UPDATED REPRINT

H63D: The Other Mutation (2021 Version)

David Seideman, Lucas Smith, Carolina Diamandis

Corresponding Authors

LCG Lazar Research
Dr. Carolina Diamandis
16 Kifissias Avenue
115 26 Athens, Hellenic Republic
www.your-doctor.com

Supported by the International H63D Consortium.

Abstract

In 2010, the Iron Disorders Institute published the first seminal article on the underestimated risk of a homozygous HFE gene H63D mutation. This short but important article has lost none of its relevance. Since it is in danger of being forgotten and disappearing from more and more websites, we are publishing a reprint of the still seminal article, expanded with some new findings.

What we know

Homozygous mutations of HFE Gene H63D has been taken not seriously enough for many decade. This although homozygous mutation of HFE Gene H63D is Pandora's box. It has been associated with liver disease, bone and joint disease, diabetes mellitus, heart disease, hormone imbalances, porphyria cutanea tarda (PCT), infertility, stroke, severe neurodegenerative disorders, cancer, venous peripheral artery disease and H63D syndrome.

In the years since discovery of HFE and its mutations, researcher shave 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 mutation may lead to mild to moderate hepatic (liver) iron overload, especially when in combination with other mutations. C282Y/ S65C compound heterozygotes have demonstrated elevated se- rum 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 stiff- ness, 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 ear- lier 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).

As Jacobs, Papadopoulos Kaufmann, and colleagues (2012, 2015, 2017, 2019, 2020, 2021) impressively demonstrated using solid patient data, the numerous damages in parenchymal tissue and the brain (substantia nigra and basal ganglia) can be explained by insidious poisoning with non-transferrin-bound iron (NTBI) as a consequence of chronic transferrin saturation of >50%. This constellation (H63D

syndrome) is similar to Wilson's disease, except that NTBI iron, rather than copper, is the culprit here. In addition, the damage caused by H63D syndrome is more widespread in the body, affecting not only the liver but also the heart, brain and, in men, the testes. Synucleinopathies are a major problem in H63D syndrome, but other forms of cognitive decline are also common.

Connor continues that HFE H63D cells were shown to have more oxidative stress, further support- ing 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.

Conflicts of interest

None.

References

–Environ Health Perspect. 2010; HFE H63D Polymorphism as a Modifier of the Effect of Cumulative Lead Exposure on Pulse Pressure: the Normative Aging Study. Zhang A, Park SK, Wright RO, Weisskopf MG, Mukherjee B, Nie H, Sparrow D, Hu H.

–Pol Arch Med Wewn. 2010120(4):127-31. HFE gene mutations in patients with alcoholic liver disease. A prospective study from northwestern Poland. Raszeja-Wyszomirska J, Kurzawski G, Zawada I, Suchy J, Lubinski J, Milkiewicz P.

–Respirology. 2010 Jan;15(1):141-9. Population-based study of cystic fibrosis disease severity and haemochromatosis gene mutations.Pratap U, Quinn S, Blizzard LB, Reid DW.

–J Exp Clin Cancer Res. 2010 Mar 2;29:18.Association between C282Y and H63D mutations of the HFE gene with hepatocellular carcinoma in European populations: a meta-analysis. Jin F, Qu LS, Shen XZ.

–J Alzheimers Dis. 2010 Apr;20(1):333-41. Prevalent iron metabolism gene variants associated with increased brain ferritin iron in healthy older men. Bartzokis G, Lu PH, Tishler TA, Peters DG, Kosenko A, Barrall KA, Finn JP, Villablanca P, Laub G, Altshuler LL, Geschwind DH, Mintz J, Neely E, Connor JR.

–J Diabetes Complications. 2010 Mutation H63D in the HFE gene confers risk for the development of type 2 diabetes mellitus but not for chronic complications. Colli ML, Gross JL, Canani LH. –Diabetes Care. 2001 Jul;24(7):1187-91. Role of hemochroma-

tosis C282Y and H63D mutations in HFE gene in development of type 2 diabetes and diabetic nephropathy.

