DNA-methylation signature of microRNA coding genes associated with chronological age in a high-cardiovascular risk Mediterranean population. Sex-specific analysis

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Background and aims: DNA-methylation has been associated with biological age and several epigenetic clocks have been reported (Hovarth) MicroRNA (miRNA) are short single-stranded RNA molecules implicated in the regulation of gene expression. As well as protein-coding genes, miRNA-coding genes may be targets for DNA methylation. However, the role of this methylation on aging and cardiovascular risk is still poorly studied. Our aim is to analyze the DNA methylation in miRNA-coding genes in a high-cardiovascular risk Mediterranean population, and its association with age considering sex-specific differences.

Methods: A DNA-methylation analysis of miRNA genes was analyzed using the EPIC850K array (figure 1), in high-cardiovascular risk 414 subjects aged 55-75y. We obtained Beta and M-values for CpGs located in the miRNA genes and their association with age in multivariate models adjusted for confounders (sex, leukocytes, batch-effect, diabetes, BMI). Sex-specific analyses were conducted.

Results: In the whole population, significant associations between miRNA-gene methylation and chronological age were obtained. Outstanding the MIR34B (cg26561785; p=3,9x10^{-8}; hypermethylation associated with higher age; r=0.28). Previous studies have linked miR-34a to vascular aging and arteriosclerosis. The following most significant associations (p=4,7x10^{-7}-1,5x10^{-6}) were obtained with CpG in MIR663(r=0.26), MIR9-3(r=0.26), MIR495(r=-0.26) and MIR203A(r=0.25), as main components of the methylation signature in the whole population (table 1). Sex-specific analysis detected sex-specific differences (table 2). The top-ranked CpGs in men were MIR34B (cg26561785;p=9.2x10-6) and MIR9-3 (cg12530503;p=1.8x10^{-05}); whereas in women were MIR376B (cg05348084;p=4.3x10-7) and MIR203A (cg24454784;p=3.9x10^{-06}).

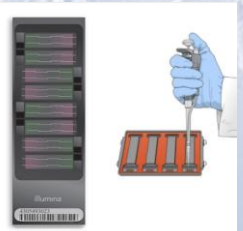

Figure 1. DNA-methylation analysis of miRNA genes was analyzed using the EPIC850K array

Whole Population

Gene	p-value	r-value
MIR34B (cg26561785)	3.9x10^{-8}	0.28
MIR663	4.7x10^{-6}	0.26
MIR9-3	4.7x10^{-6}	0.26
MIR495	4.7x10^{-6}	0.26
MIR203A	4.7x10^{-6}	0.25

Table 1. In the table we can see the ignificant associations between miRNA-gene methylation and chronological age were obtained in Whole population

Differences by Sex

Men		Women	
Gene	**p-value**	**Gene**	**p-value**
MIR34B (cg26561785)	9.2x10^{-6}	MIR376B (cg05348084)	4.3x10^{-7}
MIR9-3 (cg12530503)	1.8x10^{-5}	MIR203A (cg24454784)	3.9x10^{-6}

Table 2. In the table we can see the ignificant associations between miRNA-gene methylation and chronological age were obtained by sex differences

Conclusions: Altered methylation in MIR genes is associated with chronological age, and this association may be different between men and women with high-cardiovascular risk.

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