, brain and retina [48,83]. Like ALDH1A1, ALDH1A2 catalyzes the oxidation of both all-*trans*-retinal and 9-*cis*-retinal to RA [23]. Compared with other ALDH isozymes [84], ALDH1A2 appears to exhibit the highest specificity (V_{max}/K_m = 49 nmol·min^{-1}·mg^{-1}·μM^{-1}) for all-*trans*-retinal[43,44]. This property may be due to a unique disordered loop in its active site that binds all-*trans*-retinal in a distinct manner [85].

ALDH1A2 is involved in several developmental processes and may be a key regulator of RA synthesis in developing tissues [86]. *Aldh1α2*$^{-/-}$ mice die in early embryonic stages due to defects in early heart morphogenesis [23,87]. They display a lack of axial rotation, incomplete neural tube closure, reduction of the trunk region [23], and many of the features of human DiGeorge/velocardiofacial syndrome, a disorder characterized by cleft palate, heart abnormalities and learning disabilities [88]. Abnormalities in endothelial cell cycle progression during early vascular development have also been identified in *Aldh1α2*$^{-/-}$ embryos [89]. Various animal models have identified *Aldh1a2* as a key regulator in the development of numerous tissues including kidney [90], retina [91], lung [92], forebrain [93], pancreas [94], and spinal cord [23].

A significant association between spina bifida in humans and three distinct *ALDH1A2* single nucleotide polymorphisms (SNPs), including one silent (A151A; c.453A > G) and two intronic (rs3784259 and rs3784260), has been found; however, their functional significance remains unclear [95]. ALDH1A2 may also play a role in congenital diaphragmatic hernia (CDH), which is associated with chromosomal 15q defects within a region that includes both *ALDH1A2* and *ALDH1A3*[96]. In addition, compounds known to induce CDH have been shown to inhibit ALDH1A2 [97].

ALDH1A2 may play a role in the defense against ethanol toxicity through either acetaldehyde detoxification or the synthesis of RA [98]. While rat ALDH1A2 oxidizes acetaldehyde inefficiently *in vitro* (K_m 0.65 mM) [44], *ALDH1A2* induction by lens epithelium-derived growth factor protects cells from ethanol-induced toxicity [99]. In addition, ALDH1A2 is decreased in *RXRα*$^{-/-}$ mice, which display increased susceptibility to alcohol-induced liver injury [56].

Similar to other ALDHs, ALDH1A2 metabolizes LPO-derived aldehydes and may protect against oxidative stress. Rat ALDH1A2 oxidizes medium-chain saturated LPO-derived aliphatic aldehydes, including hexanal (K_m 28 μM), octanal (K_m 5 μM) and decanal (K_m 3 μM), with high affinity [44].

RA synthesis by ALDH1A2 promotes differentiation, cell growth arrest and apoptosis and may have an anticancer effect (Table 2)[100,101]. Indeed, *ALDH1A2* has been suggested as a candidate tumor suppressor gene in prostate cancer [101]. *ALDH1A2* expression is induced by DNA demethylation in human prostate cancer cell lines, downregulated in prostate tumors, and low expression of ALDH1A2 is associated with shorter recurrence-free survival. In addition, overexpression of wild-type ALDH1A2 in prostate cancer cells inhibits cell growth [101].

5. ALDH1A3

ALDH1A3 is a cytosolic homodimer that participates in the synthesis of RA and plays an important role in embryonic development [102]. ALDH1A3 oxidizes both all-*trans*-retinal and 9-*cis*-retinal (K_m 0.2 μM for all-*trans*-retinal) to RA. ALDH1A3 is expressed in various late-stage embryonic and adult rodent tissues including tooth buds, intestine, kidney, brain, retina, prostate, skeletal muscle, lung, liver and pancreas [48]. In humans, ALDH1A3 expression has been observed in salivary gland, stomach, breast, kidney and fetal nasal mucosa [103,104]. *Aldh1a3*$^{-/-}$ mouse embryos die from defects in nasal development [24].

ALDH1A3 has been shown to participate in the development of the eye [105], nucleus accumbens and olfactory bulbs [106], hair follicles [107], the forebrain [108] and the cerebral cortex [109].

A number of studies have demonstrated that ALDH1A3 deficiency may play a critical role in cancer (Table 2). For example, ALDH1A3 expression is downregulated in human breast cancer MCF-7 cells [110] and *ALDH1A3* is one of two genes that are upregulated by induction of wild type *p*53 in cultured human colon cancer cells [111]. In mammary tumor-susceptible BALB/cJ mice heterozygous for *p*53, *Aldh1a3* is one of five candidate genes located within a region identified for its linkage to mammary tumorigenesis [112]. In mice resistant to induced mammary tumors (C57BL/6J), *Aldh1a3* is one of two upregulated genes [112]. *ALDH1A3* is methylation-silenced in gastric cancer cells [113] and induced by the antitumor agent IL-13 cytotoxin in glioblastoma cells [114].

Similar to ALDH1A2, ALDH1A3 may also play a role in CDH. Nitrofen-induced CDH and associated pulmonary hypoplasia of mouse fetuses is associated with ALDH1A3 upregulation, postulated to be the result of lung retinol deficiency [115]. As mentioned above, CDH is associated with human chromosome defects within a region including *ALDH1A3*[96].

ALDH1A3 also may have a role in mitigating oxidative stress by detoxifying LPO-derived aldehydes. Indeed, mouse ALDH1A3 has been shown to have very high affinity for octanal (K_m 0.7 μM), decanal (K_m 6.5 μM) and hexanal (K_m 22.1 μM) [102].

6. ALDH1B1

ALDH1B1 is a mitochondrial homotetramer expressed in various adult and fetal human tissues including liver, testis, kidney, skeletal muscle, heart, placenta, brain and lung [116,117]. To date, little is known about ALDH1B1; however, it shares 75% sequence homology with ALDH2, the primary enzyme involved in the metabolism of the ethanol metabolite, acetaldehyde. ALDH1B1 displays relatively high affinity for acetaldehyde (K_m 30 μM) and is believed to play a major role in acetaldehyde oxidation *in vivo*[117]. *In vitro*, ALDH1B1 is

upregulated in response to UV light [118] and may play a role in protecting the cornea from this environmental insult [119].

7. ALDH1L1

ALDH1L1 is a multi-domain homotetramer consisting of two distinct catalytic domains, namely an amino-terminal formyl transferase domain and a carboxy-terminal ALDH domain [120]. ALDH1L1, through a unique mode of cofactor binding, appears to prefer $NADP^+$ over NAD^+[121]. ALDH1L1 is expressed at high levels in human liver, kidney and pancreas and at moderate levels in lung, prostate, brain, skeletal muscle, heart, ovary, thymus and testis [122]. ALDH1L1 appears to be present in multiple subcellular regions including both cytosol and mitochondria [123].

ALDH1L1, also known as 10-formyltetrahydrofolate (10-FTHF) dehydrogenase (10-FTHFD), catalyzes the formation of tetrahydrofolate (THF) from 10-FTHF [124]. THF is a major metabolite of dietary folate and an important substrate in one-carbon metabolism while 10-FTHF participates in purine biosynthesis and may influence DNA replication and repair [122]. NEUT2 mice, which are *ALDH1L1* deficient, have reduced reproductive efficiency and display a substantial decrease in hepatic 10-FTHF and THF, indicating ALDH1L1 may regulate levels of 10-FTHF and THF [125].

