ALDH1A1 VIP Summary

Written in 2008; Posted on PharmGKB 2017
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Background

ALDH1A1 is one member of a family of aldehyde dehydrogenases, and is also known as the cytosolic aldehyde dehydrogenase. The human ortholog of this enzyme was first purified in 1979 [Article:224930], and the genomic structure and protein length (501 amino acids) were described ten years later [Article:2591967]. ALDH1A1 shows strong tissue expression in the liver, but is also constitutively expressed in other tissues, including erythrocytes, eye, and brain [Article:10971205]. Aldehyde dehydrogenases are of interest due to their important and diverse physiological roles, which often include the detoxification of metabolic intermediates from an aldehyde form to a carboxylic acid form.

Function

ALDH1A1 has been shown to play a role in alcohol metabolism [Article:17718394]. The alcohol metabolism process is essentially a two step process: first alcohol is converted to acetaldehyde by an alcohol dehydrogenase family member, and then the acetaldehyde is converted to acetate by an aldehyde dehydrogenase (ALDH1A1 or ALDH2) [Article:17718394]. The intermediate metabolite, acetaldehyde, is thought to be toxic at high levels, and it may be responsible for some of the adverse reactions associated with alcohol such as facial flushing, nausea, and an increased heart rate [Article:17718394]. An accumulation of acetaldehyde can occur either due to a hyperactive alcohol dehydrogenase enzyme, or an impaired aldehyde dehydrogenase enzyme [Article:17718394]. Although some genetic variation has been described for ALDH1A1 (see variant pages), it appears that genetic variation in ALDH2 plays a more important role in determining predisposition towards alcoholism [Article:17718394].

ALDH1A1 is also involved in the retinol (vitamin A) metabolic pathway [Article:12851412]. The retinol pathway and the ethanol pathway share considerable overlap, and ALDH1A1 is involved in the conversion of retinaldehyde to retanoic acid (RA) [Article:12851412]. Vitamin A (retinol) can be converted to retinal by alcohol dehydrogenase enzymes, and then further converted to RA by ALDH1A1 or other aldehyde dehydrogenases [Article:10880953]. Retinoic Acid is involved in a number of physiological processes including cell growth and differentiation [Articles:10971205, 10880953]. RA exerts its effect on the transcriptional level, by binding to retinoid receptors RAR and/or RXR, which often form a heterodimer [Article:10880953]. The RAR/RXR heterodimer is then able to transcriptionally regulate several genes. There may be some interactions between retinol and ethanol metabolic pathways, which could potentially play a role in fetal alcohol syndrome [Article:9802541].

ALDH1A1 and Drug Metabolism

ALDH1A1 has also been shown to be involved in the resistance to the chemotherapeutic agent cyclophosphamide (CP) and its derivatives [Article:15237855]. CP is used in the treatment of several types of cancer [Article:15237855]. CP is converted to 4-hydroxycyclophosphamide by several different CYP enzymes, and the 4-hydroxy-CP which can intraconvert with aldophosphamide [Article:15237855]. Aldophosphamide can undergo several metabolic fates, including the formation of acrolein and phosphoramide mustard, both of which are cytotoxic alkylating agents [Article:15237855]. Alternatively, aldophosphamide can be metabolized by ALDH1A1 (or other aldehyde dehydrogenases) to carboxyphosphamide [Article:15237855]. This is considered to be a detoxification step, as carboxyphosphamide is not cytotoxic [Article:10469894]. An increase in expression of ALDH1A1 has been shown to be correlated with CP-resistant cancers in patients [Article:16918308], and in vitro evidence suggests that tranfection with ALDH1A1 can be sufficient to confer resistance to CP-induced cytotoxicity [Article:10469894].

Important Variant: ALDH1A1*2 (rs6151031)

ALDH1A1*2 is a 17bp deletion variant in the promoter region of ALDH1A1, that was first identified by Spence *et al*. through a screening of promoter polymorphisms in diverse ethnic groups [Article:14506398]. The authors found no significant difference between ALDH1A1*2 expressing constructs and ALDH1A1*1 expressing constructs (the reference sequence) with luciferase assays conducted in both HeLa and HepG2 cells [Article:14506398].

Several studies have attempted to associate the presence of the ALDH1A1*2 allele with alcoholism or alcohol dependence in different populations with conflicting results. The initial discovery study found a non-statistically significant trend in the African American population linking carriers of the ALDH1A1*2 allele with alcoholism [Article:14506398] . Later studies conducted in Indo-Trinidadians seemed to support this contention, as they also observed an association between alcohol dependence and the presence of a ALDH1A1*2 allele [Articles:17718398, 17286337]. In contrast, studies in Southwest California Indian tribes showed the opposite trend; namely that ALDH1A1*2 was associated with a protective effect against alcoholism [Articles:17718395, 15597079]. Another study found that ALDH1A1*2 may be associated with a decreased risk of alcoholism in African Americans, contrary to the trend found in the initial discovery study [Article:17718396].

The mechanism for the effect (if any) of ALDH1A1*2 is unclear, but Spence *et al.* suggest that it is possible that the deletion encoded by ALDH1A1*2 may eliminate a c-myb (a putative transcription factor) binding site from the promoter region of ALDH1A1 [Article:14506398].

Important Variant: ALDH1A1*3

ALDH1A1*3 is a 3bp insertion variant in the promoter region of ALDH1A1, that was first identified by Spence *et al*. through a screening of promoter polymorphisms in diverse ethnic groups [Article:14506398]. In contrast to ALDH1A1*2, which was found at low frequencies in every ethnic group examined by Spence et al, ALDH1A1*3 was found specifically in African Americans [Article:14506398].
In vitro luciferase studies in HeLa and HepG2 cell lines suggest that ALDH1A1*3 has significantly lower expression than ALDH1A1*1 (the reference sequence) [Article:14506398]. This suggests that ALDH1A1*3 may not be transcribed as efficiently, and may lead to a reduction in function [Article:14506398] . In seeming agreement with this contention, Spence *et al*. found that the frequency of ALDH1A1*3 was significantly higher among African American alcoholics [Article:14506398] . However, a later study by Scott *et al*. suggested that ALDH1A1*3 actually had a protective effect against alcoholism [Article:17718396].