The importance of mitochondrial DNA damage and repair in the occurrence of insulin resistance in nonalcoholic fatty liver disease

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BACKGROUND

Nonalcoholic fatty liver disease (NAFLD) is one of the most common disorders affecting the liver. An important issue in the development of NAFLD is insulin resistance (IR), which is related to the fatty liver through the excessive accumulation of free fatty acids, chronic hepatitis, and increased oxidative stress in the liver cells. Recent literature shows the link between NAFLD and increased production of reactive oxygen species (ROS), which make the liver particularly vulnerable to oxidative stress due to a high number of mitochondria present in hepatocytes. Therefore, it can lead to an oxidative damage to the mitochondrial DNA (mtDNA), and a base excision repair (BER) is mainly responsible for repairing this type of damage.
Considering the information presented above, **the aim of the project is to determine the molecular basis of IR-related processes in NAFLD in the context of mtDNA damage accumulation and/or BER pathway impairment as well as degradation of damaged mtDNA.**

MATERIALS & METHODS

In the current academic year, the results of SNP genotyping and expression of genes related to BER were obtained. DNA and RNA were isolated from 84 NAFLD patients and 340 DNA and 40 RNA from controls. Blood RNA was transcribed into cDNA and gene expression was determined by TaqMan probes and qPCR. SNP genotyping was also performed with TaqMan probes. Statistical analysis was performed using GraphPad Prism 8. Genotyping results were calculated as odds ratio (OR) with a 95% confidence interval, and gene expression was calculated using the $2^{-\Delta Ct}$ method. GAPDH was used as the reference gene.

RESULTS

- Genotypes and alleles that may modulate the risk of NAFLD occurrence are presented in Figure 1. The odds ratio lower than 1 indicates that genotype/allele decreases risk of the disease and higher than 1 implies the increased one.
- The gene expression in the study groups was up-regulated in comparison to the control group (Figure 2.).
  * *p-value*<0.05; ** *p-value*<0.01; *** *p-value*<0.001

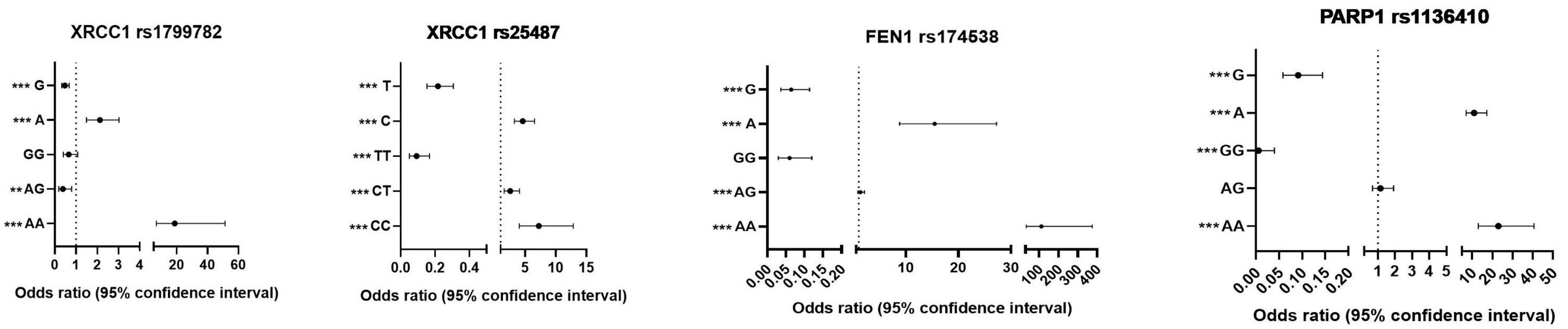

Figure 1. SNP genotyping results demonstrated as odds ratio with 95% confidence intervals. The findigs present the risk of the NAFLD occurence.

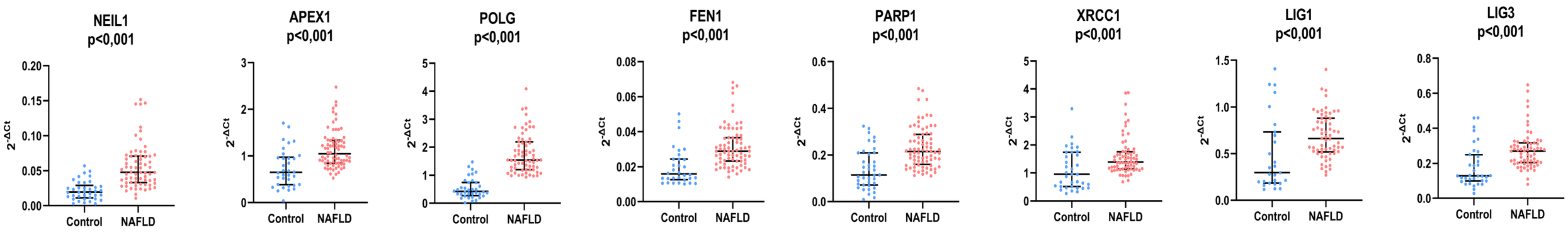

Figure 2. Gene expression in the blood samples of NAFLD and control groups.

CONLUSION

- The selected genes may modulate the risk of the fatty liver and may be associated with and development of steatosis.
- The findings allow to assume, that BER might be related to NAFLD.

ACKNOWLEDGMENT

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