ALDH1L1 may have a role in cancer by regulating cellular proliferation (Table 2). *In vitro*, ALDH1L1 overexpression in various cancer cell lines results in suppressed cellular proliferation and increased cytotoxicity, believed to be due to a catalytic function of ALDH1L1 [122]. In A549 cells, overexpression of ALDH1L1 induces the phosphorylation and translocation of *p*53 into the nucleus [126], resulting in a G1 cell cycle arrest and caspase-dependent apoptosis [127]. ALDH1L1 is significantly downregulated in human liver, lung, prostate, pancreas and ovarian cancers, which may enhance tumor proliferation [122]. During murine embryogenesis, ALDH1L1 expression correlates to regions lacking proliferating cells and is restricted to the midline of the developing CNS, suggesting it may also play a role in human neural tube defects [128]. Two intronic SNPs in *ALDH1L1* are associated with an increased (intron 4) and a decreased (intron 13) risk for postmenopausal breast cancer [129].

ALDH1L1 has an important role in methanol toxicity (Figure 5). Methanol is metabolized in the liver in two steps to the toxic metabolite, formate, which is then oxidized to carbon dioxide by a process dependent on THF, ATP, methyl-enetetrahydrofolate dehydrogenase (MTHFD) and ALDH1L1. Compared with other species, humans are particularly susceptible to methanol toxicity as a result of low formate oxidation rates due, in part, to lower liver ALDH1L1 activity [130]. In addition, methanol is highly toxic to the ocular system [123] and retinal Müller cells appear to represent a specific target [131]. Müller cells strongly and preferentially express ALDH1L1, suggesting that it may have a protective role [123]. However, low retinal THF levels may affect the ability of ALDH1L1 to participate in formate oxidation and, along with its specific localization in this target cell, suggest it may have an additional role in methanol toxicity.

ALDH1L1 may be regulated by xenobiotics. For example, rats treated with ethanol or the chemotherapeutic drug methotrexate, both known to deplete cellular folate levels, display lower hepatic ALDH1L1 activity [132,133]. In addition, acetaminophen covalently adducts to ALDH1L1 and reduces its activity [134].

8. ALDH1L2

Human *ALDH1L2*, one of the most recently discovered *ALDH* genes, is located on chromosome 12q23.3 and is composed of 23 exons that encode a protein of 923 amino acids (102 kDa).

ALDH1L2 shares 72% sequence identity with ALDH1L1 and has three domains which closely correspond to those of ALDH1L1, including a formyl-*trans-N*-formyl transferase at the amino terminal (residues 23 – 202), a formyltransferase domain in the middle (residues 226 – 327), and an ALDH domain at the carboxyl terminal (residues 451 – 910) [9]. To date, gene expression profiling has identified high expression of ALDH1L2 mRNA in the spleen and the corpus callosum [135]. *In vitro*, the treatment of human breast cancer cells with the anti-inflammatory agent, indometacin, upregulates *ALDH1L2* gene expression [136]. To date, no further information exists regarding the properties or physiological significance of ALDH1L2.

9. ALDH2

ALDH2 encodes a mitochondrial matrix protein that is constituitively expressed in a variety of tissues including liver, kidney, heart, lung and brain [137]. ALDH2 is the primary enzyme involved in the oxidation of acetaldehyde (K_m < 1 μM) during ethanol metabolism [138]. To date, several mutant ALDH2 alleles have been described, including the widely studied ALDH2*2 allele (single base pair mutation G/C → A/T), which results in an E487K substitution and consequent catalytic inactivation of ALDH2 due to a conformational change that leads to decreased nucleophilicity of the active site cysteine residue and decreased NAD^+ affinity [31,139,140]. Glu-487, located in the bridging domain, appears to maintain a stable structural scaffold and facilitate catalysis by linking together the cofactor-binding and catalytic domains through its interactions with Arg-264 and Arg-475 [31,141]. ALDH2 functions as a homotetramer; however, the mutant ALDH2*2 allele is dominant, and heterotetrameric ALDH2 proteins containing even one ALDH2*2 subunit are enzymatically inactive [142]. The ALDH2*2 allele is found in approximately 40 – 50% of individuals of Asian descent [143] and, in those who drink alcohol, alcohol-induced toxicity occurs [144] due primarily to acetaldehyde accumulation and its effects [145]. This results in a lower alcoholism rate in Asian populations [146], but a number of studies have demonstrated the association of *ALDH2*2* with an increased risk for various cancers, including oropharyngolaryngeal, esophageal, stomach, colon, lung, head and neck cancers [6,147]. Alcoholic ALDH2*2 individuals also display increased levels of acetaldehyde-derived DNA adducts, indicating a potential mechanism of DNA damage and cancer development [148]. ALDH2*2 has also been associated with alcoholic liver disease and cirrhosis in Asian individuals, even with moderate alcohol intake [21]. The ALDH2*2 allele may also be a risk factor for increased DNA damage in workers exposed to polyvinyl chloride, a carcinogen that is metabolized to the ALDH2 substrate chloroacetaldehyde [149], which produces DNA crosslinks and strand breaks [150].

ALDH2, acting as a nitrate reductase, is the principal enzyme necessary for the activation of nitroglycerin, used to treat angina and heart failure, and ALDH2*2 is associated with a lack of nitroglycerin efficacy in Chinese patients [151]. ALDH2*2 is also associated with myocardial infarction in Korean patients [152] and hypertension in Japanese patients [153]. $Aldh2^{-/-}$ mice display increased alcohol toxicity correlating with increased brain and blood acetaldehyde levels [154,155] and increased urinary 8-hydroxydeoxyguanosine and DNA-acetaldehyde adducts after both inhalation exposure to acetaldehyde [156] or oral ethanol gavage [157], as compared to $Aldh2^{+/+}$ wild-type mice, indicating that both oral ingestion and inhalation of ethanol may pose a significant risk to ALDH2*2 individuals.

Recently, an additional polymorphic locus in the promoter (G/A) region of ALDH2, believed to affect ALDH2 activity by transcriptional mechanisms, has been found to be associated with variations in alcohol consumption habits among an American Jewish population [158].

Hepatotoxicity in alcoholics may occur, in part, to competition of LPO-derived aldehydes with acetaldehyde for ALDH2-mediated metabolism. ALDH2 is believed to have a major role in

the metabolism of LPO-derived aldehydes, including 4-HNE and MDA (Figure 4)[2] and, specifically, appears to be responsible for 4-HNE elimination in hepatic Ito [159] and Kupffer cells [160]. In the brain, ALDH2 enzymatic activity is elevated in the cerebral cortex of AD patients, which may be a protective mechanism against high 4-HNE levels [161]. Indeed, *in vitro*, ALDH2-deficient cells are highly vulnerable to 4-HNE-induced apoptosis [162] and, in humans, ALDH2*2 is associated with an elevated risk for late-onset AD in Japanese [22] and Chinese [163] individuals. ALDH2 is also believed to play a major role in the metabolism of the neurotoxic aldehyde metabolite of dopamine, DOPAL (K_m 4.2 μM), and ALDH2 deficiencies may contribute to the etiology of PD [5,164]. Significant impairment of DOPAL metabolism is reported in the presence of acetaldehyde, indicating competition between these substrates for metabolism by ALDH2 [165].

10. ALDH3A1

ALDH3A1 is a homodimer constitutively expressed in various tissues, including cornea, stomach, esophagus and lung, and is believed to have a crucial role in the cellular defense against oxidative stress [166]. ALDH3A1 catalyzes the oxidation of various LPO-derived aldehydes including α,β-hydroxyalkenals such as 4-HNE (K_m 45 μM) [167].

