

BACKGROUND

- Polycystic ovary syndrome (PCOS) is a prevalent disorder in adolescent girls, commonly driven by hepato-visceral fat excess, usually presenting with hirsutism and menstrual irregularity, and often followed by subfertility, obesity, and type 2 diabetes.
- The sequence of events leading to PCOS may be subject to genetic and epigenetic modulations influencing both the phenotype and possibly the outcome during and after intervention.

AIM

To study the miRNA profile of adolescent girls with PCOS, and the effects of a randomized treatment with an oral contraceptive (OC) or with a low-dose combination of spironolactone-pioglitazone-metformin (SPIOMET) for 1 year.

SUBJECTS AND METHODS

- The study population consisted of 31 Caucasian post-menarcheal girls [age, 16 yr; body mass index (BMI), 23.1 Kg/m²] with PCOS who were randomized to receive an OC (20 µg ethinylestradiol, 100 mg levonorgestrel) or SPIOMET (spironolactone 50 mg/d, pioglitazone 7.5 mg/d, and metformin 850 mg/d) for 1 year. The girls were followed in the subsequent year off treatment. Thirteen age- and BMI-matched, healthy girls served as controls. None was hirsute or taking medications, and all had regular cycles.
- Circulating miRNA profiling was performed by RNA sequencing [N=6 samples from control girls and 12 from PCOS girls (N=6 randomized to OC and N=6 randomized to SPIOMET)]; differentially expressed miRNAs were validated by qRT-PCR in the entire study population. The expression levels of the validated miRNAs were assessed after 1 year on treatment and after 1 year off treatment.
- Assessments: androgens, insulin, lipids, ovulation rate (weekly salivary progesterone during the second and fourth trimesters of the post-treatment year), body composition (DXA), hepato-visceral fat (MRI).

RESULTS

Figure 1. miRNAs differentially expressed in girls with PCOS as compared to control girls. The results are expressed as the ratio of the average expression fold change (FC) in girls with PCOS vs controls (Z-score). miRNAs depicted in dark green are those confirmed in the entire study population (13 control girls and 31 girls with PCOS).

