Genetic implications in patients with NAFLD

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Abstract

Introduction and purpose:

Non-alcoholic fatty liver disease's growing prevalence and the complications it brings constitutes a serious problem nowadays. According to this, better understanding of mechanisms laying on the ground of its pathogenesis is a crucial factor to better understand this disease and develop interventions to counter its effects. Genetic relationships with NAFLD are known and they show great variation of mechanisms underlying their impact on subjects' metabolic state. Due to this fact the assumption that it is worth collecting these connections in one place was made, so that it is easier to navigate in them. Mostly studies refer to rodents trials, we focused on studies referred to people with NAFLD diagnosis.

Material and method:

The literature was scrutinised in the Google Scholar database, in the Pubmed database with the use of following keywords: "genetics", "genes", "non-alcoholic fatty liver disease", "NAFLD", "non-alcoholic steatohepatitis", "NASH".

Results:

NAFLD as a metabolic disease has many links with metabolic pathways encoded by various genes. When it comes to genetic factors, we can specify gene expression single nucleotide polymorphisms (SNP) and genes methylation. All of these aspects affect activity of coded proteins and what follows this is its impact on human metabolism. These factors have been studied in the work of other researchers.

Conclusions:

Non-alcoholic fatty liver disease's growing prevalence and the complications it brings constitutes a serious problem nowadays. Genetic relationships with NAFLD are known and they show great variation of mechanisms underlying their impact on subjects' metabolic state.

Keywords: non-alcoholic fatty liver disease; genetics; steatosis;

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a chronic disease in which hepatic steatosis is observed. The diagnostic criteria for this disease are as follows: at least 5% of hepatocytes with steatosis and without any secondary reason for this state. Its prevalence is growing last time and is estimated to be about 32.4% in the global population [1, 2, 3]. The genetic and metabolic conditions such as: obesity, insulin resistance are responsible for pathogenesis of this disease but surprisingly, it turns out that people who are not overweight also suffer from this disease. NAFLD develops over time to non-alcoholic steatohepatitis (NASH) and even hepatic cirrhosis or hepatocellular carcinoma, thus knowledge of the underlying cause of this disease and ways to prevent its development are so important [3, 4, 5].

The purpose of this study is to present the genetic background of NAFLD in order to understand the pathomechanisms leading to its development, to enable the expansion of diagnostics in its direction and thus the development of effective methods of therapy.

Materials and methods

The primary aim of this review is to summarize the genetics associations in NAFLD pathogenesis. PubMed Database was searched without a year of publication limit. Inclusion criteria in the language of the study set as English and in the study type as clinical trials and randomized controlled trials were used, we referred only to studies relating to humans, especially with NAFLD diagnosis. In introduction we referred to one meta-analysis to show the latest available epidemiological data. The final search was performed on 1 June 2023.

In order to find adequate studies a combination of Medical Subject Headings (MeSH) terms and specific search terms were used including subsequent terms divergence: "Genetics", "Genes", "Non-alcoholic fatty liver disease", "NAFLD", "Non-alcoholic steatohepatitis", "NASH".

Comprehensible trials were downloaded and screened for fulfillment of inclusion criterias: English language studies attributing to genetic relationships with NAFLD pathogenesis. For the first screening titles, abstract or full text if unavoidable were analyzed. After this, full text copies were studied. Practicing to prospectively developed and tested template information from articles were extracted. Extracted data included the genetic aspects in NAFLD pathogenesis and general information about this disease.

As first step 38 papers were identified with no duplicates. We excluded papers which do not contain adequate information about specific genes or genetic relationships with NAFLD. In sum, one meta-analysis and seventeen randomized controlled trials papers pending the mentioned eligibility criteria's: clinical trials, randomized controlled trials and English language, were included in this study.

The results are described in adequate paragraphs containing a short delineation of relationships between genetic factors and NAFLD.

Results

NAFLD as a metabolic disease has many links with metabolic pathways encoded by various genes. When it comes to genetic factors, we can specify gene expression single nucleotide polymorphisms (SNP) and genes methylation. All of these aspects affect activity of coded proteins and what follows this is its impact on human metabolism. These factors have been studied in the work of other researchers.

Gene expression

The process of converting genetic information into its function is called a gene expression and in the biggest part it is a result of RNA molecules transcription. This process controls where and how much protein is produced. Gene expression is not the same in different cells and under different conditions. The assessment of the phenotype or the activity of its product proves the expression of a given gene.