ALDH3A1, considered a corneal crystallin, is one of the most abundantly expressed proteins in mammalian corneal epithelium, accounting for upwards of 50% of the total water-soluble protein fraction [166,168]. ALDH3A1 is undetectable in eye lens; however, corneal ALDH3A1 protects both the cornea and underlying lens against UV-induced oxidative stress [29]. *Aldh3a1*$^{-/-}$ mice display clear corneas [169]; however, upon exposure to UV light, accelerated lens opacification and cataract formation occur [29]. The lens of *Aldh3a1*$^{-/-}$ mice have increased levels of 4-HNE- and MDA-protein adducts and decreased proteasome activity associated with increased protein oxidation [29]. In humans, diseased corneas exhibit reduced ALDH3A1 expression [170] and, *in vitro*, human cornea epithelial (HCE) cells overexpressing ALDH3A1 are less sensitive to UV light and associated cytotoxicity [26]. In addition, ALDH3A1 may scavenge ROS and prevent proteins from hydroxyl radical-induced modifications through a conserved free cysteinyl residue in its active site [30]. ALDH3A1 also generates NADPH, critical for GSH maintenance, which may also absorb UV light [28] and act as a direct antioxidant [171]. Given that the water-soluble protein fraction of the cornea consists of only 17% of total protein but accounts for upwards of 50% of the total UV light absorption capacity, ALDH3A1 itself may directly absorb UV light [172]. *In vitro*, ALDH3A1 prevents UV-induced protein inactivation and, *in vivo*, UV light inactivates ALDH3A1 while other metabolic enzymes are unaffected, suggesting that ALDH3A1 may absorb UV light through a ‘suicide’ response [28,173].

ALDH3A1 may also regulate cellular proliferation and the cell cycle. Cell lines expressing high ALDH3A1 levels are more resistant to the antiproliferative effects of LPO-derived aldehydes [174] and ALDH3A1 inhibition or deficiency reduces cellular growth rates, believed to be due to aldehyde accumulation [175]. In addition to its cytosolic location, ALDH3A1 is present in the nucleus, where it may exert cell cycle regulation by reducing DNA synthesis and proliferation rates through the downregulation of cyclins A, B and E, the transcription factor E2F1, and the cell-regulatory protein p21, and through the regulation of kinase activities [13]. *In vitro*, ALDH3A1 has been shown to prevent DNA damage and reduce apoptosis from various toxins including hydrogen peroxide, mitomycin C and etoposide, indicating that ALDH3A1-mediated cell cycle delay and subsequent decreased cell growth is associated with resistance to DNA damage and may serve to facilitate DNA repair [27].

ALDH3A1, through the oxidation of oxazaphosphorines such as CP, contributes to drug resistance in various tumor types (Table 2)[176,177], and interindividual variations in

ALDH3A1 activity may account for varying clinical responses to CP in certain cancers [73, 178]. *ALDH3A1* knockdown increases cellular sensitivity to CP and its metabolite, 4-hydroperoxycyclophosphamide, in cancer cell lines [72], while *ALDH3A1* transfection in normal human peripheral blood hematopoietic progenitor cells (PBPCs) results in increased chemotherapy resistance to CP [179]. *ALDH3A1* upregulation in non-cancerous cells could protect them during cancer treatment and have clinical applications [71]. Unexpectedly, however, a study using human breast tumor samples demonstrated that ALDH3A1 levels were not a predictor of the therapeutic efficacy of CP-based chemotherapy [73]. On the other hand, *ALDH3A1* has been identified as a potential diagnostic marker for non-small-cell lung cancer [180] and *ALDH3A1* may be a candidate gene in the pathogenesis of esophageal squamous cell carcinoma [181]. Interestingly, while ALDH3A1 is poorly expressed in normal liver, its expression in hepatoma cells increases in direct correlation with the degree of tumor growth [182]. *ALDH3A1* is induced in other neoplastic tissues and cell lines [183] and its expression is differentially affected by hormones such as progesterone (downregulates) and cortisone (upregulates), suggesting a potential role in hormone-dependent tumors [184]. *ALDH3A1* expression is also induced by various xenobiotics, including polycyclic hydrocarbons (PAHs) and 3-methylcholanthrene, through multiple *ALDH3A1* xenobiotic response elements (XREs) [185,186].

11. ALDH3A2

ALDH3A2 is a microsomal homodimer expressed in various human tissues including liver, kidney, intestine, stomach, skeletal muscles, skin, lung, pancreas, placenta, heart and brain [187,188]. Apart from the major ALDH3A2 mRNA transcript, a splice variant transcript has been identified, namely the minor fatty ALDH variant (FALDH*v*)[188], which appears to be exclusively localized in peroxisomal membranes, where it is involved in phytanic acid metabolism [189].

ALDH3A2, also known as fatty aldehyde dehydrogenase (FALDH), forms, along with fatty ADH, the fatty alcohol:NAD oxidoreductase (FAO) enzyme complex that catalyzes the oxidation of fatty alcohol to fatty acid [190]. ALDH3A2 has high affinity for straight- and branched-chain aliphatic aldehydes of medium- and long-chain length, including both saturated and unsaturated aldehydes [191]. The most relevant substrates of ALDH3A2 are fatty aldehydes derived from the metabolism of fatty alcohol [192], phytanic acid [193], leukotriene B_4[194], and ether glycerolipids [195]. Dysfunction of fatty aldehyde metabolism due to ALDH3A2 deficiency results in SLS, a rare autosomal recessive neurocutaneous disorder characterized by congenital icthyosis, mental retardation and spastic tetraplegia [16] specifically diagnosed by measuring ALDH3A2 activity in cultured human fibroblasts [192]. More than 72 *ALDH3A2* mutations have been discovered in SLS patients including amino acid substitutions, deletions, insertions, and splicing errors [196]. SLS pathogenesis is attributed to the abnormal accumulation of lipids in the membranes of skin and brain, aldehyde Schiff-base adducts with amine-containing lipids and proteins, and defective eicosanoid metabolism [196]. In a recent study, human *ALDH3A2* was delivered to keratinocytes of SLS patients using recombinant adeno-associated virus-2 vectors, which resulted in both augmented ALDH3A2 activity comparable to phenotypically normal heterozygous carriers and decreased toxicity of long-chain aldehydes to near the level of unaffected keratinocytes, indicating that *ALDH3A2* gene therapy could be an effective treatment for SLS [197].

ALDH3A2 may have a role in diabetes and associated oxidative stress-induced complications. Insulin increases ALDH3A2 expression through the phosphatidylinositol 3-kinase (PI3K)-dependent pathway in the liver and white adipose tissues of normal rats, while no increase is seen in insulin-resistant mouse models [198]. In addition, fatty aldehydes accumulate in insulin-resistant diabetic rat livers due to failure of ALDH3A2 induction [199]. *In vitro*,

ALDH3A2 protects against cytotoxicity induced by the LPO-derived aldehyde, dodecanal [189]; and 4-HNE treatment in mouse adipocytes overexpressing ALDH3A2 results in decreased ROS production [198].

12. ALDH3B1

ALDH3B1 encodes a protein highly expressed in the kidney and liver and moderately expressed in lung and various regions of the brain including the cortex, striatum, hippocampus, brainstem and cerebellum [200]. While relatively little is known about ALDH3B1, it is a catalytically active enzyme that has distinct substrate specificity towards medium- and long-chain (six carbons and longer) saturated and unsaturated aliphatic aldehydes including the LPO-derived aldehydes hexanal, 4-HNE, nonanal, octanal, *trans*-2-hexenal, *trans*-2-nonenal, and *trans*-2-octenal, and the aromatic aldehyde benzaldehyde [200]. By contrast, short-chain aldehydes, such as MDA and acetaldehyde, appear to be poor substrates. While ALDH3B1 is capable of utilizing either NAD^+ or $NADP^+$ as cofactor, cofactor preference may be substrate-specific [200].