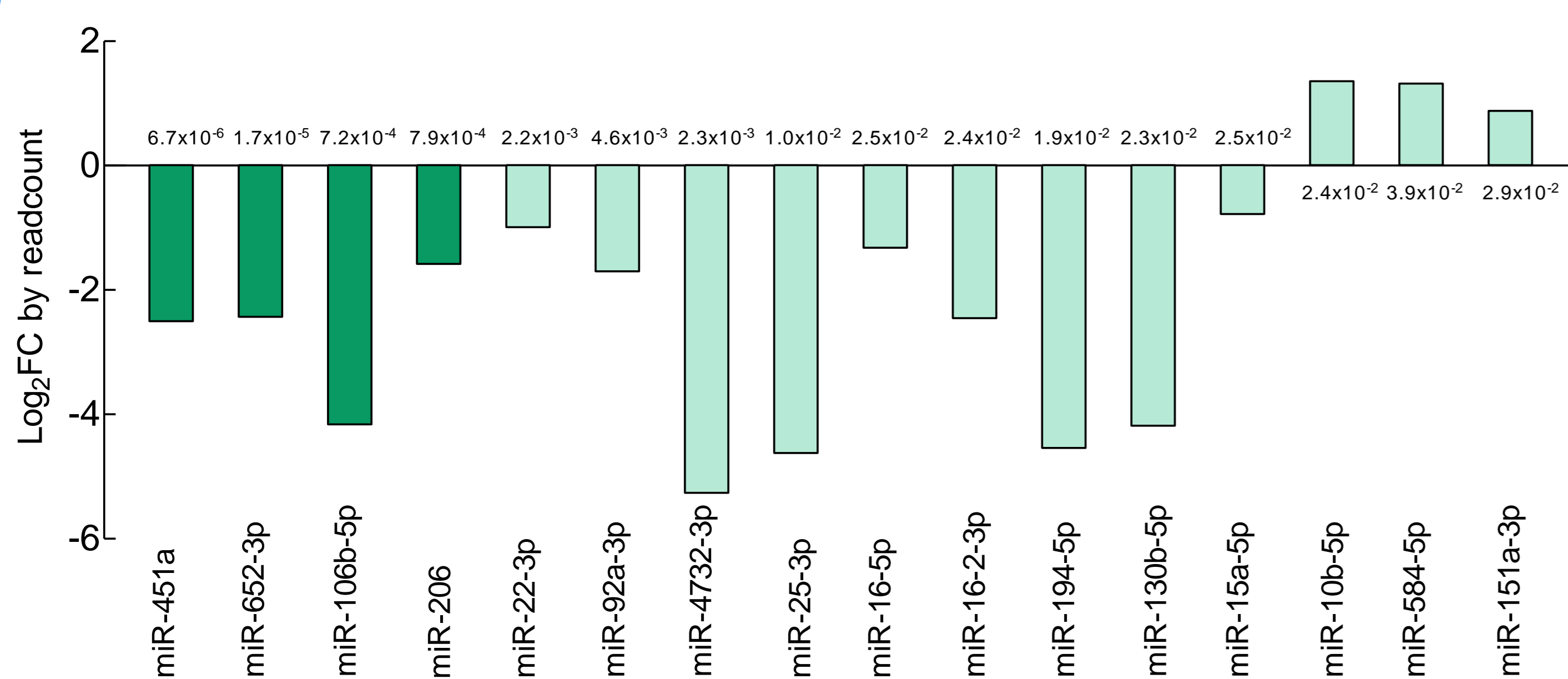


Figure 3. miR-451a ROC curve for diagnosing girls with PCOS vs control girls

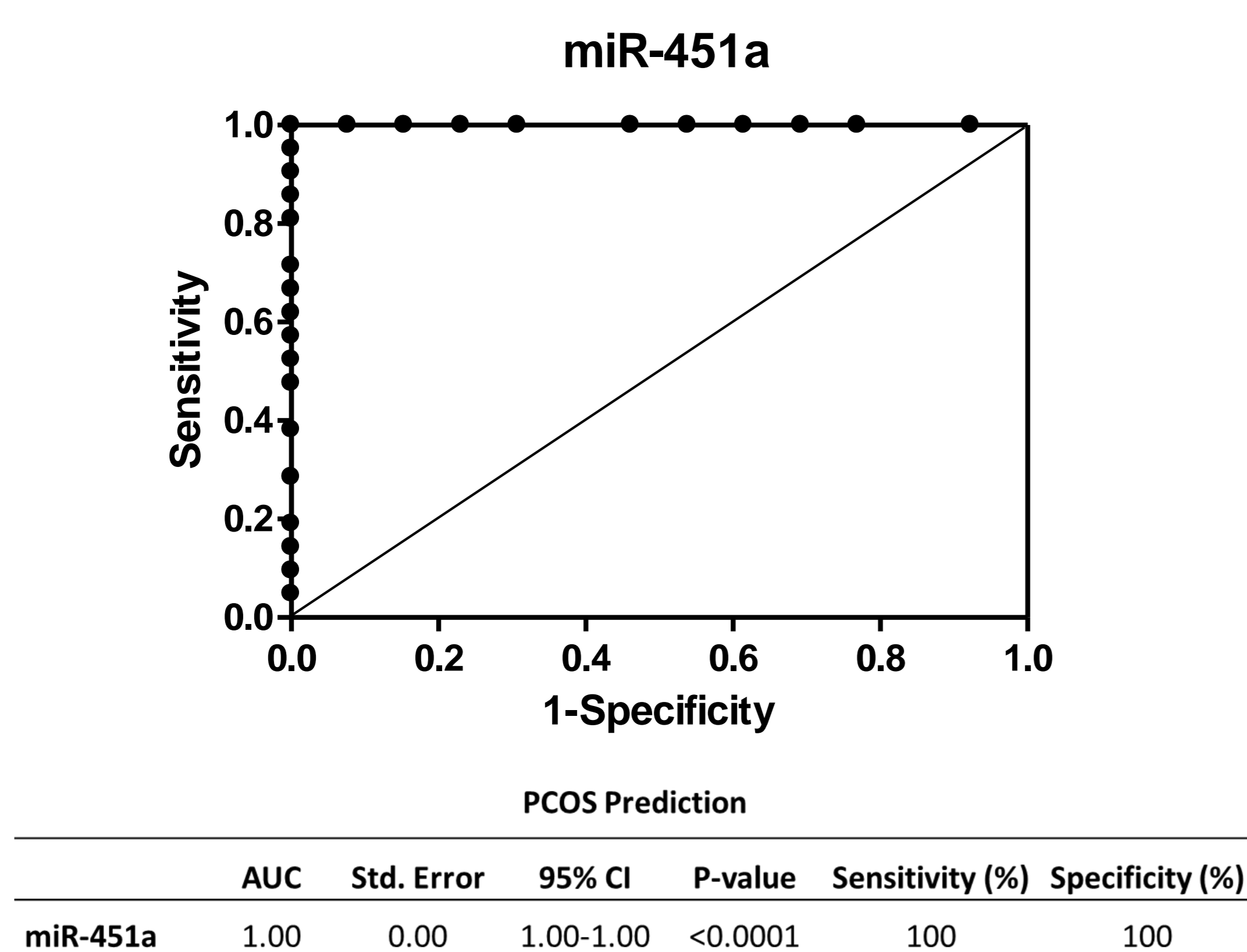


Figure 2. Left Panel: Relative expression of selected candidate miRNAs in adolescent