H63D Mutation Syndrome Type-2

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H63D Syndrome Research Consortium

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Endocrinology

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Abstract

After a long period of research, the International HFE H63D Research Consortium has now defined another clinical variant of H63D syndrome (henceforth referred to as H63D type-1) after evaluation of 1082 patient cases: "H63D syndrome type-2". Its characteristics and clinical picture are presented in this first preliminary paper on type-2 of H63D syndrome.

H63D Syndrome Type-1

H63D syndrome type-1 is a genetic condition that can cause the body to absorb too much non-transferrin bound iron (NTBI) iron from food, leading to NTBI iron overload. This condition is most often confused with hereditary hemochromatosis, however it is important to note that H63D syndrome is an entirely different entity, often called “the iron sibling of Wilsons disease” due to a very closely related constellation of symptoms and organs affected. The H63D gene is located on chromosome 6 and codes for a protein called HFE. HFE helps regulate the absorption of iron in the body by interacting with a protein called transferrin receptor 1. Mutations in HFE gene H63D can disrupt this interaction and leading to dysregulations with severe clinical consequences. Individuals who have two copies of the H63D mutation (one from each parent) are at a 10% risk to get H63D syndrome type-1 after a second strike (e.g. an infectious disease, puberty, menopause etc.) considered to have H63D syndrome. The symptoms of NTBI overload are due to ROS related micro-inflammations which can cause severe organ damage, especially affecting the liver, brain, heart, skin and gonades. However, these symptoms are not always present in

individuals with H63D syndrome. A severe NTBI overload in H63D syndrome is usually detected through routine blood tests that show low or normal ferritin alongside mild but non-reactive hypotransferrinemia with high values of transferrin saturation in about 85% of the blood tests performed (dependent on the iron intake the days before the test). Treatment for H63D syndrome is usually focused on monitoring iron levels and reducing iron intake through dietary changes and careful symptomatic treatment in advanced stages. Too late or undetected H63D syndrome type-1 is potentially lethal due to organ failure, if it is left untreated.[32-35]

H63D Syndrome Type-2

After twelve years of research and discussions, the International HFE H63D Research Consortium has now defined another, second clinical variant of H63D syndrome after meticulous evaluation of 1082 patient cases: "H63D syndrome type-2". Its characteristics and clinical picture are presented in this very first paper on H63D syndrome type-2.

Symptoms of H63D syndrome type-2 has a wide range of symptoms that make the syndrome difficult to recognize as such. It can include hyper-pigmented skin, hepatomegaly, arthralgia, diabetes mellitus, heart failure, arrhythmia, joint pain, abdominal pain, fatigue, weakness, loss of libido, impotence, bronze or gray skin color, motor dysfunction, postural instability, narcolepsy, cognitive and psychiatric conditions of different kinds etc.

As in H63D syndrome type-1, the determining factor in type 2 are systemic micro-inflammations[35], but less strongly related to the amount of non-transferrin bound iron (NTBI). Rather, a homozygous mutation in H63D syndrome type-2 leads to subtle sterile inflammatory processes in the brain and parenchymal tissues that via other cascades which cannot be detected by normally used inflammatory parameters. One must not forget: histopathologically NTBI iron is not stainable! As a result, the common denominator of the myriad possible symptoms is easy to miss, even for seasoned endocrinologists. An examination of kynurenine metabolism in the urine (downstream) can be an indication, as can an absolute (not relative) eosinophilia or basophilia, especially if transferrin saturation in plasma is significantly elevated at the same time. This is why H63D syndrome type-1, H63D syndrome type-2 has less specific symptom constellations and is therefore even easier to overlook as a syndrome. However, it is by no means harmless and requires close monitoring and treatment of the affected patients. It has been, as mentioned before, associated with liver dysfunction, bone and joint disease, diabetes mellitus, heart disease, hormone imbalances, infertility, stroke, severe neurodegenerative disorders, certain cancers, venous peripheral artery disease and organ function issues. In the years since discovery of the HFE genes and their mutations, researchers had focused studies primarily on the C282Y mutation because of its prominence in people with elevated iron levels. 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 alcohol intolerance, acute lymphoblastic leukemia (ALL), decreased sperm production, high risk of type-2 and type-3 diabetes. Being a carrier of the a homozygous H63D mutation is an independent risk factor for earlier onset and longer duration of kidney disease in type-2 diabetic patients. Even heterozygote mutations of HFE gene H63D are associated with a higher risk of liver cancer in cirrhotic patients regardless of their underlying liver disease.