Osorio-Conles et al. [5] study analyzed 75 genes expression both in subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) of obese females with NAFLD and without NAFLD. The expression of 15 genes in SAT and 8 genes in VAT was significantly different between mentioned groups. Study found that in visceral adipose tissue (VAT), the expression of hypoxia-inducible factor 1-alpha (HIF1A), angiopoietin 2 (ANGPT2) and the thermoregulatory gene cell death-inducing DFFA-like effector A (CIDEA) was slightly downregulated in NAFLD subjects. The authors built a multinomial logistic regression model that included 7 genes that explained 100% of the NAFLD variance among the study population [5].

The correlation between hepatic messenger ribonucleic acid (mRNA) expression of angiopoietin-like protein 8 (ANGPTL8) / betatrophin with NAFLD was revealed and it is higher than in healthy subjects. Patients suffering from this disease also have higher levels of circulating betatrophin which is also related with lipid metabolism and what follows with this, alterations in lipid profile. Both hepatic and circulating ANGPTL8 have correlation with liver steatosis [6]. It has been proven that expressions of nuclear factor kappa B (NF-κB), Interleukin 6 (IL-6) and Interleukin 10 (IL-10) genes are related to NAFLD treatment and pathogenesis. NF-κB is a mediator of inflammatory response, increasing Tumor necrosis factor α (TNF-alpha) and IL-6 productions which affect hepatic inflammatory processes. In turn IL-10 is an anti-inflammatory cytokine whose role can be described as protecting the liver from steatosis [7].

In NAFLD, increased expression of Aldo-Keto Reductase Family 1 Member B10 (AKR1B10) was observed along with other genes involved in retinoid metabolism (ADH1A, ADH1B, ADH1C, RDH5, RDH10, RDH 11, DHRS3, ALDH1A1 and ALDH1A3) compared with healthy subjects. It is worth mentioning that altered retinol metabolism has been identified as one of the different pathways involved in the complex process of hepatic fibrosis. The HOMA-IR index also positively correlated with AKR1B10 expression [8].

The connection between deoxyribonucleic acid (DNA) methylation patterns which affects gene expression and liver fat content is the subject of current research. The Yaskolka Meir et al. [9] study revealed significant reverse correlation between liver fat amounts among obese patients and DNA methylation in AC074286.1, Calcium Release Activated Channel Regulator 2A (CRACR2A), Alpha-2-Macroglobulin Pseudogene 1 (A2MP1), and ARH/RhoGEFand Pleckstrin Domain Protein 1 (FARP1) genes. FARP1 rs9584805 due to its connections with DNA methylations and liver fat is considered the best epigenetic indicator [9].

SNP genotype correlation with NAFLD

Genetic diversity among humans is evidenced by SNPs, which is evidence of a divergence in nucleotides. SNP could change the nucleotide in a DNA. Mostly they are found between genes, and they can be used as predictors of the disease or predict treatment outcome.

Nowadays SNPs are being studied for clinical utility in detecting various diseases, including NAFLD. Recently the connection between peroxisome proliferator–activated receptor-γ coactivator (PGC)-1α gene (PPARGC1A) with NAFLD pathogenesis was revealed. Gene PPARGC1A encodes a PGC-1α protein which is responsible for lipid and glycemic maintenance, oxidative stress and functions of mitochondria. PGC-1α plays an important role in hepatic homeostasis due to gluconeogenesis and fatty acids β-oxidation in mitochondria pathways. When it comes to NAFLD pathogenesis alterations in lipogenesis and gluconeogenesis plays a role. The strong relationship in obese children group was revealed especially for PPARGC1A rs8192678 risk A allele. In addition, in general population mentioned polymorphism is frequent. This study also revealed that in this population patatin-like phospholipase domain containing 3 (PNPLA3) rs738409 polymorphism is associated with severity of NAFLD [10].

Lin et al. [11] study revealed the significant correlation between NAFLD risk development and types of SNP genotypes of two genes: glucokinase regulatory protein (GCKR) and PNPLA3. These relationships were proven in obese children group for GC (1.608 times higher risk) and GG (2.812 times higher risk) genotypes of PNPLA3 rs738409 and for the TT (1.997 times higher risk) genotype of GCKR rs780094 [11]. When it comes to PNPLA3 rs738409 it was revealed that it has the strongest relationship with NAFLD development and progression in comparison to other SNPs of this gene or even: Sorting And Assembly Machinery of the mitochondrial outer membrane (SAMM50) and Parvin Beta PARVB[12]. The PNPLA3 rs738409 G-allele is also postulated to have a relationship with dietary approach response to liver fibrosis in NAFLD patients [13].