girls with PCOS (n=31) at baseline. Results are expressed as Z-scores derived from the relative expression in control girls (n=13). *** P<0.0001; ** P=0.007

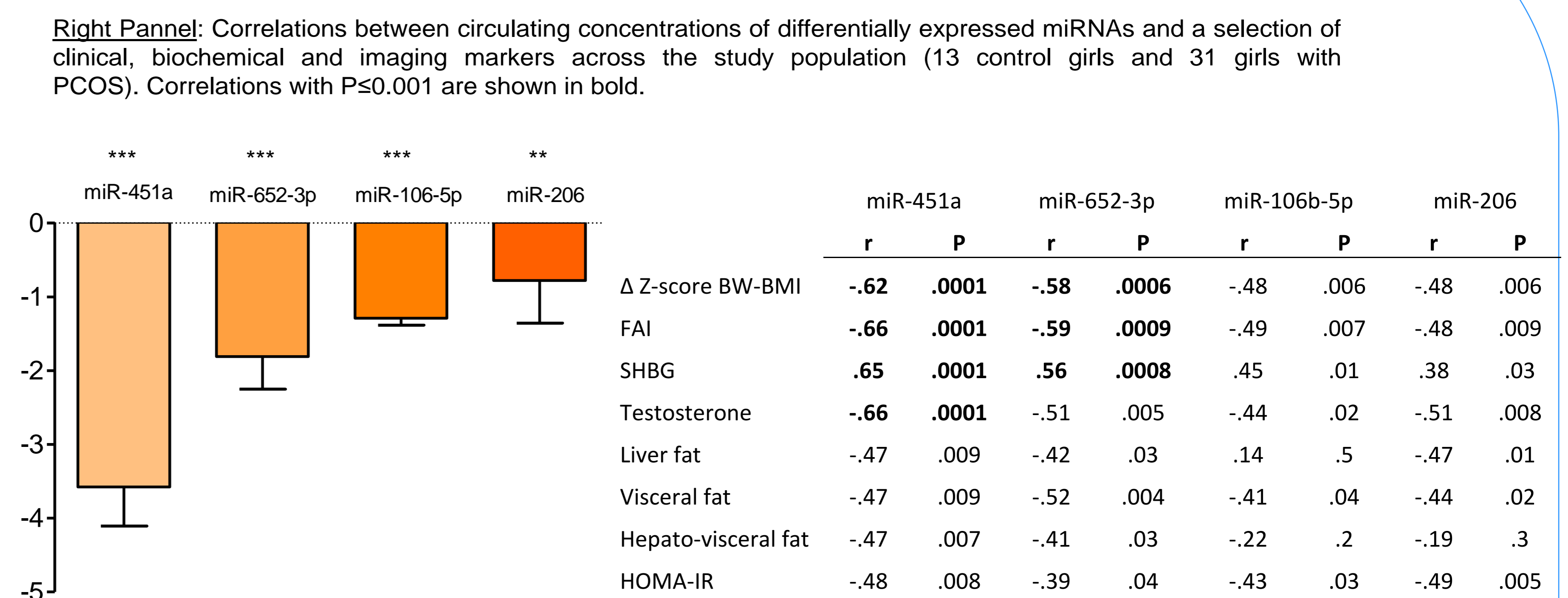
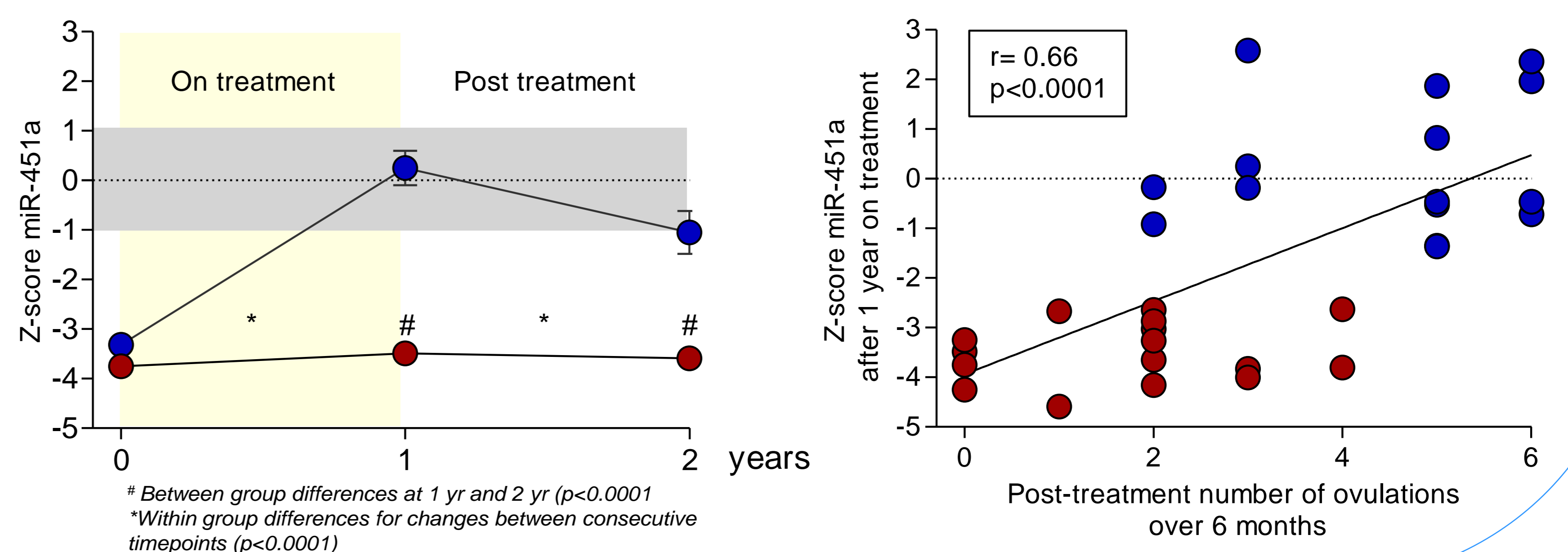