A SNP in intron 2 (rs581105; T/G) of *ALDH3B1* has recently been linked to the development of paranoid schizophrenia and proposed to be involved in an alteration of dopamine metabolism [201,202]. While ALDH3B1 is present in the brain, initial studies indicate that the dopamine-derived aldehyde DOPAL is a poor substrate [200]. However, ALDH3B1 may be involved in protecting the brain through the detoxification of other aldehydes, such as those produced during oxidative stress. In support of this, ALDH3B1 overexpression protects cells *in vitro* from toxicity induced by the LPO-derived aldehyde octanal [200]. An alternative splice variant of human *ALDH3B1* exists that lacks both exons 3 and 4 (corresponding to amino acids 55 – 91) and encodes a shorter ALDH3B1 protein isoform b, which may prove to have altered enzymatic activity and pathophysiological implications [200].

13. ALDH3B2

ALDH3B2, located upstream from *ALDH3B1* on chromosome 11q13.2, encodes a protein that shares 83% sequence identity with ALDH3B1. *ALDH3B2* contains an in-frame stop codon at codon 17, suggesting it may be a pseudogene; however, *ALDH3B2* transcripts have been found in human salivary gland tissue, indicating that *ALDH3B2* retains promoter activity [203]. Microarray data indicate that *ALDH3B2* is expressed in various organs including prostate, lung, kidney, liver and brain [204].

14. ALDH4A1

ALDH4A1, also known as pyrroline-5-carboxylate (P5C) dehydrogenase, is a mitochondrial matrix homodimer highly expressed in liver, skeletal muscle and kidney [205]. ALDH4A1 is involved in proline degradation and catalyzes the NAD^+-dependent conversion of P5C to the neurotransmitter, glutamate (Figure 6), which prevents the accumulation of P5C [206,207]. *ALDH4A1* mutations cause type II hyperprolinemia, an autosomal recessive disease characterized by seizures, mental retardation and high levels of P5C in physiological fluids [17,208]. Patients with type II hyperprolinemia have a frame shift (G521fs(+1)) or missense (S352L) mutation in *ALDH4A1* that results in ablated enzyme activity [208]. The phenotype associated with type II hyperprolinemia is the result of P5C-mediated deactivation of the vitamin B_6 derivative pyridoxal phosphate (PLP) through a Knoevenagel-type condensation reaction (see ALDH7A1; Figure 7)[209]. PLP is a required cofactor in a wide range of reactions, including the biosynthesis of neurotransmitters, and its inactivation is known to cause deleterious effects [210].

In addition to its role in proline metabolism, ALDH4A1 may be involved in protection against oxidative stress. ALDH4A1 appears to be a major enzyme responsible for the oxidation of short- and medium-chain aliphatic LPO-derived aldehydes [211] and, *in vitro*, cells overexpressing ALDH4A1 produce lower levels of intracellular ROS after hydrogen peroxide and UV treatment [212]. *ALDH4A1* is upregulated in response to DNA damage; this process appears to be *p*53-dependent, indicating that ALDH4A1 may have a role in DNA repair and cell survival [212]. Indeed, inhibition of ALDH4A1 expression in human glioblastoma cells results in increased susceptibility to *p*53-mediated apoptosis [212].

15. ALDH5A1

ALDH5A1 is a mitochondrial homotetramer found in liver, kidney, skeletal muscle, and brain [213]. ALDH5A1, also known as succinic semialdehyde (SSA) dehydrogenase (SSADH), catalyzes the NAD^+-dependent conversion of SSA (K_m 6.3 μM) to succinate (Figure 6) in the last step of GABA catabolism [213]. While SSA is primarily oxidized by ALDH5A1 to succinate, a small fraction is reduced by cytosolic SSA reductase to γ-hydroxybutyric acid [214], a compound with neurotransmitter- and neuromodulator-like properties normally only found in small quantities in the CNS [215]. *ALDH5A1* mutations, of which more than 50 have been identified, are responsible for γ-hydroxybutyric aciduria, a rare autosomal recessive disorder characterized by neurological and cognitive defects due to the accumulation of GABA, γ-hydroxybutyric acid, and SSA in tissues and physiological fluids [18].

Aldh5A1$^{-/-}$ mice, used as a model to study γ-hydroxybutyric aciduria, display absence seizure onset at 2 weeks that progresses to generalized tonic-clonic seizures and early death [216]. These mice also display altered brain phospholipid composition and significant downregulation of genes associated with myelin sheath thickness and compaction, indicating that ALDH5A1 may have a role in neurotransmission efficiency [217,218]. While the effects of γ-hydroxybutyric acid are not completely understood, the compound increases thiobarbituric acid-reactive substance (TBARS) levels and decreases the total antioxidant potential in rat cerebral cortex homogenates, suggesting elevated LPO and an association with oxidative stress processes [219]. Interestingly, ALDH5A1 is inhibited by the LPO-derived aldehydes acrolein and 4-HNE (IC_{50} 15 μM and 110 μM, respectively) [220].

16. ALDH6A1

ALDH6A1 is a mitochondrial tetramer expressed at high levels in the liver, kidney and heart and at lower levels in muscle and brain [221]. Also known as methylmalonate semialdehyde (MMS) dehydrogenase (MMSDH), ALDH6A1, the only known CoA-dependent human ALDH, is involved in valine and pyrimidine catabolism and catalyzes the oxidative decarboxylation of malonate semialdehyde (K_m 4.5 μM) and MMS (K_m 5.3 μM) to acetyl-CoA and propionyl-CoA, respectively [222].

ALDH6A1 mutations lead to a disorder characterized by a variety of metabolic abnormalities, including increased levels of 3-amino and 3-hydroxyisobutyric acids, β-alanine and 3-hydroxypropionic acid, usually accompanied by some degree of psychomotor delay [223]. To date, the *ALDH6A1* mutations involved are not well characterized; however, one patient was found to have a transversion (1336G > A) in *ALDH6A1* leading to the replacement of a highly conserved glycine with an arginine (G446R) [223].

ALDH6A1 is upregulated by valine carbon utilization for lipogenesis during the differentiation of 3T3-L1 fibroblasts into mature adipocytes [224]. ALDH6A1 has also been identified as a cardiac protein that undergoes oxidative modification via tyrosine nitration in aged rats, possibly contributing to age-dependent heart degeneration [225]. ALDH6A1, through the

metabolism of malonate semi-aldehyde, is also involved in the metabolism of the LPO-derived aldehyde, MDA, to acetyl-CoA (Figure 4).

17. ALDH7A1

ALDH7A1 is a homotetramer expressed in a wide range of tissues. High levels of ALDH7A1 are observed in rat heart, liver and kidney [226], while ALDH7A1 in black seabream fish (sbALDH7A1) is highly expressed in the liver and kidney but not the heart [227]. In human fetal tissues, ALDH7A1 has been detected at high levels in the cochlea, eye, ovary, heart and kidney, while moderate levels are observed in the liver, spleen, muscle, lung and brain [228].

