

H63D: The Other Mutation



Mutations of the hemochromatosis gene HFE have been associated with liver disease, bone and joint disease, diabetes mellitus, heart disease, hormone imbalances, porphyria cutanea tarda (PCT), infertility, stroke, neurodegenerative disorders, cancer, venous and peripheral artery disease.

In the years since discovery of HFE and its mutations, researchers have focused studies primarily on the C282Y mutation because of its prominence in people with elevated iron levels. About 85% of individuals with abnormally high iron possess two copies of C282Y, therefore this mutation has been more extensively studied. Other mutations such as S65C or H63D have not garnered the attention of researchers. The S65C muta-

tion may lead to mild to moderate hepatic (liver) iron overload, especially when in combination with other mutations. C282Y/S65C compound heterozygotes have demonstrated elevated serum iron indices and iron overload.

When examined, H63D stands out as a significant modifier of disease onset, progression and even response to therapy. H63D is associated with arterial stiffness, pro-oxidation, higher total and low-density lipoprotein cholesterol when alcohol is consumed; acute lymphoblastic leukemia (ALL); decreased sperm production; higher risk of type II diabetes mellitus. Being a carrier of the H63D hemochromatosis mutation is a risk factor for earlier onset and longer duration of kidney disease in type II diabetic patients.

Alcoholic liver disease is more prominent in the H63D homozygote. Being a carrier (heterozygote) of H63D mutation is associated with a higher risk of liver cancer in cirrhotic patients regardless of their underlying liver disease. H63D was present in 42% of in patients with alpha-1-antitrypsin deficiency who had cirrhosis. H63D mutation was an independent factor associated with viral response to therapy for chronic hepatitis C patients.

The most striking risk associated with H63D is for the neurodegenerative diseases. Connor, et al were among the first investigators to consider the role of H63D in brain iron accumulation, oxidative stress and neurotransmitter performance. Connor reported that the H63D HFE variant contributes to many of the processes associated with Alzheimer's Disease (AD). These processes include increased cellular iron, oxidative stress (free radical activity), glutamate dyshomeostasis (abnormal balance), and an increase in tau phosphorylation (abnormal levels of tau proteins can result in dementias such as Alzheimer's).

Connor continues that HFE H63D cells were shown to have more oxidative stress, further supporting their role as neurodegenerative disease modifiers. Connor found that patients homozygous for H63D had earlier signs of mild cognitive impairment and earlier onset of Alzheimer's compared to those with normal HFE or H63D heterozygotes. ■



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