The studies showing genetic impact on NAFLD patients have been presented in Table I.

Table I. Genetic associations with NAFLD pathogenesis and their impact on it in humans with NAFLD or obesity.

Author	Study group	Tissue of expression assessment	Genetic factor	Results
Gene expression				
Osorio-Conles et al. (2021) [5]	48 obese females (24 with NAFLD)	Subcutaneous adipose tissue	↑:CD68, MRC1, MSR1, VEGFB, ANGPT1, LEP, TGFB1, UCP2, COL1A1, COL4A1, COL6A1 ↓: P16, LEPR, PGC1A, TIMP3	Increased expression of SAT-TGFB1, SAT-UCP2, VAT-MGLL genes correlated with increased risk of NAFLD
		Visceral adipose tissue	↑: LEP, MGLL, ATG12 ↓: HIF1A, ANGPT2, P53, P16, CIDEA	Increased expression of the VAT-P53, VAT-CIDEA, SAT-ATG5, SAT-MRC1 genes correlated with reduced risk and severity of NAFLD
von Loeffelholz et al. (2017) [6]	Subgroups from 2 independent studies	Liver	ANGPTL8 / betatrophin mRNA expression	Correlation with hepatic steatosis (S), hepatocyte ballooning degeneration (S), HOMA-IR (S)

Tutunchi et al. (2020) [14]	76 patients (34 with NAFLD)	Peripheral blood mononuclear cells (PBMCs)	UCP 1 UCP 2 PPAR-α	Upregulation of this genes expression results in: ↑Thermogenesis → ↓ weight, ↑Satiety → ↓ weigh, Improvement in fatty acids oxidation, lipid profile and glucose maintenance
Tauriainen1et al. (2018) [15]	138 patients (94 with NAFLD)	RNA from liver tissue	NPC1L1 mRNA expression	Higher expression of this gene in liver of subjects with NAFLD in comparison to non-NAFLD (S), Regulation of serum intestinal absorption, hepatic bile excretion
Tutunchi et al. (2021) [7]	76 patients with NAFLD	Fresh blood	NF-κB, IL-6 genes IL-10 gene	In the NAFLD decrease of NF-κB, IL-6 genes and increase of IL-10 gene expression may have a beneficial outcome
Pettinelli et al. (2018) [8]	63 patients (39 with NAFLD)	Liver	↑: AKR1B10 ↓: ALDH1A2 ↓: ALDH1A3	Increased expression of AKR1B10 in NAFLD is associated with the presence of oxidative stress. ALDH1A2, ALDH1A3 are involved in the oxidation of retinaldehyde to retinoic acid

Zhu et al. (2022) [16]	312 subjects (74 with NAFLD)	PBMCs	Inflammasome NLPR3 gene including (NLRP3, caspase-1, IL-1β, and IL-18)	Upregulation of this genes was observed in samples from patients with NAFLD compared to non-NAFLD, Increased plasma levels of IL-1β and IL-18
Single nucleotide polymorphism				
Yaskolka Meir et al. (2021) [9]	120 obese patients	Fasting blood samples	FARP1 rs9584805 SNP	Association with intrahepatic fat level (S) and NAFLD prevalence (S)
Kitamoto et al. (2013) [12]	1306 (372 with NAFLD)	Blood samples	PNPLA3rs738409 *, rs2896019, rs381062 SAMM50 rs2143571, rs3761472, rs738491 PARVBrs6006473, rs5764455, rs6006611	Decrease of serum TG, Increase of serum AST, ALT, Correlation with NAFLD activity score and steatosis grade, Underlined SNPs are related with fibrosis, SNPs except of rs5764455 are correlated with increased ferritin serum level