Human ALDH7A1 has a primary role in the pipecolic acid pathway of lysine catabolism, catalyzing the oxidation of alpha-aminoadipic semialdehyde (AASA) (K_m 180 μM) to alpha-aminoadipate (Figure 7)[229]. *ALDH7A1* mutations are the molecular basis for pyridoxine-dependent epilepsy (PDE), an autosomal recessive disorder characterized by the onset of intractable seizures during infancy and early childhood, preventable by daily, high dose supplementation with pyridoxine (Vitamin B_6)[19]. Due to ALDH7A1 deficiency, increased concentrations of AASA and its cyclic Schiff base, piperidiene-6-carbxylate (P6C), occur in patients, which results in the inactivation and depletion of the coenzyme PLP through a Knoevenagel adduction reaction (Figure 7)[19]. PLP is a required coenzyme that is especially important in amino acid and neurotransmitter pathways, including those involving GABA, serotonin and noradrenaline [210]. The underlying cause of seizures in PDE has been attributed to PLP inactivation and subsequent disruption in neurotransmitter metabolism [19].

Aside from its role in AASA metabolism, little kinetic information exists regarding mammalian ALDH7A1 activity towards other substrates; however, *sb*ALDH7A1 shares 83% identity to the human protein and is active, albeit with low affinity, with a variety of common aldehydes including acetaldehyde (K_m 3.6 mM), propionaldehyde (K_m 1.2 mM), and benzaldehyde (K_m 0.45 mM). It has similar affinity for NAD^+ as mammalian ALDH7A1 [227]. *sb*ALDH7A1 is not active towards 4-HNE, MDA, SSA, betaine aldehyde or all-*trans* retinaldehyde.

ALDH7A1 shares 60% amino acid sequence identity with the osmotic stress-induced 26 g pea turgor plant protein, refered to as plant ALDH7B1, thought to be involved in the regulation of osmotic pressure within plant cells [226]. Plant ALDH7B1 expression increases in response to cellular stresses such as dehydration, temperature flunctuations and high salinity [230]. Sequence conservation between evolutionarily distant species, such as human ALDH7A1 and plant ALDH7B1, often indicates a functional similarity; however, ALDH7A1 levels *in vitro* do not appear to be affected by exposure to a variety of stress-inducing treatments such as heat shock, dehydration, ionizing irradiation, glucocorticoids, iron or t-butylhydroperoxide [226]. In addition, screening of the *sbALDH7A1* promoter region has identified no regions with homology to known osmotic response elements [231]. Interestingly, ALDH7A1 expression in the cochlea of the ear, dependent on the proper maintenance of internal hydrostatic pressure, indicates that mammalian ALDH7A1 may be involved in osmotic regulation with a potential role in hearing disorders. However, to date, no connection has been found, including in patients with Menière disease, an inner-ear disorder affecting hearing and balance [232].

ALDH7A1 is highly and differentially expressed during porcine oocyte maturation, including during the first and second meiotic stages [233]. Screening of the *sbALDH7A1* promoter region has revealed *cis*-elements related to cell cycle regulation [231].

18. ALDH8A1

While little information exists regarding ALDH8A1, it is a cytosolic enzyme with high expression in liver and kidney and moderate expression in brain, spinal cord, mammary gland,

thymus, adrenal, testis, prostate and gastrointestinal tract [234]. Along with the ALDH1 family, ALDH8A1 is also believed to participate in the biosynthesis of RA through the oxidation of retinal and displays a distinct preference for 9-*cis*-retinal, as opposed to all-*trans*-retinal [234], which is unique among the retinal-oxidizing ALDHs [235]. ALDH8A1 also metabolizes aliphatic aldehydes, including acetaldehyde (K_m 10.2 mM), decanal, octanal, hexanal and propanal, with activity that increases with chain length [234]. ALDH8A1 is also active towards several important metabolic aldehydes including SSA and glutaraldehyde [234].

19. ALDH9A1

ALDH9A1 encodes a cytosolic tetramer that is highly expressed in the liver, skeletal muscle, kidney and brain [236]. ALDH9A1, involved in an alternate biosynthesis pathway of GABA, catalyzes the oxidation of γ-aminobutyraldehyde (K_m 8 – 14 μM), the metabolite of the biogenic amine putrescine, to GABA (Figure 6)[237,238]. ALDH9A1 may also play a role in the metabolism of catecholamine-derived aldehydes such as the toxic dopamine metabolite, DOPAL (K_m 2.6 μM) [5,238]. ALDH9A1 also oxidizes betaine aldehyde [239], γ-trimethylaminobutyraldehyde, which is involved in carnitine biosynthesis [240], and acetaldehyde (K_m 40 – 50 μM) [237]. High affinity of ALDH9A1 for γ-aminobutyraldehyde, DOPAL, and acetaldehyde indicates that these substrates may compete for metabolism by ALDH9A1, which may affect GABA and dopamine pathways and brain development. In a Japanese fish model, ALDH9A1 is developmentally regulated and ethanol treatment downregulates *ALDH9A1* expression during embryogenesis, suggesting ALDH9A1 may play a role in the teratogenic effects of ethanol [241]. ALDH9A1 is also a candidate gene in inflammation-mediated aggravation of human non-alcoholic steatohepatitis [242].

20. ALDH16A1

ALDH16A1, one of the most recently identified ALDHs, was sequenced from a human uterine cDNA library by the Mammalian Gene Collection (MGC) consortium [243]. The 2627 bp transcript has been traced to human chromosome 19q13.33 and is composed of 17 exons, which encode an 802 amino acid protein containing a putative NAD^+-dependent ALDH domain, with a theoretical molecular weight of 85 kDa and an isoelectric point of 6.77. ALDH16A1 orthologues have since been identified in a variety of species including chimpanzee (98% identity), mouse (81% identity), rat, dog and zebra fish. Microarray data indicate that *ALDH16A1* is widely expressed in a variety of tissues including bone marrow, heart, kidney and lung [204]. To date, the physiological significance and function of ALDH16A1 remains to be established.

21. ALDH18A1

ALDH18A1, also known as Δ-pyrroline-5-carboxylate synthase (P5CS), is a bifunctional inner mitochondrial membrane enzyme containing an N-terminal γ-glutamyl kinase domain and a C-terminal γ-glutamyl phosphate reductase domain that is expressed at high levels in human pancreas, ovary, testis and kidney, and moderate levels in colon, small intestine, placenta, heart and skeletal muscle [244]. ALDH18A1 catalyzes the ATP- and NADPH-dependent reduction of glutamate to P5C, which is further converted to ornithine (Figure 6)[244]. This pathway is extremely important in the *de novo* synthesis of the amino acids proline and arginine; defects in ALDH18A1 lead to a variety of metabolic and neurologic abnormalities, including hypoprolinemia, hypoornithinemia, hypocitrullinemia, hypoargininemia and hyperammonemia with cataract formation, neurodegeneration and connective tissue anomalies [245,246]. Various *ALDH18A1* mutations have been described, including a missense mutation resulting in the replacement of a highly conserved leucine with a serine (L396S) [245], and an arginine to glutamine substitution (R84Q) at a conserved residue within the γ-glutamyl kinase domain [20]. While alternative splicing of *ALDH18A1* gives rise to two distinct isoforms,

namely ALDH18A1_i1 and ALDH18A1_i2, differing by a two amino acid insert very close to the γ-glutamyl kinase active site, mutations in either lead to deficient ALDH18A1 activity and metabolic abnormalities [20]. However, sensitivity to ornithine inhibition (K_i 0.25 mM), thought to play a regulatory role, is observed only in the shorter ALDH18A1_i2, which is expressed primarily in the gut, where it contributes to arginine biosynthesis [20]. ALDH18A1_i1 is expressed in multiple tissues and is predominantly involved in proline biosynthesis. ALDH18A1 is downregulated in the auditory midbrain of mice displaying age-dependent hearing loss, potentially due to accumulation of the ALDH18A1 substrate, glutamate, indicating that ALDH18A1 may play a role in preventing auditory toxicity by modulating glutamate levels [247].

