How to diagnose H63D Syndrome Type-2

Dr. Carolina Diamandis[1], Ali Shirazi[1], Riku Honda[1], Fabio Rocha[1], and Alexander Bartels[1]

[1]Affiliation not available

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Abstract

H63D Syndrome Type-2 is a complex genetic disorder with diverse manifestations, including erratic iron metabolism, micro-inflammatory cascades, neuropsychiatric issues, organ damage, and other rare multi-faceted symptoms. A comprehensive understanding of the pathophysiology underlying this condition is essential for accurate diagnosis, appropriate management, and the development of targeted therapeutic approaches. Healthcare professionals should adopt a multidisciplinary approach to patient care and emphasize the importance of early detection, intervention, and patient education in the management of H63D Syndrome Type-2. Future research should focus on gene editing technologies and novel therapies to address the underlying genetic mutation and the diverse symptoms associated with the disorder.

Ali Shirazi, Riku Honda, Fabio Rocha, Alexander Bartels, Carolina Diamandis
Correspondence to team@h63d.org

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Short report

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H63D syndrome type-2

H63D Syndrome Type-2 is a complex genetic disorder caused by a mutation in the HFE gene, which is responsible for regulating iron metabolism. The H63D mutation has been associated with a range of symptoms, including liver disease, bone and joint disease, diabetes mellitus, heart disease, hormone imbalances, porphyria

cutanea tarda (PCT), infertility, stroke, neurodegenerative disorders, cancer, and venous and peripheral artery disease (Iron Disorders Institute, 2020). This short paper aims to provide an overview of one apecific phenotype of a homozygous gene H63D mutation, H63D Syndrome Type-2, an easy to miss syndrome whose hallmarks are an erratic iron metabolism, micro-inflammatory cascades, neuropsychiatric issues, organ damage, and some other rare multi-faceted symptoms.

Erratic Iron Metabolism

The HFE gene is responsible for producing the HFE protein, which plays a crucial role in regulating iron absorption in the body. A single point mutation in the HFE gene, resulting in the substitution of histidine (H) with aspartate (D) at position 63, leads to H63D Syndrome Type-2 (Feder et al., 1996). This mutation impairs the functionality of the HFE protein, causing what can only be called an erratic iron metabolism (Hanson et al., 2001), other than H63D Syndrome Type-1 which causes a rather Wilson's like disease due to an accumulation of non-transferrin bound iron (NTBI) due to a chronic and static hypotransferrinemia. In some carriers of a homozygous HFE gene H63D mutation the clinical phenotype is a classic hereditary hemochromatosis, while many many other carriers of the mutation will never experience any clinically relevant consequence. Most likely a "second hit" is needed to cause a clinically relevant course of events which leads to H63D syndrome or to classic hemochromatosis.

Micro-inflammatory cascades

Iron overload can result in the production of reactive oxygen species (ROS), which cause oxidative stress and cellular damage. In H63D Syndrome Type-2, increased oxidative stress can lead to the development of micro-inflammatory cascades, exacerbating tissue damage and further impairing iron regulation (Valko et al., 2007). The H63D mutation has therefore also been associated with an increased risk of neurodegenerative diseases. Connor et al. (2001) reported that the H63D HFE variant contributes to many of the processes associated with brain damage, including increased cellular iron, oxidative stress, glutamate dyshomeostasis, and an increase in tau phosphorylation. Furthermore, patients homozygous for the H63D mutation have been found to have earlier signs of mild cognitive impairment and an earlier onset of dementia compared to those with normal a normal HFE result or H63D heterozygotes.

Organ damages

H63D Syndrome Type-2 has been linked to various types of organ damage, including liver disease and cirrhosis, heart disease, and kidney disease. The H63D mutation has also been associated with a higher risk of liver cancer in cirrhotic patients, regardless of their underlying liver disease (Iron Disorders Institute, 2020). In addition to the these symptoms, H63D Syndrome Type-2 has been linked to several rare multi-faceted symptoms like, infertility, stroke, and venous and peripheral artery disease. Furthermore, H63D carriers have been reported to have a higher risk of type II diabetes mellitus and a longer duration of kidney disease in type II diabetic patients as well as a high risk for arthralgia and a variety GI symptoms (Iron Disorders Institute, 2020).

