De Especialidades Quirúrgicas, Bioquímica E Inmunología, Facultad De Medicina, Universidad De Málaga, Universidad de Málaga, Málaga, Spain; [2] *1. unidad De Gestión Clínica Intercentros De Oncología Médica, Hospitales Universitarios Regional Y Virgen De La Victoria, IBIMA, Malaga, Spain;* [3] *2. obesity And Metabolism Laboratory, Biomedical Research Institute of Murcia (IMIB), Murcia, Spain*

Background and Aims : Metabolic-associated liver disease (MAFLD) is a growing health problem in developed country, being associated to environmental factors such as diet and lifestyle conditions that can influence the epigenetic landscape of the cells. In this study we performed ATAC-seq and RNA-sequencing in liver tissue of subjects with and without NASH to assay the chromatin openness and its effects on transcription during NASH etiology.

Methods: Liver samples (n=12) were processed to purify the cell nuclei, and ATAC reaction was performed. ATAC and RNA libraries were sequenced using Novaseq PE150 (Illumina). Bioinformatic analysis were then performed using R Studio and Python-based software.
Results: Subjects with NASH showed transcriptional downregulation for pathways related to lipid and glucose metabolism such as ABC-transporters, AMPK, FoxO or insulin pathways, compared to non-NASH. We found 229 deregulated genes (ATAC and RNA) in NASH vs non-NASH. Such genes encoded for factors related to lipid transport, nuclear receptor binding, dicarboxylic-acid-transporter, and PPARA-lipid regulation. Such promoters were enriched for motif sequences for TF as ZBTB12, Sox2 or Stat3. Interpolation of ATAC data with known liver enhancer regions showed differential openness at 8 enhancers, some of them linked to genes involved in lipid metabolism, such as FASN, or glucose homeostasis, such as GCGR.
Conclusions: Chromatin is altered in NASH compared to non-NASH. Such alteration might be related to changes in the transcriptional profile which can explain the etiology and pathophysiology of the disease. We demonstrated the importance of the epigenetic landscape in MAFLD, guarantying more studies that could result in the development of new epigenetic-based treatments.

EP512 / #955, TOPIC: *ASA03 - DYSLIPIDEMIA AND RISK FACTORS / ASA03-14 EPIGENETICS AND MICRORNA*, POSTER VIEWING SESSION. GENETIC RISK SCORE OF HYPERTIGLYCERIDEMIA AND ITS INTERACTION WITH CLINICAL VARIANTS

V. Esteve Luque [1,2], M. Fanlo Maresma [1], E. Corbella [1,2], X. Pintó [1,2,3,4]. [1] *Internal Medicine, Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Spain;* [2] *Idibell, Institut de Recerca Biomedica, Hospitalet de Llobregat, Spain;* [3] *Ciberobn, Instituto Carlos III, Spain, Spain;* [4] *Facultat De Medicina, Universidad de Barcelona, Spain, Spain*

Background and Aims : Numerous single nucleotide polymorphisms (SNPs) related to plasma TG have been identified and different genetic risk scores (GRS) have been developed to predict the risk of hypertriglyceridemia (HTG). However, there is a wide variability in TG concentration that is not explained by these scores, which may be due to a gene-environment interaction.

Methods: In this study, 276 Spanish individuals with primary HTG aged 18-80 years were selected. Six allelic variants related to TG concentrations, c.724C> G (ZPR1 gene), c.56C> G (APOA5 gene), c.1337T> C (GCKR gene), g.19986711A> G (LPL gene), c. 107 + 1647T> C (BAZ1B gene) and g.125478730A> T (TRIB gene) were studied. An unweighted GRS was created by summing the number of mutated alleles present in each individual for each of the six allelic variants. Multiple linear regression models were performed to analyze the effect of the GRS with the highest levels of TG and the interactions with other clinical variables such as BMI, diet, alcohol consumption physical activity and HbA1c were studied.
Results: A GRS ranging between 4-11 was observed in the individuals from this study. The GRS was associated with the concentration of TG and explained 7% of the variability of TG concentrations. Significant interactions between BMI and GRS were found regression coefficient 0.15 CI(0.03-0,28), p(0.02), and also with HbA1c RC 0.93 CI(0.13-1.74) p(0.02), whereas no evidence of such interactions with other clinical variables were found.
Conclusions: An interaction between GRS and BMI explains part of the variability of TG concentration in the individuals studied.

