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Article

DHCR7 Mutation Carriers and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: No Associations According to DecodeME Data

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Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating multisystem disorder whose pathogenesis is associated with metabolic and immune dysfunction. Dysfunction of cholesterol metabolism and vitamin D deficiency are considered potential pathogenic factors. The *DHCR7* gene, encoding 7-dehydrocholesterol reductase, catalyzes the final step in cholesterol biosynthesis and simultaneously determines the availability of provitamin D. Pathogenic *DHCR7* mutations, leading to the development of Smith-Lemli-Opitz syndrome (SLOS) in the homozygous state, are characterized by a high prevalence in the population as heterozygous carriers (~1%). Therefore, it was hypothesized that heterozygous carriage of *DHCR7* mutations may be associated with an increased predisposition to the development of ME/CFS. **Materials and Methods:** We used open-source genetic data from the DecodeME project (n = 15,579 ME/CFS patients, 259,909 controls). We analyzed the frequency of 11 pathogenic *DHCR7* mutations: IVS8-1G>C, W151X, T93M, V326L, R404C, R352W, E448K, R352Q, G410S, R242C, and F302L. The association with the ME/CFS phenotype was assessed using a χ^2 test in six datasets (the overall sample (gwas_1), subsamples of men (gwas_1_male), women (gwas_1_female), spontaneous CFS development (gwas_1_non-infectious_onset), CFS development with infectious onset (gwas_1_infectious_onset), and a subsample with a 1:10 patient: control ratio (gwas_2)). ***Results***. Only the IVS8-1G>C mutation was detected in the DecodeME data (carrier frequency ~1%). A statistically significant association (p-value ≈ 0.013) was observed in only one subsample (gwas_2) but was not replicated in the others. The remaining mutations were not detected in the DecodeME data. ***Conclusions***. The obtained results do not support the hypothesis of a link between carriage of SLOS-inducing *DHCR7* mutations and ME/CFS. This negative result is important for the correct refinement of metabolic hypotheses regarding pathogenesis and the prioritization of research areas. Further study of sterol metabolism and metabolomic biomarkers in patient subgroups is recommended.

Keywords: *Smith–Lemli–Opitz syndrome, multiple sclerosis, myalgic encephalomyelitis, chronic fatigue syndrome, DHCR7 gene, association search*

1. INTRODUCTION

Smith–Lemli–Opitz syndrome (SLOS) is a rare autosomal recessive disorder caused by mutations in the *DHCR7* gene on chromosome 11 (locus 11q12–q13). *DHCR7* defects result in a deficiency of the enzyme 7-dehydrocholesterol reductase, the final step in cholesterol synthesis. As a result, patients with SLOS have dramatically reduced cholesterol levels and an accumulation of its intermediate precursors (e.g., 7-dehydrocholesterol). Clinically, the disease is characterized by multiple developmental defects, intellectual disability, and severe neurological impairment. Cholesterol deficiency disrupts the myelination of nerve fibers, contributing to the neurological symptoms of SLOS. The incidence of SLOS is approximately 1 in 30,000 live births, with a higher prevalence in Caucasians. Despite the rarity of the disease,

carriage of *DHCR7* mutations is widespread—up to ~1% in the Caucasian population. Carriers (heterozygotes) of pathogenic alleles are generally phenotypically healthy, but have partially reduced activity of the cholesterol metabolism enzyme [1]. Given the key role of cholesterol in the formation and maintenance of myelin sheaths, disturbances in its biosynthesis, even partial, may be significant not only in rare hereditary syndromes but also in the context of diseases with a multifactorial etiology, such as multiple sclerosis.

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system in which the immune system damages the myelin sheaths of neurons in the brain and spinal cord. This leads to the development of multiple foci of demyelination and a variety of neurological symptoms (motor, sensory, and cognitive impairments). The etiology of MS is multifactorial: a combination of genetic predisposition and external factors (immune disorders, viral infections, etc.) is believed to be involved [2]. One of the key risk factors is vitamin D deficiency: low vitamin D levels have been shown to significantly increase the likelihood of developing MS. Reduced vitamin D status is associated, among other things, with genetic variants in vitamin D metabolism genes, such as *CYP2R1*, *CYP24A1*, and *DHCR7* [3]. In particular, the rs12785878 polymorphism near the *DHCR7* gene, a known determinant of vitamin D deficiency, is associated with an increased risk of MS (Odds Ratio ≈ 1.10) [4]. Thus, the *DHCR7* gene indirectly influences neuroimmune processes through cholesterol and vitamin D metabolism, making it an interesting candidate for study in the context of demyelinating and immune diseases.

