

INTRODUCTION

Problem: Effective pregnancy risk screening is key to optimising outcomes by personalising care. Because at-risk women are not identified by traditional assessment, the overall value of care is diminished.

Our solution is the development of novel bloodborne markers based on placental dysfunction genomic signatures.

Gestational diabetes mellitus (GDM) is one of the most common pregnancy complications. A placental metabolic stress response has been implicated in GDM, yet how placental function is linked to maternal features such as the requirement for medication to control blood glucose levels is unknown. Here, we report **distinct genetic profiles** in GDM pregnancies and evidence of regulation by microRNAs

Aim: To determine the utility of genetic profiling of the maternal circulation to improve the prediction of GDM severity

METHODS

- This cohort study included 24 participants: **uncomplicated**, **GDM-diet-treated (GDMD)**, and **GDM-medicated (GDMM)** pregnancies (n=8/group; matched for BMI and maternal age).
- Placental gene expression (84 stress-related genes) was analysed in term placentas (≥37 gestational weeks).
- Circulating gene expression (84 diabetes-related genes) and microRNAs (800 untargeted) were profiled in maternal blood at 24–28 gestational weeks.
- MicroRNA target interactions were predicted using miRNet (version 2.0). The workflow of the study is shown in Figure 1.

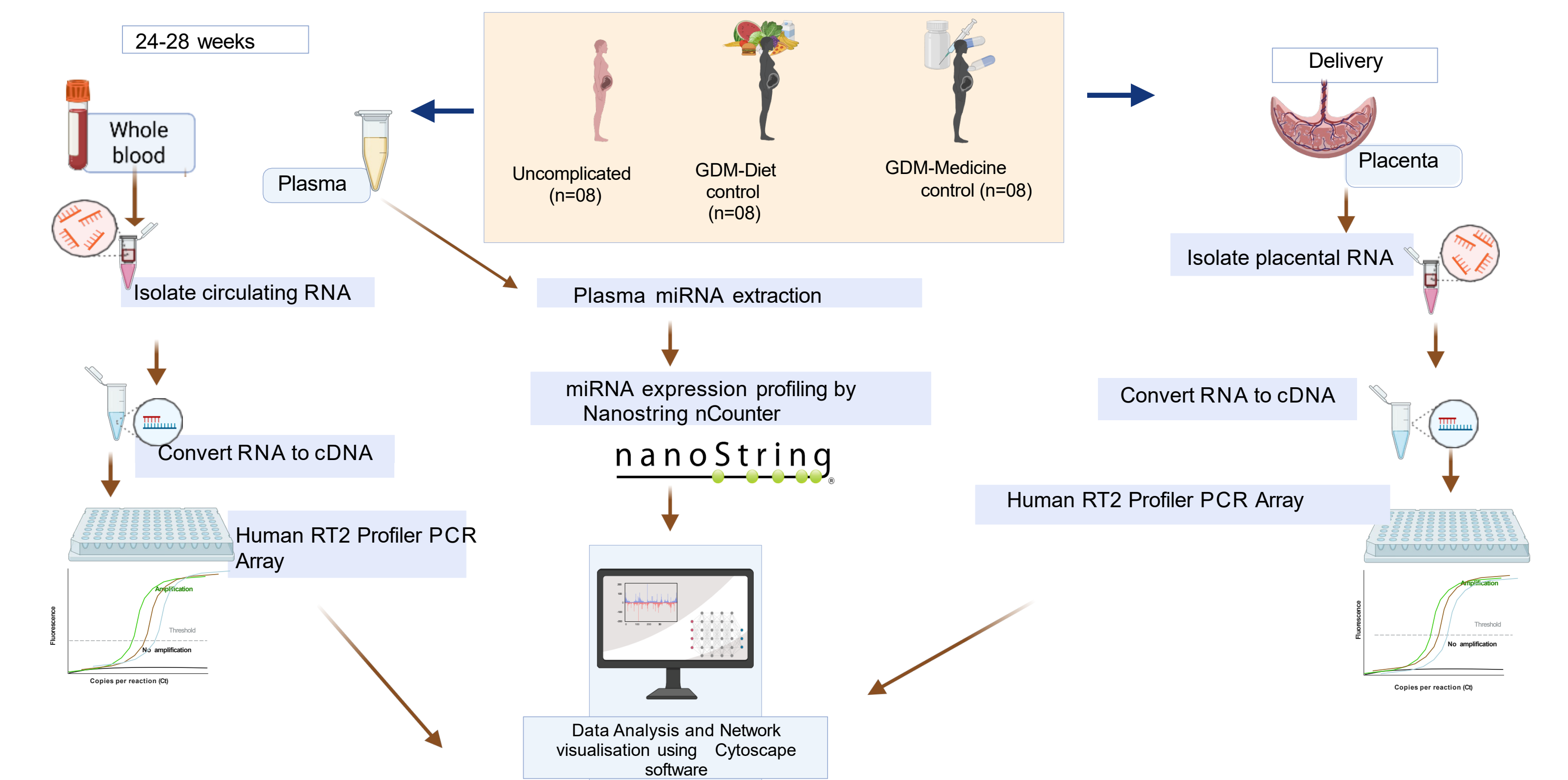


Figure 1. Overview of the study

RESULTS

Placental Gene Changes

In the placenta, 3 gene expression pattern sets were observed in GDM relative to controls: (1) 16 genes were upregulated in GDMD and downregulated in GDMM, (2) 5 genes were downregulated in both GDMD and GDMM, and (3) 4 genes were upregulated in both GDMD and GDMM (Figure 2).

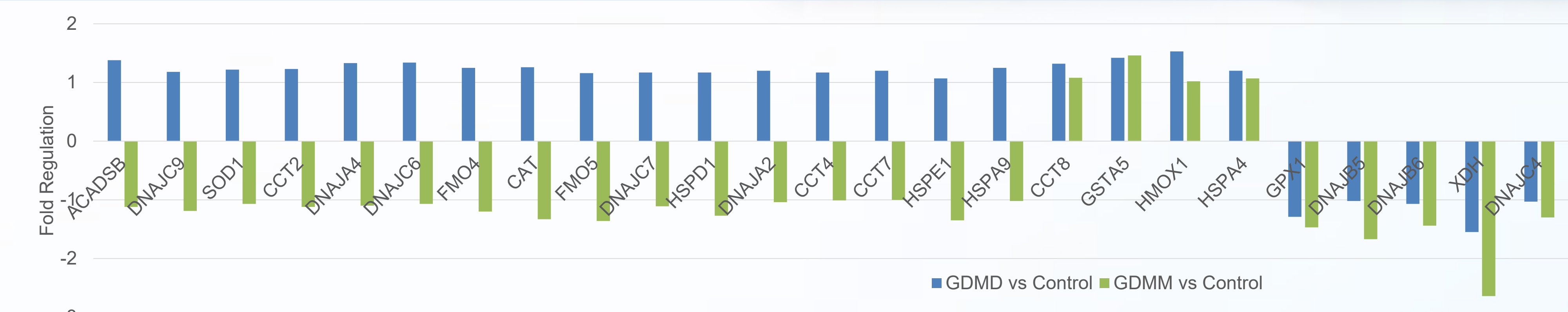


Figure 2. Placental gene expression changes in GDMD and GDMM relative to control

Maternal Circulating mRNA Changes

In the maternal circulation, 2 gene expression pattern sets were observed in GDM relative to controls: (1) 6 mRNAs were downregulated in GDMD and upregulated in GDMM, and (2) 2 mRNAs were downregulated in both GDMD and GDMM, relative to controls (Figure 3).

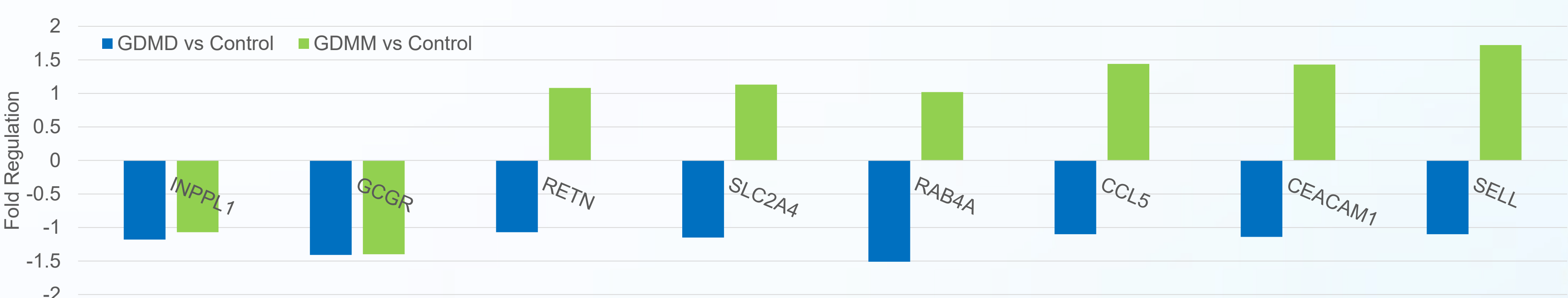


Figure 3. Circulating gene expression changes in GDMD and GDMM relative to control

Regulation

Five upregulated microRNAs (hsa-miR-210-3p, hsa-miR-525-5p, hsa-miR-377-3p, hsa-miR-503-5p, hsa-miR-520f-3p) were predicted to regulate placental genes involved in oxidative stress response (CAT, HMOX1), protein folding and chaperone activity (DNAJC6, DNAJC7, DNAJC4, DNAJA4, HSPA9, HSPD1, CCT2, CCT7, CCT4), and fatty acid metabolism (ACADSB) (Figure 4A).