–Diabetes Metab. 2002 Feb;28(1):33-8. Clinical expression and insulin sensitivity in type 2 diabetic patients with heterozygous mutations for haemochromatosis.Van Lerberghe S, Hermans MP, Dahan K, Buysschaert M.

–Endocrine. 2004 Jul;24(2):111-4. The HFE gene is associated to an earlier age of onset and to the presence of diabetic nephropathy in diabetes mellitus type 2.Oliva R, Novials A, Sánchez M, Villa M, Ingelmo M, Recasens M, Ascaso C, Bruguera M, Gomis R.

–Gut. 2002 Nov;51(5):723-30. Mild iron overload in patients carrying the HFE S65C gene mutation: a retrospective study in patients with suspected iron overload and healthy controls. Holmström P, Marmur J, Eggertsen G, Gåfvels M, Stål P.

–J Hepatol. 2002 Apr;36(4):474-9. Frequency of the S65C muta- tion of HFE and iron overload in 309 subjects heterozygous for C282Y. Wallace DF, Walker AP, Pietrangelo A, Clare M, Bomford AB, Dixon JL, Powell LW, Subramaniam VN, Dooley JS.

–Biochim Biophys Acta. 2010 Apr;1802(4):389-95. Prolyl-peptidyl isomerase, Pin1, phosphorylation is compromised in association with the expression of the HFE polymorphic allele, H63D. Hall EC 2nd, Lee SY, Simmons Z, Neely EB, Nandar W, Connor JR.

–Neurobiol Aging. 2009 Expression of the HFE allelic variant H63D in SH-SY5Y cells affects tau phosphorylation at serine residues. Hall EC 2nd, Lee SY, Mairuae N, Simmons Z, Connor JR.

–Neurobiol Aging. 2009 HFE polymorphisms affect cellular glutamate regulation. Mitchell RM, Lee SY, Simmons Z, Connor JR.

–Neurobiol Aging. 2004 Apr;25(4):465-74. Evaluation of HFE (hemochromatosis) mutations as genetic modifiers in sporadic AD and MCI. Berlin D, Chong G, Chertkow H, Bergman H, Phil- lips NA, Schipper HM.

–Ann Hematol. 2009 An extensive analysis of the hereditary hemochromatosis gene HFE and neighboring histone genes: associations with childhood leukemia. Davis CF, Dorak MT.

–Pediatr Blood Cancer. 2009 Dec 15;53(7):1242-8. Hereditary hemochromatosis gene (HFE) variants are associated with birth weight and childhood leukemia risk.Dorak MT, Mackay RK, Relton CL, Worwood M, Parker L, Hall AG.

–Leuk Lymphoma. 2006 Nov;47(11):2331-4. HFE gene mutations in patients with acute leukemia. Viola A, Pagano L, Laudati D, D'Elia R, D'Amico MR, Ammirabile M, Palmieri S, Prossomariti L, Ferrara F.

–Leuk Lymphoma. 2006 Nov;47(11):2269-70. HFE H63D variant and leukemia susceptibility. Dorak MT.

–Hepatology. 2010 Apr;51(4):1311-8. HFE C282Y homozygotes are at increased risk of breast and colorectal cancer. Osborne NJ, Gurrin LC, Allen KJ, Constantine CC, Delatycki MB, McLaren CE, Gertig DM, Anderson GJ, Southey MC, Olynyk JK, Powell LW, Hopper JL, Giles GG, English DR.

–Circ Cardiovasc Genet. 2009 Feb;2(1):34-7. HFE C282Y homozygosity is associated with lower total and low-density lipoprotein cholesterol: The hemochromatosis and iron overload screening study. Adams PC, Pankow JS, Barton JC, Acton RT, Leiendecker-Foster C, McLaren GD, Speechley M, Eckfeldt JH.

–Gastroenterology. 2010 Mar;138(3):905-12. HFE genotype, parenchymal iron accumulation, and liver fibrosis in patients with nonalcoholic fatty liver disease. Valenti L, Fracanzani AL, Bugianesi E, Dongiovanni P, Galmozzi E, Vanni E, Canavesi E, Lattuada E, Roviaro G, Marchesini G, Fargion S.