Mutated variants of HFE gene H63D is present in 40% of 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. It has become evident that a H63D HFE variant contributes to many of the processes associated with different types of dementia. These processes

include increased cellular iron, oxidative stress (free radical/ ROS 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%. Connor found that patients homozygous for H63D had earlier signs of mild cognitive impairment and earlier onset of dementia compared to those with a wild-type HFE H63D gene or in the carriers of heterozygote mutations.[10,11,12,35]

Onset and treatment of type-2

It is important to note that type-2 of H63D syndrome may not become clinically apparent until later in life, whereas in type-1 the first symptoms can usually be traced back to childhood and adolescence. The prognosis for H63D syndrome type-2 is generally good if it is detected early and treated appropriately. If left untreated, however, the disease can cause brain damage, heart or liver failure, all other conditions mentioned above, and death.

Currently, treatment has still to be primarily symptom-based. As mentioned earlier, urinary kynurenine metabolism (downstream) testing may provide circumstantial evidence for the presence of the syndrome, but a negative result does by no means exclude the presence of a H63D syndrome type-2. Monitoring of patients should be performed closely. Several research groups are currently working on the question of diagnostic and treatment algorithms. On the basis of well established scientific knowledge and what is known about the rather well studied H63D syndrome type-1, a low-dose basic therapy with prednisolone (normally 2mg to 7.5mg once daily, highrt in severe cases) could be carefully tried by the treating physician as an individual therapeutic trial under close monitoring of the patient's wellbeing.

As always with corticosteroid therapies, the principle applies: as much as necessary but as little as possible. In addition, it is crucial for the treatment of both H63D syndromes that the symptoms, which are distributed over several organ systems, are understood as a syndromic constellation, as one disease, and are also treated as such. Treatment should therefore converge with one responsible physician so that he or she can maintain a general overview and coordinate treatment with the appropriate specialists.[1-31]

Conclusion

While still being under further research, H63D syndrome type-2 is clinically relevant. It is a serious reality based on the mass of matched patient data and the preliminary work previously done by many research groups. To dismiss H63D syndrome type-2 because it has not yet been fully explored would be unethical and would most likely constitute malpractice. Many major diseases have not yet been exhaustively researched, from cancer to AIDS to idiopathic heart failure. Of course, one should not wait until the next generations of scientists will have completely resolved all of the questions regarding these diseases some distant day, but one should treat the suffering patients here and now with the existing and constantly expanding knowledge which is already available. Why should this be different for H63D syndrome, both the well researched type-1 and the now newly described type-2? Treating physicians must be aware that many statements of formerly pioneering scientists like Brissot et al. are now outdated, even if they are still quoted habitually because of their linguistic elegance and seductively plausible but partly wrongly interpreted data.

Conflicts of interest

None declared.

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References

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. 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 hemochromatosis C282Y and H63D mutations in HFE gene in development of type 2 diabetes and diabetic nephropathy.
7. 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.
8. 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.
9. 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.
10. 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.
11. 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.
12. Neurobiol Aging. 2009 HFE polymorphisms affect cellular glutamate regulation. Mitchell RM, Lee SY, Simmons Z, Connor JR.

13. 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, Phillips NA, Schipper HM.
14. Ann Hematol. 2009 An extensive analysis of the hereditary hemochromatosis gene HFE and neighboring histone genes: associations with childhood leukemia. Davis CF, Dorak MT.
15. 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.
16. 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.
17. Leuk Lymphoma. 2006 Nov;47(11):2269-70. HFE H63D variant and leukemia susceptibility. Dorak MT.
18. 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.
19. 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.
20. 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.
21. 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.
22. 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.
23. 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.
24. 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.
25. 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.
26. 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.
27. 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.
28. 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.

29. 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.
30. 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.
31. 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.
32. Researchsquare, 2021: Incidence of a clinically relevant H63D syndrome in carriers of a homozygous mutation of HFE gene H63D. Diamandis C. et al.
33. Brissot P, Ropert M, Le Lan C, Loréal O. Non-transferrin bound iron: a key role in iron overload and iron toxicity. Biochim Biophys Acta. 2012 Mar;1820(3):403-10. doi: 10.1016/j.bbagen.2011.07.014. Epub 2011 Aug 9. PMID: 21855608.
34. H63D H63D Syndrome Consortium 2020: Consensus Paper of the International H63D Research Consortium (English Edition). Sørensen S. et al.
35. Carolina Diamandis, Ali Shirazi, Riku Honda, et al. The seductive temptation of ignorance: how micro-inflammation can cause serious diseases such as diabetes, obesity, heart problems or cancer - and yet be ignored because they are difficult to detect in the laboratory . *Authorea*. February 21, 2023. doi: 10.22541/au.167701296.62598991/v1