Wang et al. (2014) [17]	300 patients with NAFLD	PBMCs	GG genotype and G carrier (CG + GG) of SREBP-2 rs2228314 G > C	Increased risk of NAFLD, Regulation of lipid metabolism, Correlation with DM2 and lipid disturbances, The possibility of using this polymorphism as a biomarker of NAFLD development is being investigated
Di Costanzo et al. (2019) [18]	230 overweight patients aged 6-16 years (105 with NAFLD)	Whole blood sample	CG and GG genotypes of PNPLA3 rs738409 CT + TT genotypes of TM6SF2	Higher prevalence in subjects with NAFLD in comparison to non-NAFLD (S for both genes), For PNPLA3 the risk of NAFLD is 14.9 times higher risk of NAFLD development, for TM6SF2 this risk is respectively 3.9 times higher, Decrease of eGFR (S) for PNPLA3 G allele carriers, Increase of median urinary albumin in PNPLA3 CG carriers (S)
Lin et al. (2013) [10]	781 obese children	Venous blood	PPARGC1A rs8192678 risk A allele	AST (S), ALT (S), HOMA-IR (S), insulin concentration (S) differences in comparison to allele nanocarriers

Kaliora et al. (2019) [19]	44 patients with NAFLD	Blood samples	STAT3 rs2293152 risk G allele	Association with NAFLD progression to HCC, this gene is involved in cytokine signaling pathways Risk G allele carriers in comparison to non-G carriers has better outcomes of Mediterranean diet intervention, Elevated visfatin levels among G-carriers after dietary intervention compared with C-carriers
Lin et al. (2014) [11]	797 obese children aged 7-18 years	Fasting venous blood	GCKR rs780094 (TT genotype) PNPLA3 rs738409 (GC and GG genotype)	Increased risk of NAFLD development among obese children
Lutz et al. (2019) [20]	170 subjects without diabetes	Blood samples	FGFR4 388Arg allele	388Arg allele is associated with elevated liver fat amounts in individuals following a healthy diet compared with carriers of 388Gly allele

Nobili et al. (2013) [21]	60 children with NAFLD	ND	PNPLA3 148M allele homozygote	Weakness of response to DHA supplementation in liver steatosis decreasement in comparison to heterozygotes, Increase of severe steatosis development risk, triglycerides and ALT elevation
			PNPLA3 148I allele homozygote	Betterment of response to DHA supplementation in liver steatosis decreasement in comparison to heterozygotes

Abbreviations:

AKR1B10 - Aldo-Keto Reductase Family 1 Member B10, ALDH1A2 - AldehydeDehydrogenase 1 Family Member A2, ALDH1A3 - AldehydeDehydrogenase 1 Family Member A3, ALT - alanineaminotransferase, ANGPT1 - Angiopoietin 1, ANGPTL8 - 1-alpha angiopoietin-like protein 8, APOC3 - gene for Apolipoprotein C, AST - aspartateaminotransferase, ATG12 - AutophagyRelated 12, ATG5 - autophagy related 5, ApoE - Apolipoprotein E, b3AR - gene for Adrenergic receptor, CIDEA - cell death activator, COL1A1 - CollagenType I Alpha 1 Chain, COL4A1 - CollagenType IV Alpha 1 Chain, COL6A1 - CollagenType VI Alpha 1 Chain, Coactivator 1 Alpha, DHA - docosahexaenoic acid, eGFR - estimated glomerular filtration rate,

ND - no data

NS - statistically insignificant

S - statisticallysignificant

↑ - upregulation

↓ - downregulation

* - the strongest relationship in mentioned study

Conclusions

Nowadays genetics is a rapidly developing science and undoubtedly represents the future, although many mechanisms and connections are still unknown. As we see there are numerous genetic associations involved in NAFLD pathogenesis. Mostly authors indicate PNPLA3 SNPs variants which seem to be in a strongest relationship with NAFLD among mentioned genes. There are a few genetic factors for which a better therapeutic effect of the applied procedures has been proven e.g.,PNPLA3 148 allele M or I homozygotes, so we can choose a patient's treatment in terms of his sensitivity to specific procedures, thanks to the knowledge of these genes. This review showed many different linkage mechanisms between genetics and NAFLD. What was our intention may provide an indication to researchers for which genes the intervention should be tested for. Perhaps in the future, based on genetic tests, it will be possible to determine the risk of developing NAFLD in a patient and implement methods of management before the disease and its consequences develop. What is more, knowledge of the expression products of these genes, it will be possible to apply targeted treatment tailored to a particular patient.

Disclosure

Institutional Review Board Statement

Not applicable – Not required

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The data presented in this study is available upon request from the correspondent author.

Conflict of interest

The authors deny any conflict of interest

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