Fifteen upregulated microRNAs (hsa-miR-449a, hsa-miR-27b-3p, hsa-miR-221-3p, hsa-miR-520d-3p, hsa-miR-28-5p, hsa-miR-148b-3p, hsa-miR-210-3p, hsa-miR-133a-3p, hsa-miR-129-2-3p, hsa-miR-130a-3p, hsa-miR-9-5p, hsa-miR-125a-5p, hsa-miR-103a-3p, hsa-miR-124-3p and hsa-miR-18a-5p) were predicted to regulate circulating genes associated with immune cell recruitment and adhesion (CCL5, CEACAM1, SELL) (Figure 4B).

Notably, hsa-miR-210-3p targeted both placental and circulating genes, suggesting that it may be a key regulator (Figure 4A and B).

CONCLUSION

In more severe GDM pregnancies requiring medication, the placenta may not be responding effectively to metabolic stress. This **placental dysfunction** may link to **maternal metabolic dysregulation**, and we suggest the mechanism for these changes in microRNA regulation.

Targeted circulating maternal **genetic profiling** could be used to **monitor placental function** and help predict the need for medication intervention in GDM.

We plan to determine if these markers can be combined with routinely collected data to deliver an accurate and personalized risk assessment of GDM severity.

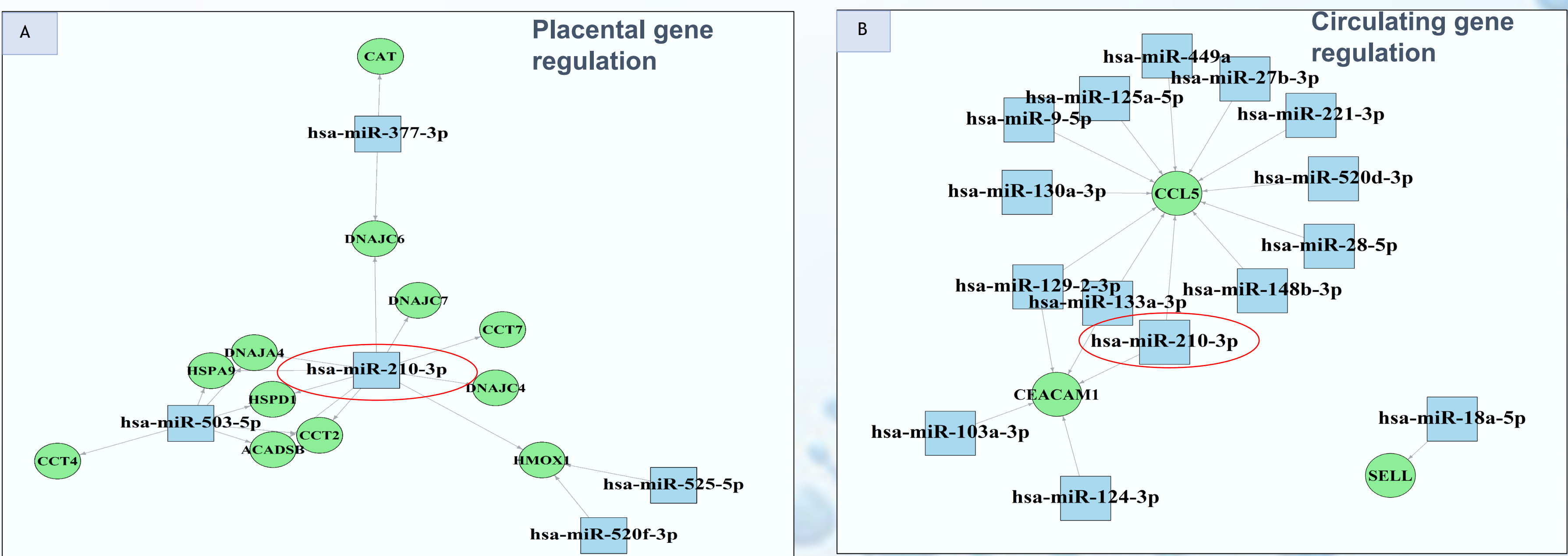


Figure 4. Predicted networks of upregulated microRNAs with placental and circulating genes.