22. Expert opinion and conclusion

Aldehydes are ubiquitous in nature and the environment, and are produced during numerous physiological processes and biotransformation events. It is known that several are essential to certain physiological processes (e.g., retinal for vision), and many aldehydes previously believed to be merely cytotoxic intermediates appear to have multiple functions including roles in signal transduction, gene regulation and cellular proliferation. Nonetheless, the toxicity of aldehydes is well characterized, most notably their ability to adduct macromolecules such as proteins and DNA. In this regard, it is not surprising that several enzyme systems (e.g., ADH, AKR, AO, XO, SDR, and ALDH) catalyze the metabolism of aldehyde species, many with broad overlapping substrate specificity. Of these, the ALDH superfamily clearly plays a very important role in the oxidative pathway of aldehyde detoxification.

Although the physiological role of several of the 19 human ALDH isozymes is unknown or not fully characterized, many have been shown to be critical in the detoxification of specific aldehyde substrates. The clinical importance of the ALDH superfamily is evidenced from human phenotypes directly linked to mutations in *ALDH* genes leading to the absence, deficiency or inactivation of ALDH proteins. Multiple disease states are associated with ALDH dysfunction including many cancers, metabolic diseases and neurological abnormalities. Aside from those that have been causally linked to the ALDH family, numerous other pathologies have been proposed to be influenced by these isozymes. ALDH genotype has also been shown to affect the efficacy of drug treatment for various diseases and disorders, including cancer. In this regard, it has been demonstrated for several drug therapies (e.g., nitroglycerin, cyclophosphamide) that patient ALDH genotype should be taken into consideration in order to design the most efficacious treatment strategy. Investigations focusing on ALDH genes and isozymes as therapeutic targets in certain disease states have shown promise and will no doubt be a part of future research efforts.

Aside from their demonstrated importance in aldehyde metabolism, the ALDH superfamily also exhibits multiple catalytic and non-catalytic functions. These enzymes may have important, yet to be clearly defined, roles in ester metabolism, drug bioactivation, ROS scavenging and the absorption of UV light. The significance of the capacity of several ALDHs to bind various endogenous (e.g., thyroid hormone) and exogenous (e.g., acetaminophen, daunorubicin) compounds remains to be elucidated. The recent discovery of ALDH isozymes present in multiple subcellular compartments – including the nucleus, where they may exert effects on gene expression and cellular proliferation – is exciting, and points to unique physiological roles of these enzymes as governed by subcellular localization. It is our belief that as research of the ALDH superfamily expands, these isozymes will be found to be critical in a number of diseases and developmental processes, making human ALDH genotype an important factor in clinical treatment strategies.

Acknowledgements

We thank our colleagues, especially Dr David Thompson, for valuable discussions and critical reading of this manuscript. This work was supported by NIH/NEI grants EY11490 and EY17963. S Marchitti was supported by NIH/NIAAA predoctoral Fellowship AA016875.

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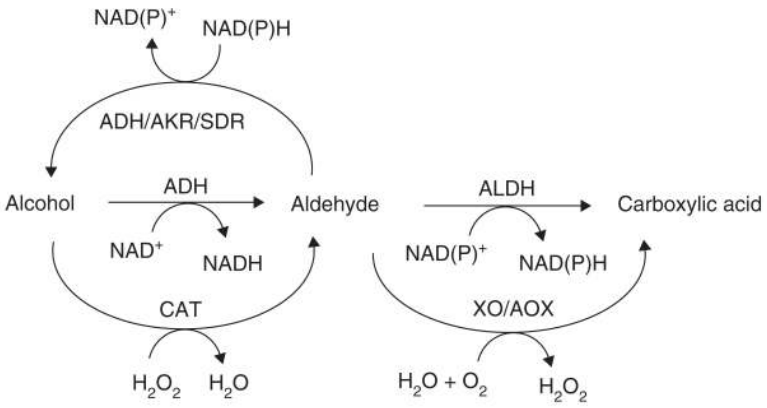

Figure 1. Non-P450 enzymatic metabolism of aldehydes

ADH: Alcohol dehydrogenase; AKR: Aldo-keto reductase; ALDH: Aldehyde dehydrogenase; AO: Aldehyde oxidase; CAT: Catalase; SDR: Short chain dehydrogenase/reductase; XO: Xanthine oxidase.

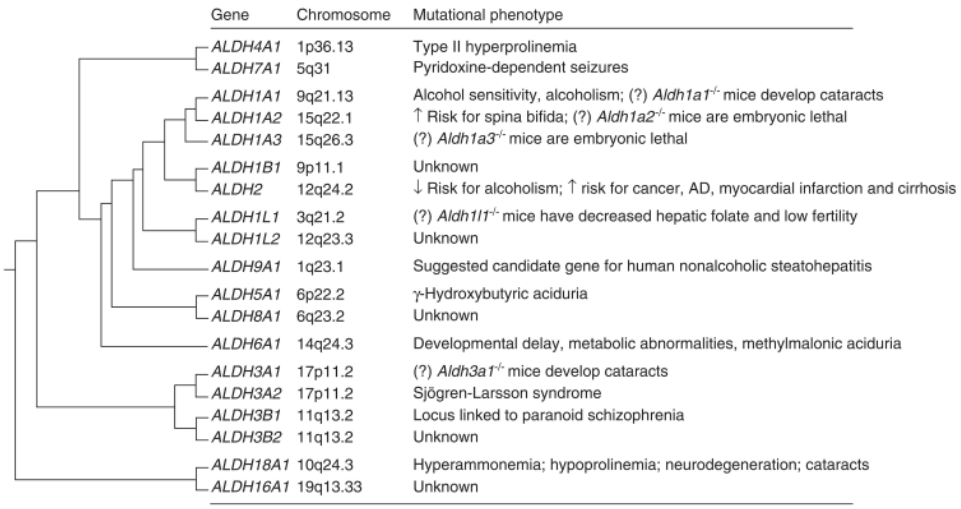

Figure 2. Evolutionary relationship and mutational phenotypes of the nineteen human ALDH genes

Clustering dendogram illustrates the evolutionary relationship of the nineteen human ALDH genes from a common ancestral gene ~ 3 billion years ago. Chromosomal location is also described. (?) indicates phenotype demonstrated in animals but not yet described in humans.

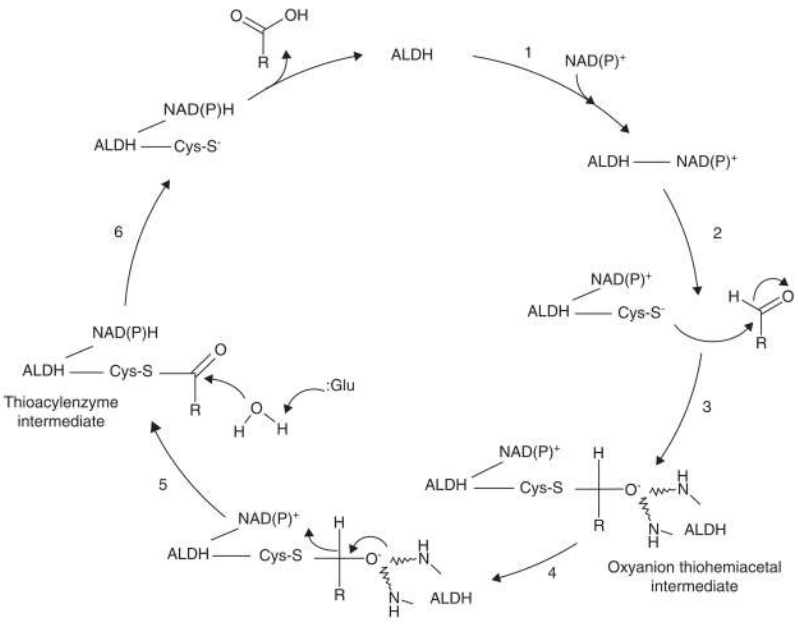

Figure 3. Proposed non-CoA dependent ALDH catalysis mechanism

1, Cofactor binding results in a conformation change of the enzyme and activation of the catalytic thiol (Cys-S^{-}); 2, Nucleophilic attack of the aldehyde substrate; 3, Oxyanion intermediate stabilized by two NH groups of the ALDH peptide chain; 4, Hydride transfer to cofactor. 5; Glutamate residue acts as a base catalyst in the hydrolysis of the thioacylenzyme intermediate; 6, Release of carboxylic acid product followed by cofactor.