EP513 / #1340, TOPIC: *ASA03 - DYSLIPIDEMIA AND RISK FACTORS / ASA03-14 EPIGENETICS AND MICRORNA*, POSTER VIEWING SESSION. EFFECT OF INCREASING DOSES OF STATINS ON THE LEVEL OF SERUM MICRORNAS INVOLVED IN REVERSE CHOLESTEROL TRANSPORT AND INFLAMMATION

V.A. Kudinov [1], R.I. Artyushev [1], M.Y. Zubareva [2], T.A. Rozhkova [3], K.K. Baskaev [4], J.A. Shuvalova [3], A.I. Kaminny [3], I.V. Sergienko [2]. [1] *Scientific Group Of Phospholipid Drugs, Institute of Biomedical Chemistry, Moscow, Russian Federation;* [2] *Laboratory Of Atherosclerosis Phenotypes, FSBI National medical research center of cardiology Ministry of Health of the Russian Federation, Moscow, Russian Federation;* [3] *Department Of Atherosclerosis, FSBI National medical research center of cardiology Ministry of Health of the Russian Federation, Moscow, Russian Federation;* [4] *Experimental Drug Research And Production Department, Institute of Biomedical Chemistry, Moscow, Russian Federation*

Background and Aims : Circulating microRNAs as a component of such epigenetic mechanism of posttranscriptional regulation of mRNA translation may serve as blood biomarkers of CVDs, moreover, the study of circulating miRNAs may help to identify potential therapeutic targets. We investigated changes in the serum level of 4 circulated microRNAs (miR-33a, miR-33b, miR-146a, and miR-146b) in patients with coronary artery disease and disorders of carbohydrate metabolism under the influence of up-titrated doses of two widely used statins (atorvastatin and rosuvastatin).

Methods: RNA was isolated from blood plasma samples obtained from clinical trial participants (n=16; 14 males and 2 females; mean age64.25±9.19) just before and 30days after treatment. To investigate microRNAs levels, RT-qPCR analysis was performed. Exogenous cel-miR-39 was used as a reference. Changes in miRs circulating levels were evaluated, the significance level $p \leq 0.05$.
Results: All Ct's for each patient, obtained by RT-qPCR, normalized on Ct for control. Statistically significant changes in expression noted: decreasing for miR-33a(p=0.0043) and -33b(p=0.0009); increasing for miR-146a(p=0.0054). For miR-146b no significant changes were observed (p=0.5014).
Conclusions: Our study has demonstrated that increasing doses of Rosuvastatin and Atorvastatin may influence miR-33a/b (decreasing) and miR-146a (increasing) serum levels. This data pointed that the pharmacological effect of up-titrated doses may also be explained additional pleiotropic effects on key serum miRNAs involved in the regulation of lipid metabolism and inflammation.

EP514 / #358, TOPIC: *ASA03 - DYSLIPIDEMIA AND RISK FACTORS / ASA03-14 EPIGENETICS AND MICRORNA*, POSTER VIEWING SESSION. ANALYSIS OF MICRORNA BIOMARKERS IN INFLAMMATORY PATHWAYS REGULATION OF PRE-MATURED ATHEROSCLEROSIS IN RATS MODEL

Z. Othman [1], C. Rustin [2], I.S. Kamaruddin [2], L. Herawati [3], N. Abdul Karim [4], M.A. Fatima [5]. [1] *Faculty Of Health & Life Sciences, MANAGEMENT & SCIENCE UNIVERSITY, SHAH ALAM, Malaysia;* [2] *School Of Graduate Studies, MANAGEMENT & SCIENCE UNIVERSITY, SHAH ALAM, Malaysia;* [3] *Faculty Of Medicine, AIRLANGGA UNIVERSITY, SURABAYA, Indonesia;* [4] *Faculty Of Medicine, UNIVERSITI KEBANGSAAN MALAYSIA, KUALA LUMPUR, Malaysia;* [5] *Research Management Centre, MANAGEMENT & SCIENCE UNIVERSITY, SHAH ALAM, Malaysia*

Background and Aims : MicroRNAs are highly up-regulated within atherosclerotic plaque complex indicating their heavy involvement in inflammatory genes regulation in atherosclerosis pathways. Hence, microRNA considered as a promising biomarker for the aforementioned disease. This study aims to investigate the changes in inflammatory microRNA

expression in pre-matured atherosclerosis Sprague Dawley (SD) rats induced with high-fat diet.