Diagnostic path

As complex as the syndrome may be, it is easy to diagnose once the essentials are understood.

The following algorithm has so far proven successful in several test series:

Patient has organ damage(s) or neuropsychiatric and/or neurologic and/or rheumatologic and/or cardiological and/or hematologic and/or endocrine and/or immunological function issues (at least 2)

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Test ferritin, transferrin, transferrin saturation, binding capacity, labile iron pool (LIP), and basal iron

↓ ↓

Normal — Erratic irregularities of the iron metabolism

↓ ↓

Repeat test three times within a time period of 2 years — Genetic testing of HFE, H63D homozygous mutation or 282Y mutation, S65C mutation

↓

H63D Syndrome Type-2 highly likely

The diagnostic algorithm for type-1 of H63D syndrome can be found online on several academic servers, most easily on Zenodo.

Therapeutic Approaches and Future Research

Because the genetic mutation cannot be corrected, current therapeutic approaches for H63D syndrome type-2 are primarily symptom-oriented. In the few patients who have ferritin overload (hyperferritinemia), phlebotomy and iron chelation might help to reduce this protein-bound iron. (Brissot et al., 2018). However, the same procedure in patients with NTBI overload and relatively low ferritin (as is the case in the vast majority of patients with H63D syndrome) would be harmful and highly dangerous, if not life-threatening. These treatments do not address the genetic mutation anyway, nor do they address the resulting micro inflammatory cascades, neuropsychiatric problems, organ damages, and other rare, multifaceted symptoms.

In general, treatment for H63D Syndrome Type-2 should be individualized based on the patient's specific constellation of symptoms, as it is a highly variable and also dynamic clinical entity. In many cases, anti-inflammatory treatment is necessary and beneficial. Understanding the complex pathophysiology and diverse symptoms associated with H63D Syndrome Type-2 has significant implications for clinical practice and patient care.

Healthcare professionals should be aware of the varied manifestations of the disorder to ensure accurate diagnosis and appropriate management of patients. Early detection and intervention are critical to mitigate the harmful effects of iron metabolism disorders and consequently prevent quite severe complications such as organ damage. Routine screening for H63D mutations in high-risk populations and comprehensive patient monitoring can facilitate early detection and prompt intervention. Moreover, clinicians should adopt a multi-disciplinary approach to managing H63D Syndrome Type-2, involving specialists in gastroenterology, neurology, hematology, endocrinology, and other relevant fields. This comprehensive approach is essential for addressing the myriad symptoms and complications associated with the disorder. Lastly, patient education and support are

vital components of care for individuals with the syndrome. Healthcare professionals should educate patients about the disorder, its potential complications, and the importance of adherence to therapeutic interventions. Support groups and patient advocacy organizations, such as the Iron Disorders Institute, can provide valuable resources and emotional support for patients and their families.

Conclusion

H63D Syndrome Type-2 is a highly complex genetic disorder with extremely diverse manifestations, including erratic iron metabolism, micro-inflammatory cascades, neuropsychiatric issues, organ damage, and other rare multi-faceted symptoms.

A comprehensive understanding of the pathophysiology underlying this H63D Syndrome type-2 is essential for accurate diagnosis, appropriate management, and the development of targeted therapeutic approaches.

Healthcare professionals should adopt a multi-disciplinary approach to patient care and emphasize the importance of early detection, intervention, and patient education in the management of H63D Syndrome Type-2. Future research should focus on gene editing technologies and novel therapies to address the underlying genetic mutation and the diverse symptoms associated with the disorder.

Conflicts of interest

None.

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H63D Syndrome Research Consortium