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating condition of unknown etiology, characterized by long-term chronic fatigue, post-exertion weakness, pain, cognitive impairment, and a number of other symptoms in the absence of an alternative diagnosis. ME/CFS is characterized by heterogeneity of manifestations and the absence of specific biomarkers, which complicates diagnosis. Dysregulation of the immune system (e.g., decreased NK cell activity, increased proinflammatory cytokines), as well as metabolic disturbances, are discussed in the origin of the syndrome. A number of metabolomics studies have shown changes in the lipid profile in ME/CFS – disturbances in the levels of phospholipids, triglycerides, cholesteryl esters, and cholesterol itself [5]. A decrease in high-density lipoprotein (HDL) levels was also noted in patients with chronic fatigue compared to healthy controls [6]. These data suggest a possible role for lipid and sterol metabolism (including cholesterol) in the pathogenesis of ME/CFS[5].

Based on the above, we hypothesized that heterozygous carriage of pathogenic *DHCR7* gene mutations (resulting in SLOS syndrome in homozygotes) may increase susceptibility to certain chronic neuroimmune diseases, such as ME/CFS (and potentially MS). In other words, even a single copy of *DHCR7* mutation can cause subclinical cholesterol and/or vitamin D deficiency, which negatively impacts the functional state of the nervous and immune systems. This association has not been previously studied, and its verification is important in the context of the search for metabolic markers and genetic risk factors for ME/CFS.

In this study, the aim was to evaluate the association between carriage of known pathogenic *DHCR7* variants and the presence of the ME/CFS phenotype.

2. MATERIALS AND METHODS

2.1. Population and Data

Data from the DecodeME project, the largest genetic study of ME/CFS to date, was used to test the hypothesis. Tens of thousands of participants were genotyped within DecodeME: according to the latest data, the analysis included nearly 16,000 ME/CFS patients and ~250,000 controls [7], primarily of European ancestry. Genotyping and allele frequency data are publicly available (DecodeME project OSF repository). We analyzed the summary statistics of the GWAS (genome-wide association studies) from DecodeME, including several subsamples: the overall sample ("gwas_1", all cases and controls), as well as stratified subsamples by gender (males "gwas_1_male" and females "gwas_1_female" separately) and by the type of disease onset (post-infectious "gwas_1_infectious_onset" and spontaneous "gwas_1_non_infectious_onset"); and an additional subsample "gwas_2" with an artificially reduced sample of controls (with the case: control ratio equal to 1:10).

2.2. Selected DHCR7 Gene Variants

We selected a number of known pathogenic *DHCR7* mutations inducing SLOS, with a special focus on the two most common mutations: IVS8-1G>C (splice site mutation, rs138659167) and W151X (nonsense mutation, rs11555217) [8]. According to the literature, these two variants are the most frequent causative alleles of SLOS in patients of European ancestry [8], together accounting for a significant proportion of mutant chromosomes. In addition, several other known mutations were included in the analysis: T93M, V326L, R404C, R352W, E448K, R352Q, G410S, R242C, F302L (all

missense amino acid substitutions previously described in patients with SLOS), based on their documented pathogenicity and prevalence in populations [9].

2.3. Data Analysis

Each of the DecodeME genetic datasets was searched for the specified *DHCR7* allelic variants. To assess the association between the presence of the mutation and the disease, the distribution of carriers in groups was calculated (2x2 contingency tables – "mutation carriage" vs. "disease status"). The statistical significance of potential associations was tested using the Pearson χ^2 test for each of the 6 datasets. Absence of differences in the proportion of carriers between ME/CFS patients and controls was set as the null hypothesis.

3. RESULTS

3.1. Allele Frequencies in the DecodeME Data

The analysis showed that the vast majority of the studied *DHCR7* mutations are absent from the DecodeME data (**Table 1**). In particular, no carriers were identified for 10 of the 11 pathogenic variants tested: rs11555217 (W151X), as well as rs80338853 (T93M), rs80338859 (V326L), rs61757582 (R404C), rs80338860 (R352W), rs80338864 (E448K), rs121909768 (R352Q), rs80338862 (G410S), rs80338856 (R242C), and rs80338858 (F302L) – these alleles were not detected in any cases or controls. This absence is unsurprising, given their extremely low population frequency (pathogenic SLOS mutations occur in ~1% of individuals in heterozygotes overall, with each specific variant occurring an order of magnitude less frequently).