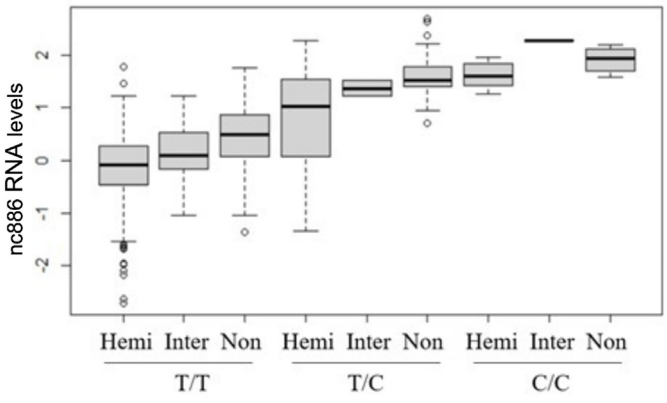
Methods: Rats (n=10) were randomly divided into High Fat Diet (HFD) and normal diet (ND) groups. Blood was collected for biochemistry analysis of lipid profiling, histology assessment of tunica intima on aorta by Haematoxylin and Eosin (H&E) staining and microRNAs analysis conducted in week 6 and week 12 using Real-Time PCR.
Results: Biochemistry analysis shown significant correlation between HFD and ND and Low-Density Lipoprotein (LDL), High-Density Lipoprotein (HDL), Triglyceride (TG) and Total Cholesterol (TC) level from week 0 to 12, $p<0.05$. MicroRNA analysis revealed that, rno-miR-17-1-3p, rno-miR-210-5p, rno-miR-181a-2-3p and rno-miR-155-5p was expressed in both HFD and ND. There was significantly higher ($p<0.05$; $t=11.80$) expression of microRNAs in HFD group (27.15 ± 8.90) compared to ND group (30.82 ± 1.72). [z1] [z2] Microscopic analysis reveals the thickening on tunica intima of aorta due to inflammation activities in HFD (152.497 ± 7.518 μm) compared to ND (148. 408 ± 1.94 μm).
Conclusions: High calorie diet influenced the expression pattern of the inflammatory microRNA biomarkers. The microRNA may play important role in the regulations of inflammatory gene in the development of premature atherosclerosis.

EP515 / #195, TOPIC: *ASA03 - DYSLIPIDEMIA AND RISK FACTORS / ASA03-14 EPIGENETICS AND MICRORNA*, POSTER VIEWING SESSION. GENETIC AND EPIGENETIC REGULATION OF NC886 RNA LEVELS AND THEIR ASSOCIATION TO CARDIOMETABOLIC PHENOTYPES

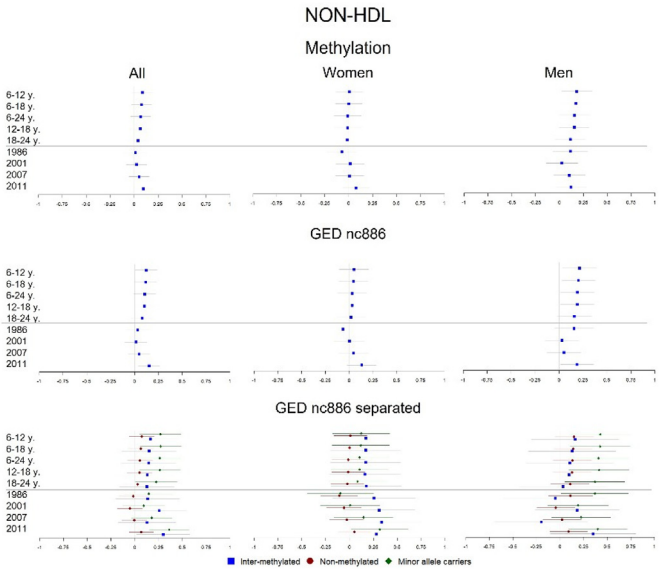
S. Rajic [1], S. Marttila [2], P. Mishra [2], N. Mononen [2], O. Raitakari [3], L.-P. Lyytikäinen [2], M. Kähönen [1], N. Hutri-Kähönen [2], M. Waldenberger [4], T. Lehtimäki [2], E. Raitoharju [2]. [1] *Faculty Of Medicine And Health Technology, Tampere University, Tampere, Finland;* [2] *Medicine And Health Technology, Tampere University, Tampere, Finland;* [3] *Research Centre Of Applied And Preventive Cardiovascular Medicine, University of Turku, Turku, Finland;* [4] *Research Unit Of Molecular Epidemiology, Helmholtz Zentrum München, Neuherberg, Germany*

