Second Trimester Maternal Urine for the Diagnosis of Trisomy 21 and Prediction of Poor Pregnancy Outcomes

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A novel strategy was presented for the detection of deviations in the composition of maternal urine, to define metabolite fingerprints for the recognition of trisomy 21 (T21) and fetal malformations (FM) and prediction of preterm delivery (PTD), intra-uterine growth restriction (IUGR), preeclampsia (PE) and gestational diabetes mellitus (GDM). The challenge is set by the hundreds of metabolites present in urine, which result in complex analytical records from which meaningful variations are to be retrieved/quantified. The tools/strategies used here are applicable not only to biofluids in disease research, such as the present study, but also to other biological samples (tissues, cells) in contexts as varied as exposure to contaminants, pharmaceuticals or (bio)materials.

In this work, ^{1}H Nuclear Magnetic Resonance (NMR) metabolomics was used to find specific metabolic excretory signatures of the conditions specified above. Figure 1a shows an expansion of the NMR spectrum of control urine, with a large number of signals covering a wide range of intensities. Although visual differences are noted between control and disease spectra (Figure 1a,b), comparison of full matrixes was handled by partial least squares discriminant analysis (PLS-DA) and subsequent Monte Carlo cross validation (MCCV) and permutation tests. Analysis of original datasets resulted in weak models and, hence, several variable importance to the projection (VIP)- and b-coefficient-based variable selection methods were tested (gray dots in Figure 1b represent variables selected for T21 identification). The variable selected subsets led to improved PLS-DA models and specific metabolite signatures (Figure 1c,d), with applicability in T21 and FM diagnosis and identification of PTD, IUGR, PE and GDM *pre-clinical* markers. This work demonstrated, for the first time, the value of maternal urine profiling as a complementary means of prenatal diagnostics and early prediction of several poor pregnancy outcomes.

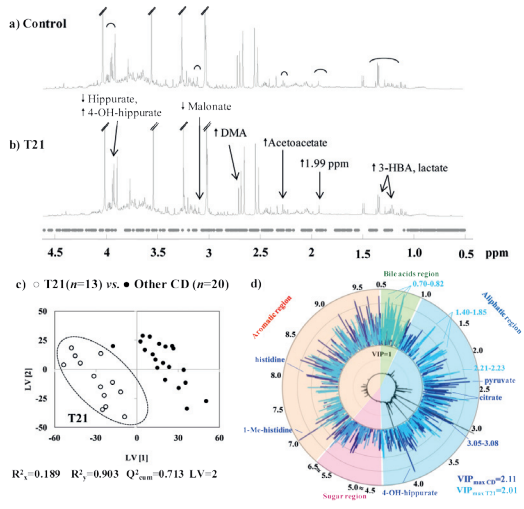

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FIGURE 1

Expansion (0.5-4.6 ppm) of average ^{1}H NMR spectra of maternal urine for a) control and b) T21 groups, with indication of main visual differences (curved lines), some assignments and variables selected (gray dots); c) PLS-DA scores plot obtained for T21 cases vs. other CDs; d) VIP-wheel representation of the urinary signatures obtained for the general CDs (dark blue) and T21 (light blue) groups. The average ^{1}H NMR spectrum of controls is represented in the inner circle, with the corresponding ppm scale shown in the outer black circle. Each dot represents a selected variable (spectral data point), positioned in a radial Variable importance for the projection (VIP) scale. Distinguishing features of T21 include changes in bile acids and most other spectral regions.