The only *DHCR7* variant present in DecodeME is the splice mutation IVS8-1G>C (rs138659167). Carriers of this allele were found among both ME/CFS patients and controls in all 6 datasets. The frequency of the alternative allele was approximately the same in both groups: approximately ~1% in both ME/CFS patients and controls. Thus, the overall prevalence of IVS8-1G>C in the study sample corresponded to the expected carriage rate of SLOS mutations in the general population (~1%) [1], with no apparent excess in patients.

Table 1. Frequency of *DHCR7* mutations in the DecodeME sample (15,579 patients vs. 259,909 controls)

Mutation	rsID	HVGS notation	Position (GRCh38)	Type	Consequence	Carriers among cases	Carriers among controls	χ^2	*P*-value
IVS8-1G>C	rs138659167	c.964-1G>C	11:71435840	Splice	Loss of a splice site	155 (0,99%)	3015 (1,16%)	3,53	0,06
T93M	rs11555217	c.452G>A (p.Trp151*)	11:71444036	Nonsense	Stop gained	0	0	–	–
W151X	rs80338853	c.278C>T (p.Thr93Met)	11:71441401	Missence	Thr → Met	0	0	–	–
V326L	rs80338859	c.976G>T (p.Val326Leu)	11:71435827	Missence	Val → Leu	0	0	–	–
R404C	rs61757582	c.1210C>T (p.Arg404Cys)	11:71435593	Missence	Arg → Cys	0	0	–	–
R352W	rs80338860	c.1054C>T (p.Arg352Trp)	11:71435749	Missence	Arg → Trp	0	0	–	–
E448K	rs80338864	c.1342G>A (p.Glu448Lys)	11:71435461	Missence	Glu → Lys	0	0	–	–
R352Q	rs121909768	c.1055G>A (p.Arg352Gln)	11:71435748	Missence	Arg → Gln	0	0	–	–
G410S	rs80338862	c.1228G>A (p.Gly410Ser)	11:71435575	Missence	Gly → Ser	0	0	–	–
R242C	rs80338856	c.724C>T (p.Arg242Cys)	11:71438986	Missence	Arg → Cys	0	0	–	–
F302L	rs80338858	c.906C>G (p.Phe302Leu)	11:71437869	Missence	Phe → Leu	0	0	–	–

Note: *χ^2 was calculated only for rs138659167; other mutations are not present in the DecodeME dataset. Frequencies are shown as the proportion of carriers in each group; "–" indicates data unavailable for analysis.*

3.2. ME/CFS Association Analysis

A χ^2 statistical test was performed for the IVS8-1G>C variant across 6 datasets (**Table 2**). In the overall sample (all cases vs. all controls, n ≈ 16k/250k), differences in carrier rates did not reach significance level (p-value > 0.05). In other words, no association was found between the presence of the rs138659167 allele and ME/CFS in the overall GWAS sample. Similarly, no statistically significant association was found in stratified analyses by gender and onset type: mutation carrier rates did not differ in male cases vs. male controls and in female cases vs. female controls, nor in the subgroups with postinfectious and spontaneous onset of the disease (p-value > 0.05 in all these subsamples).

Interestingly, only one of 6 datasets—gwas_2—a subsample with a reduced number of controls—yielded a nominally significant result: in gwas_2, the IVS8-1G>C mutation was slightly more common in ME/CFS patients than in controls, and the χ^2 test yielded a p-value ≈ 0.013. However, this effect was not reproduced in any other dataset (**Table 2**). Given the multiple comparisons (analysis of several subgroups), an isolated significant p-value ≈ 0.01 is highly likely a random statistical fluctuation rather than a true signal and must be interpreted with caution.

Table 2. Statistical significance of IVS8-1G>C – ME/CFS association in 6 DecodeME datasets

DecodeME dataset	χ^2	*P*-value	Statistical significance
gwas_1	3.529	0.0603	No
gwas_1_male	1.099	0.2945	No
gwas_1_female	2.503	0.1136	No
gwas_1_infectious_onset	3.402	0.0651	No
gwas_1_non_infectious_onset	0.044	0.8339	No
gwas_2	6.159	0.0130	Yes, P* < 0.05

4. DISCUSSION

We found no statistical evidence of an association between carriage of classic *DHCR7* mutations and the risk of developing ME/CFS. Of 11 known SLOS-associated variants, only one (IVS8-1G>C) was present in the DecodeME data, and its frequency among patients was virtually identical to that in controls (approximately 1% in both groups). Formally, a statistically significant signal (p-*value* ≈ 0.013) was obtained in one of the six subsamples, but it was not confirmed when considering the full sample and other subgroups. Most likely, this association is random in nature and may represent a statistical anomaly. Given the sample size, correction for multiple comparisons is necessary, taking into account which the significance threshold should be significantly lower than 0.01; therefore, the observed value of p-value ≈ 0.013 does not indicate reliable replication of the effect. Moreover, the coincidence of the overall carrier frequency (~1%) in cases and controls directly indicates the absence of an association.