Background and Aims : A non-coding nc886 RNA is transcribed from a polymorphically imprinted metastable epiallele. Methylation status of this locus is affected by the periconceptional conditions and both the methylation status and the level of nc886 RNAs are shown to be associated with health traits in later life. We have previously shown that, in addition to the methylation status of the nc886 locus, genetics have an independent effect on nc886 RNA levels. As genotypic and methylation data are more commonly available in existing population cohorts than RNA levels, we set out to investigate whether we can leverage this information to further study the cardiometabolic associations of nc886 RNAs.

Methods: We created a variable that acts as an RNA level proxy by combining the effects of a lead SNP and methylation status and performed association analyses of it with the cardiometabolic phenotypes in a population cohort.



Results: Individuals with a genotype/epigenotype combination reflecting higher nc886 RNA levels have elevated insulin throughout their early lives, elevated LDL and non-HDL cholesterols in early and later life, elevated total cholesterol in later life, and decreased glucose in early and later life. Moreover, we found association with this genotype/epigenotype combination and prevalence of type 2 diabetes. We also performed sex-stratified analyses with similar results.



Conclusions: Our hope for the future is to use this variable to study the effect of nc886 RNA levels across different cohorts and further explore the association between nc886 levels and the relevant cardiometabolic phenotypes.

EP516 / #1152, TOPIC: *ASA03 - DYSLIPIDEMIA AND RISK FACTORS / ASA03-14 EPIGENETICS AND MICRORNA*, POSTER VIEWING SESSION. THE IMPACT OF CHOLESTEROL LOWERING DRUGS ON METABOLISM AND EPIGENETICS

A. Rose [1], J.R. Rodriguez-Aguilera [1], G. Schicht [2], A. Lohrenz [2], A. Tvardovskiy [3], J. Büscher [4], A. Hoffmann [1], G. Damm [2], U. Laufs [5], D. Seehofer [2], M. Blüher [1], B. Sheikh [1]. [1] *Vascular Epigenetics, Helmholtz-Institut für Metabolismus-, Adipositas- und Gefäßforschung (HI-MAG), Leipzig, Germany;* [2] *Hepatobiliary And Transplant Surgery, University of Leipzig, Leipzig, Germany;* [3] *Institute Of Functional Epigenetics, Helmholtz Zentrum Muenchen, Neuherberg, Germany;* [4] *Metabolomic, Max-Planck-Institute of Immunology and Epigenetics, Freiburg, Germany;* [5] *Kardiologie, Klinik und Poliklinik fuer Kardiologie am Universitaetsklinikum Leipzig, Leipzig, Germany*

Background and Aims : Cardiovascular diseases (CVDs) are the leading cause of death globally. In patients with CVDs, treatment with cholesterol lowering drugs has been shown to reduce cardiovascular events. Bempedoic acid is a novel drug for lowering low-density lipoprotein cholesterol that has recently been approved for clinical use. Bempedoic acid specifically inhibits ATP citrate lyase (ACLY) in the liver, an enzyme that converts citrate to acetyl-CoA and acts at the interface of carbohydrate and lipid metabolism. ACLY is not only cytoplasmic, but is also found in the nucleus, where it regulates histone acetylation levels. Yet, it is unknown if and how bempedoic acid impacts ACLYs regulatory function in the nucleus.

Methods: By combining chromatin immunoprecipitation sequencing, transcriptomics, tracer metabolomics and mass-spectrometry based histone post-translational modification analysis in primary human hepatocytes, we systematically investigate the impact of bempedoic acid on ACLY at different regulatory levels.
Results: Our data from mouse liver tissue revealed binding of ACLY to promoter regions of metabolic genes. Consistently, gene expression