Figure 4. Left Panel: Longitudinal changes in the relative expression of circulating miR-451a, as expressed in Z-score, in girls with PCOS, who received OC (N=16, red dots) or SPIOMET (N=15, blue dots) for 1 year, and no treatment over the subsequent year. The upper and lower limits of the grey zone correspond, respectively, to a Z-score of +1 and -1 in control girls.

Right Panel: Post-treatment number of ovulations over 6 months (15-18 + 21-24) vs expression levels of circulating miR-451a after intervention in girls with PCOS who were randomized to receive an OC (n=16, red dots), or low-dose SPIOMET (n=15, blue dots) for one yr.



CONCLUSION

- SPIOMET treatment over a year normalizes the expression of several down-regulated miRNAs related to glucose homeostasis, energy metabolism, and the control of the cell cycle.
- Circulating miR-451a may become a biomarker contributing to guide the diagnosis and treatment of PCOS in adolescent girls.

*Institut de Recerca Pediàtric Hospital Sant Joan de Déu, University of Barcelona, 08950 Esplugues, Barcelona, Spain; †Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), ISCIII, Madrid, Spain

‡MaternoFetal Metabolic Research Group, Girona Institute for Biomedical Research (IDIBGI), 17190 Salt, Spain; §Pediatric Endocrinology Research Group, Girona Institute for Biomedical Research (IDIBGI) and Dr. Josep Trueta Hospital, 17007 Girona, Spain.

†Department of Development & Regeneration, University of Leuven, 3000 Leuven, Belgium