Stronger together

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White Paper

H63D Syndrome renamed Oslo Syndrome

ABSTRACT

Evidence-based medicine has shown for many years that homozygous mutations of the HFE gene H63D are by no means negligible. Not only can it cause, usually after a second hit, rather mild classical hemochromatosis, but it can also cause numerous other disorders of iron metabolism, such as hypotransferrinemia, changes in binding capacity, and others. In addition, it may lead - among other symptoms - to damages of the heart and the substantia nigra via a causal relationship that remains to be investigated, most likely via a cascade dysfunction in iron metabolism. The clinical facts are compelling. Any physician who dismisses mutations of the HFE gene H63D as clinically irrelevant risks the health and life of his patient. Therefore all main researcher working on H63D Syndrome decided to raise awareness for the “iron brother” of Morbus Wilson by renaming H63D Syndrome.

INTRODUCTION

Homozygous mutations of the HFE gene H63D have not been taken seriously enough for many decades. This mutation of gene H63D is a Pandora's box. It has been linked to liver disease, bone and joint disease, diabetes mellitus, heart disease, hormonal disorders, porphyria cutanea tarda (PCT), infertility, stroke, severe neurodegenerative disease,

cancer, venous peripheral artery disease, hereditary hemochromatosis (after a second hit), and H63D syndrome. In the years since the discovery of HFE and its mutations, researchers have focused their studies primarily on the C282Y mutation because it is particularly common in people with elevated iron levels. About 85% of people with abnormally high iron levels have two copies of C282Y, so this mutation has been studied more intensively. Other mutations, such as S65C or H63D, have not attracted the attention of researchers. The S65C mutation can lead to mild to moderate hepatic (liver) iron overload, especially in combination with other mutations. Increased serum iron indices and iron overload have been observed in C282Y/ S65C compound heterozygotes. In scientific evaluation, H63D stands out as a significant modifier of disease onset, disease progression and even response to therapy. H63D is associated with arterial rigidity, pro-oxidation, higher total and low-density lipoprotein cholesterol, acute lymphoblastic leukemia (ALL), decreased sperm production, and higher risk of type II diabetes mellitus, and hereditary hemochromatosis after a second hit. Being a carrier of the H63D hemochromatosis mutation is also a risk factor for earlier onset and longer duration of kidney disease in type II diabetics. The most striking risk associated with H63D is that for neurodegenerative disease. Connor and colleagues were among the first researchers to examine the role of H63D in brain iron accumulation, oxidative stress, and neurotransmitter performance. Connor reported that the HFE variant H63D contributes to many of the processes associated with various types of dementia. 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 lead to dementias such as Alzheimer's disease). As demonstrated by Jacobs, Papadopoulos Kaufmann, and colleagues (2012, 2015, 2017, 2019, 2020, 2021) using solid patient data, the numerous damages in parenchymal tissues, heart, and brain (substantia nigra and basal ganglia) can be explained by insidious non-transferrin-bound iron (NTBI) intoxication 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 of H63D Syndrome, but other forms of cognitive decline are also common. Connor states further that HFE H63D cells have been shown to have more oxidative stress, further supporting their role as modifiers of neurodegenerative diseases. He found that patients homozygous for H63D had earlier signs of mild cognitive impairment and earlier onset of dementia disease than patients with normal HFE H63D or H63D heterozygote individuals. Despite this fact, which has been known for 25 years, many clinicians still dismiss homozygous HFE-H63D mutations as irrelevant. Even some of the highest authorities in the field of iron metabolism seem to be trapped in the knowledge of the early 1990s.[1-17] As physicians specialized in rare diseases, we regularly see patients with complex syndromes consistent with those mentioned before. Just as regularly homozygous mutations of HFE gene H63D are found as primum movens (primary cause) of complex metabolic and toxic syndromes. It is also typical for treating colleagues to ignore this finding, as old textbooks (and new ones copy-pasted from old ones) still state that the HFE gene H63D or its homozygous mutation would be clinically irrelevant. This is false, misleading and potentially fatal misinformation. The knowledge about the high clinical relevance is neither new nor a fringe topic. HFE H63D is not a strong hemochromatosis gene, however, with a second hit it can easily cause hereditary hemochromatosis. But even more important than this, a homozygous mutation of the HFE gene H63D is, according to overwhelming evidence, responsible for many cases of complex syndromes associated with heterogeneously altered iron metabolism.[1-69]

RENAMING H63D SYNDROME

It is evident from all this that H63D Syndrome is a not so very distant relative of Wilson's disease, only with NTBI iron instead of copper as the causative agent. But why does every GP have at least some basic knowledge of Wilson's disease and not H63D Syndrome? We concluded after professional discussion in the centers of competence that the term H63D syndrome is difficult to remember and, moreover, does not do justice to the multifaceted nature of the disease.

Therefore, all 137 main researchers from around the world who are conducting research on H63D syndrome and working in one of the competence centers have unanimously decided to assign H63D syndrome the alternative name **Oslo Syndrome**, as this it was in the capital city of the Kingdom of Norway that for the first time standardized diagnostic algorithms were established. In addition, the new name distinguishes H63D syndrome more clearly from hereditary hemochromatosis (HH) which helps avoid confusion and motivates to learn more about the disease.

Both terms, “H63D Syndrome” and “Oslo Syndrome”, should be equivalent and are interchangeable.

In the name of the

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CONFLICTS OF INTEREST

No conflicts of interest were declared.
None of the scientists involved will benefit from the renaming of the syndrome.

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