Our results are negative: the hypothesis that heterozygous *DHCR7* mutations influence susceptibility to chronic fatigue syndrome has not been confirmed. Thus, carriage of pathogenic DHCR7 alleles that cause SLOS in the homozygous state does not appear to increase the risk of ME/CFS. To our knowledge, this study is the first to attempt to establish a link between cholesterol metabolism defects (at the level of heterozygous SLOS carriers) and this syndrome. The negative results obtained are consistent with clinical observations: heterozygotes for *DHCR7* mutations are phenotypically healthy and do not differ from the general population in key health indicators (with the possible exception of minor biochemical abnormalities). No increased incidence of any neurological or autoimmune disorders has previously been reported among SLOS mutation carriers, and our study in a large ME/CFS sample confirms this lack of a significant effect. It is important to note that the negative result for rare pathogenic *DHCR7* mutations is consistent with data implicating cholesterol and vitamin D-dependent metabolism in the pathogenesis of ME/CFS. It has previously been shown that ME/CFS is associated with changes in the lipid profile, including cholesterol and its derivatives, as well as disturbances in energy and mitochondrial metabolism [10,11]. However, these effects are likely mediated either by polygenic regulatory variants or secondary metabolic and immune shifts, rather than by rare, highly penetrant mutations characteristic of monogenic syndromes.

An important point for interpreting the results is that the study only examined rare, highly pathogenic *DHCR7* variants. There are over 200 different pathogenic *DHCR7* mutations [9], and theoretically, a different (especially a milder) variant of the gene could have a different effect on the phenotype. For example, the general population variant rs12785878 near *DHCR7* is known to affect vitamin D levels and is statistically associated with the risk of developing multiple sclerosis [4]. Large meta-analyses of GWAS of multiple sclerosis have found that polymorphisms in the *DHCR7*, *CYP2R1*, and *CYP24A1* loci are significantly associated with the disease (probably indirectly through vitamin

D-dependent mechanisms) [3]. In the case of ME/CFS, recently published genomic studies (including the DecodeME project) have identified several associations with this syndrome, but sterol metabolism genes are not among the main candidates [7]. On the other hand, metabolomic and immune-biochemical studies of ME/CFS indicate the presence of abnormalities in lipid and energy balance in patients [5]. Overall, the data obtained suggest that classical pathogenic *DHCR7* mutations causing SLOS do not play a significant role in ME/CFS predisposition at the population level. This highlights the need to shift the focus of future research from rare monogenic variants to an analysis of polygenic signals, regulatory elements, and the functional consequences of lipid and sterol metabolism disorders in the context of neuro-immune dysregulation in ME/CFS.

5. CONCLUSION

According to the analysis, heterozygous carriage of the most common mutations in the *DHCR7* gene (SLOS syndrome) is not associated with an increased risk of developing ME/CFS. In the largest sample of patients and controls available from DecodeME project, no significant difference in the frequency of such mutations was found between groups. The single observation of statistical significance in a separate subsample is likely a random fluctuation and is not confirmed in the overall cohort. These data indicate that carriage of SLOS-associated mutations has no effect on the development of chronic fatigue syndrome.

Our study represents a negative result, which is important to prevent biased publications. Since the original hypothesis was biologically sound (through the role of cholesterol and vitamin D in the nervous system), documenting its refutation helps clarify the direction of further research. In the future, it would be worthwhile to study more subtle aspects of sterol metabolism in ME/CFS: for example, by directly measuring the levels of 7-dehydrocholesterol, cholesterol, and its metabolites (oxysterols) in patients compared to healthy controls. It also remains an open question whether non-genetic factors influencing *DHCR7* enzyme activity (e.g., hormonal, dietary, or environmental influences) could influence the course or symptoms of ME/CFS. Finally, to definitively rule out the role of rare *DHCR7* variants in other diseases, similar association studies should be conducted in cohorts of multiple sclerosis and other autoimmune/neurometabolic disorders. Publication of negative results like ours will allow for a more effective redistribution of scientific resources to promising areas and avoid duplicating obviously unpromising hypotheses.

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Data Availability Statement: DecodeME Genotype data was obtained from DecodeME open dataset (OSF, 2025), available at: https://osf.io/rgqs3/files/osfstorage.

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