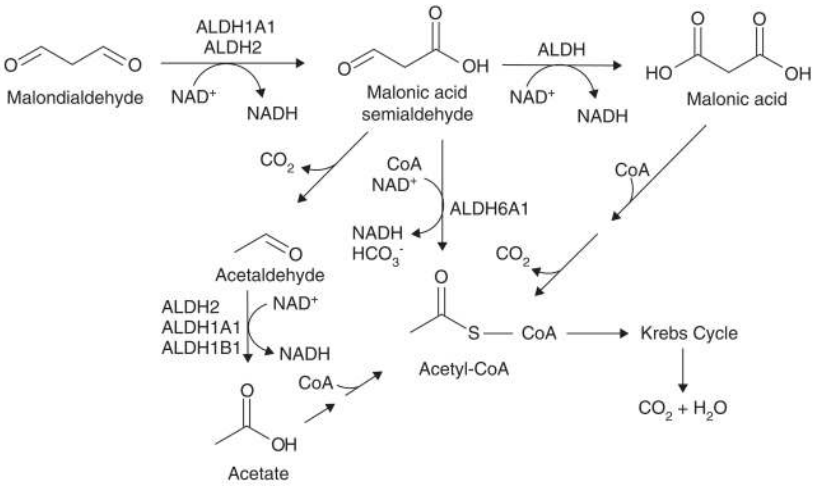

Figure 4. The role of ALDH isozymes in the metabolism of malondialdehyde (MDA)

MDA is the major aldehyde product of lipid peroxidation. The proposed pathway of MDA metabolism involves ALDH1A1, ALDH2 and ALDH6A1.

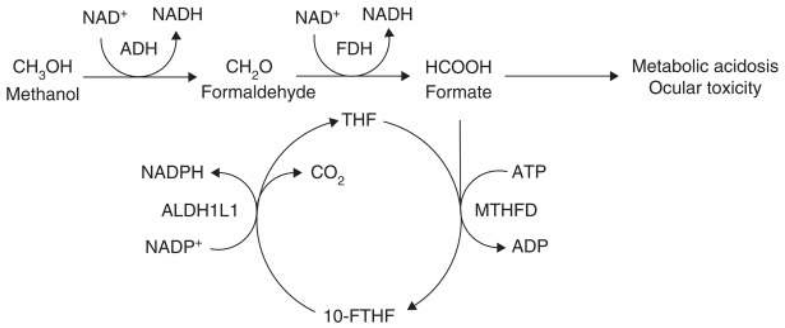

Figure 5. The role of ALDH1L1 in methanol metabolism and toxicity

Methanol is metabolized to the end product, carbon dioxide, through a pathway in which it is first converted to formaldehyde by ADH, which in turn is rapidly metabolized to formate by FDH. A build-up of formate is thought to cause the majority of the deleterious effects associated with methanol poisoning. Formate can enter the folate pathway through its conjugation to THF by MTHFD to form 10-FTHF, which is converted back into THF by ALDH1L1, accompanied by the release of carbon dioxide.

10-FTHF: 10-formyltetrahydrofolate; ADH: Alcohol dehydrogenase; ALDH1L1: Aldehyde dehydrogenase 1 family, member L1; FDH: Formaldehyde dehydrogenase; MTHFD: Methylenetetrahydrofolate dehydrogenase; THF: Tetrahydrofolate.

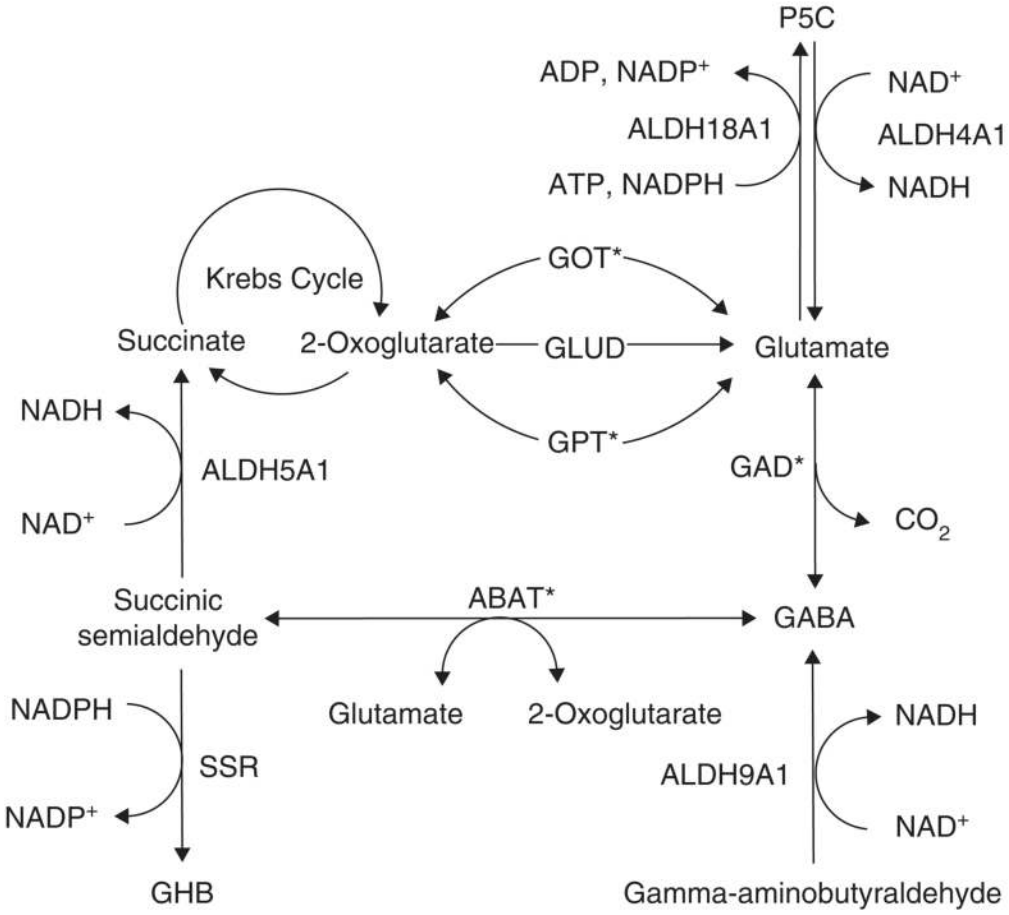

Figure 6. The role of ALDH isozymes in glutamate and GABA pathways

ALDH4A1, ALDH5A1, ALDH9A1 and ALDH18A1 play many important roles in the synthesis and catabolism of the neurotransmitters glutamate and γ-aminobutyric acid, and mutational defects in these ALDH genes result in a variety of neurological disorders.

