Non-coding RNA biomarkers of diabetes complications

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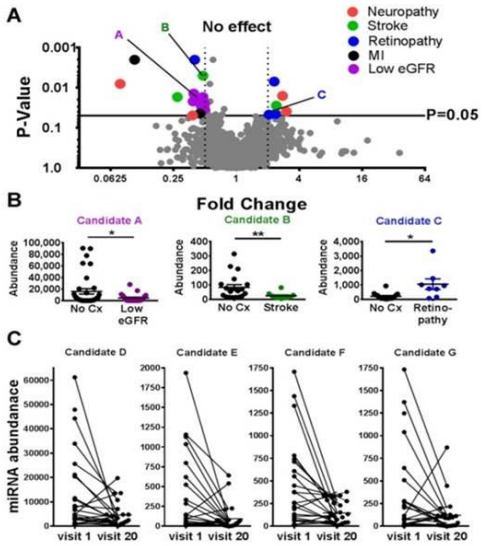
Background and aims: Type 2 Diabetes (T2D) increases the risk of cardiovascular disease (CVD), and other vascular complications including retinopathy and neuropathy and is now well-accepted to be an outcome of intra-uterine programming and exposure to environmental (lifestyle) factors during post-natal life. It is essential and timely to identify early biomarkers of T2D and its complications. In recent years microRNAs (miRNAs), a subset of small non-coding (nc) RNAs, have been detected in circulation and demonstrated as promising biomarkers, mostly in cancer research. We aim to validate circulating ncRNA and DNA methylation signatures for T2D and its vascular complications using two unique longitudinal cohorts i) the Pune Maternal Nutrition study (PMNS) comprising of 18 year follow up study of undernourished children and their parents from preconception period, 20% of whom have now developed insulin resistance at 18 years of age ii) the FIELD study, which demonstrated that, relative to placebo, long-term fenofibrate improved some CVD and all microvascular complications with 9,795 subjects enrolled in study and analysed at baseline, 1 and 5 years and in 1,744 of these individuals at 12 years. We present epigenetic (DNA methylation) and ncRNA signatures for T2D and its complications over lifetime and response to therapy, enabling early management of at-risk individuals and facilitating development of novel therapeutics.
Materials and methods: Circulating miRNAs in plasma were assessed from i) PMNS study subjects at 18, 12 and 6 years as well as at their birth and from their parents (at conception) and ii) T2D subjects in the FIELD cohort (Fenofibrate Intervention and Event Lowering in Diabetes) with retinopathy, neuropathy, low eGFR, ACR, non-fatal stroke or non-fatal myocardial infarction and were compared to individuals without complications using ultra-high throughput qPCR profiling. DNA methylation in both study cohorts was assessed on Illumina 450K DNA methylation arrays.
Results: We observed that circulating miRNAs in five T2D complication groups Vs no complications were differentially expressed as seen in volcano plot (Figure 1A). Some of the miRNAs identified in the initial high throughput analysis (+/- 2-fold change and P<0.05) were also found to be significantly different in multiple samples when validated using low-throughput high sensitivity quantitative (q)PCR. We also found serum levels of four candidate microRNAs related to vascular health to be lower in FIELD T2D subjects at visit 20 (5 years) Vs visit 1 (baseline).
Conclusion: miRNAs are found to be differentially expressed in individuals with diabetic complications, which could allow early identification of at risk individuals, thereby providing a vital opportunity to improve heath prior to clinical onset.



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