–J Clin Endocrinol Metab. 2009 Nov;94(11):4391-7. Mutations in HFE causing hemochromatosis are associated with primary hypertriglyceridemia. Solanas-Barca M, Mateo-Gallego R, Calmarza P, Jarauta E, Bea AM, Cenarro A, Civeira F.

–Hepatology. 2009 Jul;50(1):94-101. HFE C282Y/H63D compound heterozygotes are at low risk of hemochromatosis- related morbidity. Gurrin LC, Bertalli NA, Dalton GW, Osborne NJ, Constantine CC, McLaren CE, English DR, Gertig DM, Delatycki MB, Nicoll AJ, Southey MC, Hopper JL, Giles GG, An- derson GJ, Olynyk JK, Powell LW, Allen KJ; HealthIron Study Investigators.

–Mod Pathol. 2010 May;23(5):637-43. HFE mutations in alpha- 1-antitrypsin deficiency: an examination of cirrhotic explants. Lam M, Torbenson M, Yeh MM, Vivekanandan P, Ferrell L.

–Eur J Gastroenterol Hepatol. 2010 The H63D genetic variant of the HFE gene is independently associated with the virological response to interferon and ribavirin therapy in chronic hepatitis C. Carneiro MV, Souza FF, Teixeira AC, Figueiredo JF, Villanova MG, Secaf M, Passos A, Ramalho LN, Carneiro FP, Zucoloto S, Martinelli AL.

–World J Gastroenterol. 2009 Jan 7;15(1):106-11. Iron homeo- stasis and H63D mutations in alcoholics with and without liver disease. Machado MV, Ravasco P, Martins A, Almeida MR, Camilo ME, Cortez-Pinto H.

–Mol Biol Rep. 2009 Sep;36(7):1709-14. Hereditary haemochromatosis gene (HFE) H63D mutation shows an association with abnormal sperm motility. Gunel-Ozcan A, Basar MM, Kisa U, Ankarali HC.

–Neurobiol Aging. 2009 Feb;30(2):330-2. HFE variants, APOE and Alzheimer's disease: findings from the population-based Rotterdam study. Alizadeh BZ, Njajou OT, Millán MR, Hofman A, Breteler MM, van Duijn CM.

–Rev Esp Enferm Dig. 2007 Jul;99(7):376-81 The H63D muta- tion in the HFE gene is related to the risk of hepatocellular carcinoma Ropero P, Briceño O, López-Alonso G, Agúndez JA, González Fernández FA, García-Hoz F, Villegas Martínez A, Díaz-Rubio M, Ladero JM.

–Hepatol Res. 2008 Mar;38(3):319-23. Epub 2007 Oct 16. Non-prescription supplement-induced hepatitis with hyperferritinemia and mutation (H63D) in the HFE gene. Fujii H, Takagaki N, Yoh T, Morita A, Ohkawara T, Yamaguchi K, Minami M, Sawa Y, Okanoue T, Ohkawara Y, Itoh Y.

–Tissue Antigens. 2007 Oct;70(4):294-300. Elevated MCP-1 serum levels are associated with the H63D mutation and not the C282Y mutation in hereditary hemochro- matosis. Lawless MW, White M, Mankan AK, O'Dwyer MJ, Norris S.

–Am J Hematol. 2007 Dec;82(12):1076-9. Hemochromatosis-associated gene mutations in patients with myelodysplastic syndromes with refractory anemia with ringed sideroblasts. Nearman ZP, Szpurka H, Serio B, Warshawksy I, Theil K, Lichtin A, Sekeres MA, Maciejewski JP.

–Researchsquare, 2021: Incidence of a clinically relevant H63D syndrome in carriers of a homozygous mutation of HFE gene H63D. Diamandis C. et al.

–H63D H63D Syndrome Consortium 2020: Consensus Paper of the International H63D Research Consortium (English Edition). Sørensen S. et al.

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