*Indicates enzymes that require pyridoxal phosphate (PLP) as cofactor.

ABAT: 4-Aminobutyrate aminotransferase GABA, γ-aminobutyric acid; GAD: Glutamate decarboxylase; GHB: γ-hydroxybutyric acid; GLUD: Glutamate dehydrogenase; GOT: Glutamic-oxaloacetic transaminase; GPT: Glutamic-pyruvate transaminase; SSR: Succinic semialdehyde reductase.

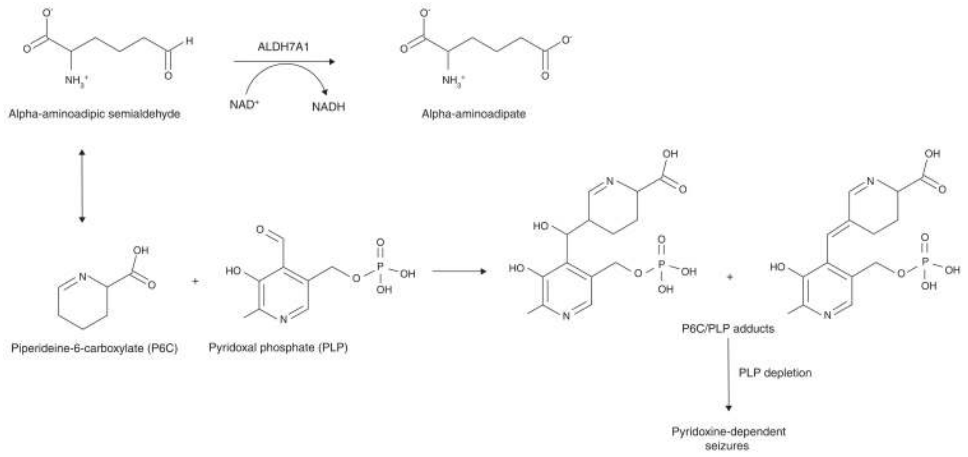

Figure 7. The role of ALDH7A1 as an alpha-aminoadipic semialdehyde (AASA) dehydrogenase

AASA is in equilibrium with its cyclic Schiff base, piperideine-6-carboxylate (P6C). Pyridoxal phosphate (PLP) is the active form of vitamin B_6 and an important cofactor in many types of reactions. Mutations in *ALDH7A1* result in the accumulation of P6C and Knoevenagel adduct products between P6C and PLP, leading to the inactivation and depletion of PLP and pyridoxine-dependent seizures.

Table 1

Human ALDH proteins.

ALDH	Subcellular location	Preferred aldehyde substrate	Additional functions and characteristics
ALDH1A1	Cytosol	Retinal	Ester hydrolysis; binds androgen, cholesterol, thyroid, daunorubicin, and flavopiridol; corneal and lens crystallin; oxidizes DOPAL, acetaldehyde
ALDH1A2	Cytosol	Retinal	High affinity for LPO-derived aldehydes
ALDH1A3	Cytosol	Retinal	High affinity for LPO-derived aldehydes
ALDH1B1	Mitochondria	Acetaldehyde	May protect the cornea from UV-light
ALDH1L1	Cytosol	10-Formyltetrahydrofolate	Binds acetaminophen
ALDH1L2	Unknown	Unknown	Induced by the anti-inflammatory agent indomethacin
ALDH2	Mitochondria	Acetaldehyde	Ester hydrolysis; nitroglycerin bioactivation, oxidizes LPO-derived aldehydes; binds acetaminophen; oxidizes DOPAL and DOPEGAL
ALDH3A1	Cytosol, nucleus[*]	Aromatic, aliphatic aldehydes	Ester hydrolysis; scavenges ROS; UV-filter; corneal crystallin; oxidizes LPO-derived aldehydes; regulation of cell-cycle; inducted by PAHs
ALDH3A2	Microsomes, peroxisomes [‡]	Fatty aldehydes	Insulin regulates gene expression
ALDH3B1	Cytosol [§]	Unknown	Oxidizes LPO-derived aldehydes
ALDH3B2	Unknown	Unknown	Unknown
ALDH4A1	Mitochondria	Glutamate γ-semialdehyde	Ester hydrolysis; may mitigate oxidative stress
ALDH5A1	Mitochondria	Succinate semialdehyde	May be involved in neurotransmission efficiency
ALDH6A1	Mitochondria	Malonate semialdehyde	Esterase activity; only known human CoA-dependent ALDH
ALDH7A1	Cytosol, nucleus, mitochondria[¶]	α-Aminoadipic semialdehyde	Closely related to plant osmoregulatory protein; may regulate cell cycle
ALDH8A1	Cytosol	Retinal	Oxidizes LPO-derived aldehydes and acetaldehyde
ALDH9A1	Cytosol	γ-Aminobutyraldehyde	Oxidizes betaine, acetaldehyde and DOPAL; involved in carnitine biosysnthesis; esterase activity
ALDH16A1	Unknown	Unknown	Unknown
ALDH18A1	Mitochondria	Glutamic γ-semialdehyde	Unknown

[*] While predominantly cytosolic, ALDH3A1 is also found in the nucleus.

[‡] A variant of ALDH3A2, FALDH*v*, is believed to be localized to the peroxisomes.

[§] Marchitti SA, Vasiliou V. unpublished data.

[¶] Brocker C, Cantore M, Pappa A, *et al.* unpublished data.

Table 2

ALDH isozymes putatively involved in cancer.

ALDH	Cancer phenotype	Ref.
ALDH1A1	Increases the resistance of tumor cells to oxazaphosphorine anticancer drugs	[71,72]
	Increases the resistance of normal cells to the oxazaphosphorine anticancer drugs	[74]
	Downregulated in human adrenocortical carcinomas	[77]
	Downregulated in mouse liver tumors	[75]
	Binds to anticancer drugs (e.g., daunorubicin, flavopiridol)	[75,76]
ALDH1A2	Candidate tumor suppressor in prostate cancer	[101]
ALDH1A3	Downregulated in human breast cancer cell lines (e.g., MCF-7)	[110]
	Downregulated in mammary tumor-susceptible BALB/cJ mice and upregulated in mammary tumor-resistant mice	[112]
	Upregulated by induction of wild-type *p*53 in cultured human colon cancer cells	[111]
	Methylation-silenced in gastric cancer	[113]
	Upregulated by the anticancer cytotoxic agent interleukin-13 in human glioma cells	[114]
ALDH1L1	Downregulated in human liver, lung, prostate, pancreas and ovarian cancers	[122]
	Over-expression in cancer cell lines suppresses cellular proliferation and induces apoptosis	[127]
	Anticancer drug methotrexate induces ALDH1L1 activity	[132]
ALDH2	ALDH2 dysfunction is associated with increased risk for multiple cancers including upper digestive track cancers, stomach, colon, lung, head and neck cancers	[6]
ALDH3A1	Increases the resistance of tumor cells to oxazaphosporine anticancer drugs	[177]
	Increases chemotherapy resistance of human PBPCs to4-hydroperoxycyclophosphamide	[179]
	Detoxifies LPO-derived aldehydes in human hepatoma and lung tumor cells	[174]
	Upregulated in human cancer tissues and cell lines	[180]
	May regulate cell cycle and facilitate DNA repair	[13]
ALDH4A1	Upregulated as a result of DNA damage; may be a direct target of tumor suppressor gene *p*53	[212]
ALDH7A1	May regulate cell cycle	[231]