Short Communication
Volume 8:2, 2023

Journal of Diabetic Complications & Medicine

ISSN: 2475-3211 Open Access

In a Prospective Cohort Research, Genomic Sequencing of Slim People with NAFLD Identifies Monogenic Diseases

Smarak Ranjan*

Department of Translational Medical Sciences, University Federico II, C.so Umberto I, 40, 80138 Napoli NA, Naples, Italy

Abstract

Patient 1 was identified as having inherited fructose intolerance and carries a rare homozygous pathogenic mutation in ALDOB. A uncommon heterozygous mutation in APOB is present in patient 2. This APOB variant's pathogenicity was further confirmed in the UK Biobank and connected to decreased levels of circulating APOB. Non-alcoholic fatty liver disease is becoming more common, and some people will develop severe liver conditions such cirrhosis and hepatocellular cancer. Lean patients with non-alcoholic fatty liver disease make up the majority of the population, and observational studies have produced inconsistent findings about the severity and prognosis of the disease, which may be attributed to more diverse disease causes.

Keywords: Research • Genomic sequencing • Slim people • Monogenic diseases

Introduction

10–20% of those with non-alcoholic fatty liver disease are lean people, and they may have different disease-causing factors. Recently, we suggested testing patients with lean non-alcoholic fatty liver disease without visceral adiposity for uncommon disease-causing monogenic factors. By using whole exome sequencing, we sought to test this concept in a well-characterized cohort of patients with biopsy-proven non-alcoholic fatty liver disease [1]

124 individuals with non-alcoholic fatty liver disease who had undergone paired liver biopsies and standard research visits, including advanced magnetic resonance imaging assessment of liver stiffness and fat, were included in this prospective study. Whole exome sequencing was performed on six patients who had been classified as having lean non-alcoholic fatty liver disease. Monogenic diseases were found in two lean patients. The age, anthropometric, and magnetic resonance imaging features of the lean patients with monogenic diseases were comparable to those of the lean individuals without a monogenic disorder [2].

Patient 1 was identified as having inherited fructose intolerance and carries a rare homozygous pathogenic mutation in ALDOB. A uncommon heterozygous mutation in APOB is present in patient 2. This APOB variant's pathogenicity was further confirmed in the UK Biobank and connected to decreased levels of circulating APOB. Non-alcoholic fatty liver disease is becoming more common, and some people will develop severe liver conditions such cirrhosis and hepatocellular cancer. Lean patients with non-alcoholic fatty liver disease make up the majority of the population, and observational studies have produced inconsistent findings about the severity and prognosis of the disease, which may be attributed to more diverse disease causes [3].

In three non-obese patients with non-alcoholic fatty liver disease, a prior study proving the clinical efficacy of genomic sequencing in the identification and management of adult patients with liver disease of unclear cause found hitherto underappreciated monogenic illnesses. In order to uncover rare genetic variants that may have therapeutic implications and to understand additional pathogenic pathways, we proposed a paradigm for genomic screening of slim patients with non-alcoholic fatty liver disease who lack visceral adiposity. In order to search for uncommon, monogenic disease causes, we performed whole exome sequencing on thin people from a longitudinal cohort with well-defined phenotypes. These people had biopsy-proven non-alcoholic fatty liver disease [4].

Six patients had lean non-alcoholic fatty liver disease out of 124 participants with biopsy-proven non-alcoholic fatty liver disease who underwent longitudinal follow up. Regarding age, sex, diabetes status, lab test results, liver histology, magnetic resonance imaging proton-density-fat-fraction, and magnetic resonance elastography, lean and non-lean subjects were comparable. For individuals with lean non-alcoholic fatty liver disease and those without it, there was no difference in the longitudinal change in histology, magnetic resonance imaging proton-density-fat-fraction and PDFF, or magnetic resonance elastography. The germline DNA of six patients with lean non-alcoholic fatty liver disease was sequenced in its entirety. In two of these adult lean people with non-alcoholic fatty liver disease, we discovered a monogenic condition using the whole exome sequencing analytic method. In terms of age, BMI, and fasting insulin levels, lean patients with monogenic diseases were comparable to lean patients without a known monogenic disorder in terms of both. The protective rare mutation in CIDEB wasn't present in any of the study participants with biopsy-proven lean non-alcoholic fatty liver disease [5].

Patient 1 had a BMI of 21.3 kg/m2, biopsy-proven NASH, stage 2 fibrosis, and a 24% MRI-PDFF, which is consistent with severe steatosis. She was discovered to have an uncommon homozygous missense mutation in the aldolase B gene, ALDOB. Hereditary fructose intolerance is caused by biallelic mutations in this gene. The conversion of fructose 1,6-bisphosphate into glyceraldehyde 3-phosphate and dihydroxyacetone phosphate, as well as fructose 1-phosphate into glyceraldehyde and DHAP, is catalysed by the enzyme aldolase B. Patients afflicted by fructose or sucrose consumption may exhibit hypoglycemia, hepatic steatosis, and proximal renal tubulopathy due to the accumulation of toxic metabolites. The additional in silico prediction models Meta SVM, SIFT, and PolyPhen-2 projected that this variant would be detrimental. This missense mutation in aldolase B decreases substrate affinity, enzyme stability, and activity, according to experimental research. Individuals with hereditary fructose intolerance have been reported to have this variation in homozygosity or compound heterozygosity. This patient experienced symptoms of inherited fructose intolerance, including nausea, stomach pain, and hypoglycemia that were made worse by fruit consumption. The patient's first-degree relatives did not have a history of inherited fructose intolerance [6].

Conclusion

This study backs the use of WES for treating and diagnosing NAFLD in lean patients. It was found that two out of six NAFLD patients without visceral

***Address for Correspondence:** Smarak Ranjan, Department of Translational Medical Sciences, University Federico II, C.so Umberto I, 40, 80138 Napoli NA, Naples, Italy, E-mail: smarakranjan@gmail.com*

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Received: 02 March, 2023, Manuscript No. jdcm-23-93787; **Editor Assigned:** 04 March, 2023, PreQC No. P-93787; **Reviewed:** 17 March, 2023, QC No. Q-93787; **Revised:** 23 March, 2023, Manuscript No. R-93787; **Published:** 31 March, 2023, DOI: 10.37421/2475-3211.2023.8.201

adiposity had genetic disorders, which explained the pathophysiology of their hepatic steatosis. Additionally, we used MRI quantification of liver fat and APOB levels to confirm the pathogenicity of the p.Val1856CysfsTer2 variation in APOB. We discovered a substantial Body Mass Index rare variant interaction on ALT and liver fat, suggesting adiposity may exacerbate the effect of rare variants on fatty liver. This finding is similar to what has been shown for common variants linked to NAFLD in the past.

Acknowledgement

None.

Conflict of Interest

None.

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How to cite this article: Ranjan, Smarak. "In a Prospective Cohort Research, Genomic Sequencing of Slim People with NAFLD Identifies Monogenic Diseases." *J Diabetic Complications Med* 8 (2023): 201.