Gene by Environment Interaction and Metabolic-Associated Fatty Liver Disease in Mexican American Patients with Depression

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Background

- The Rio Grande Valley (RGV) is one of the poorest regions of the United States and experiences significant health disparities.
- The majority (90%) Mexican American population of the RGV faces disproportionately high rates of obesity (55.5%), diabetes (32.5%), and depression (19%).
- About 50% of the population is affected by metabolic fatty liver disease (MAFLD).
- Gene by Environment interaction effects (G x E) are used to determine whether or not a specific environment plays a role in the up-regulation or down-regulation of genes that contribute to a specific phenotype.
- The risk factors for MAFLD are well known, but the influence of the G x E of the MAFLD phenotype in a depression environment are not well understood.

Purpose

This study aimed to examine the impact of G x E interaction effects on MAFLD in Mexican Americans with depression in the RGV.

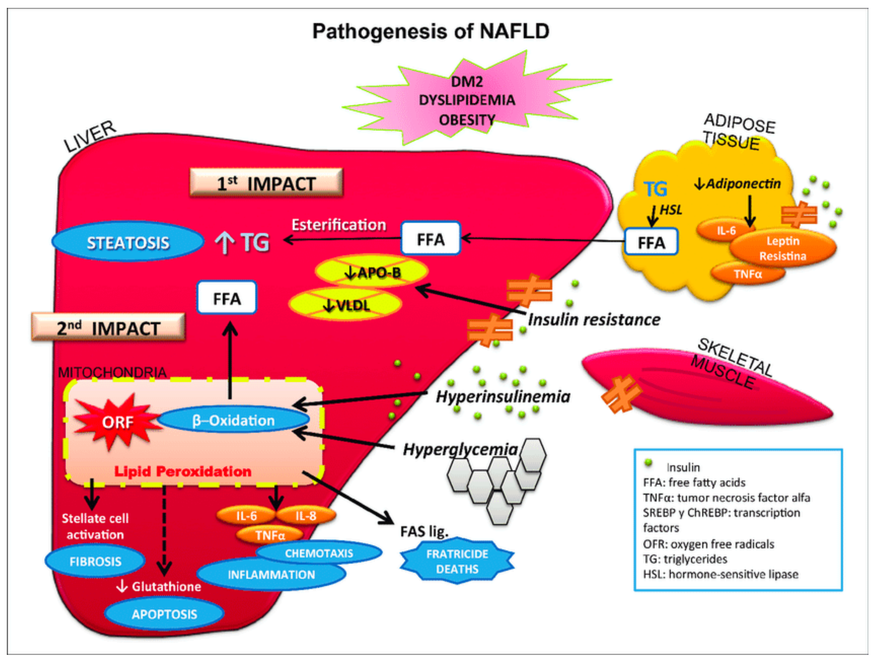

Figure 1. Pathogenesis of MAFLD (previously known as non-alcoholic fatty liver disease (NAFLD). MAFLD includes a broad spectrum of alterations that include steatosis (hepatic fatty buildup) hepatic fibrosis, and cirrhosis (worsening fibrosis and hepatic failure). Obesity, dyslipidemia, and type II diabetes are the most well understood etiologies of MAFLD, although gene x environment factors remain a possible etiology of MAFLD development [1].

Methods

- Over 500 Mexican American participants in an ongoing genetic study were evaluated
- Depression was measured by the BDI-II, a questionnaire valid for the diagnosis of major depressive disorder when administered in both Spanish and English [2,3]
- Presence of MAFLD was determined based on vibration-controlled transient elastography (FibroScan) results. The controlled attenuation parameter (CAP) was used to measure the degree of steatosis. We measured hepatic fibrosis using the Liver Stiffness Measurement LSM Youden Index and analyzed it as a continuous variable in kPa.
- We examined G x E interaction effects in response to the depression environment by modeling the additive genetic variance and correlation as continuous functions of the environment as described in Arya et al. (2017) [4]. All genetic analyses were conducted using the statistical genetics software package SOLAR developed by our laboratory [5]

Results and Discussion

Trait	N value	h^2r	p-value	SE
Hepatic fibrosis(kPa)	184	0.3910714	0.0044064	0.1555822
Steatosis (CAP)	184	0.3279800	0.0165725	0.1610810

Table 1 Heritability of traits. Analysis included 184 individuals after exclusion. We found statistically significant mild to moderate heritability for hepatic fibrosis (h^2r = 0.39, p value = 0.004) and steatosis (h^2r = 0.33, p value = 0.017).

Trait	Environment	Model	ln likelihood	LRT	p-value
Hepatic fibrosis (kPa)	BDI-II	Polygenic	-83.417021		
		Full G x E	-81.599278	3.64	0.028
Steatosis (CAP)	BDI-II	Polygenic	-84.277132		
		Full G x E	-84.277132	0	1

Table 2 Testing the G x E model against the Polygenic model. The polygenic model was compared to the G x E interaction model by means of a log-likelihood ratio test. The G x E interaction model is significantly better than the polygenic model for hepatic fibrosis but not steatosis.

Trait	Environment	Model	ln likelihood	LRT	p-value
Hepatic fibrosis(kPa)	BDI-II	Genetic correlation equals 1	-81.953998		
		Full G x E	-80.343949	3.220	0.036

Table 3 G x E Results: testing the hypothesis that the genetic correlation equals 1 against the G x E model. We observed homogenous additive genetic variance for hepatic fibrosis x BDI-II (p-value =0.036)

- We determined mild to moderate heritability for hepatic fibrosis and steatosis prior to conducting our G x E analysis. The differences in heritability between hepatic fibrosis and steatosis suggest that there may be genetic heterogeneity within pathways that influence each trait.
- Our findings demonstrate that G x E interactions are present between depression and hepatic fibrosis but not depression and hepatic steatosis.
- Thus, if a patient is experiencing depression, it is possible that the depression may trigger an altered expression of genes that only contribute to liver fibrosis, not steatosis.
- This may be explained by the finding that an increased expression of inflammatory cytokines are seen in fibrosis compared to steatosis [6].
- Patients with depression see a rise in central and peripheral inflammation [7]. It is possible that the presence of depression accelerates the development of steatosis through an upregulation of inflammatory gene expression.

Conclusions

- We have demonstrated that there are genetic interactions between depression and hepatic fibrosis but not depression and hepatic steatosis.
- Future directions are to identify the particular nature of the interaction and the specific genes involved.
- Identifying the specific genes involved in this G x E interaction may lead to the development of gene-specific therapies for MAFLD, depression, or possibly both.
- One study limitation is therelatively small sample size (n=187) due to missing data points in our population. Another limitation is that depression is shown to have a genetic component; therefore, there is a possibility for our interaction models to reflect gene x gene interactions.

References

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