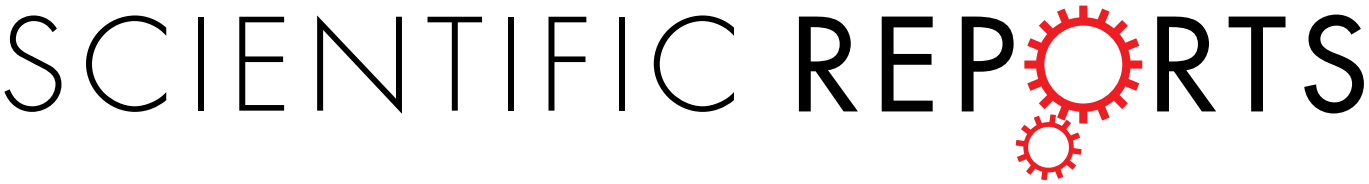

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Dysregulated miRNAs and their pathogenic implications for the neurometabolic disease propionic acidemia

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miRNome expression profiling was performed in a mouse model of propionic acidemia (PA) and in patients' plasma samples to investigate the role of miRNAs in the pathophysiology of the disease and to identify novel biomarkers and therapeutic targets. PA is a potentially lethal neurometabolic disease with patients developing neurological deficits and cardiomyopathy in the long-term, among other complications. In the PA mouse liver we identified 14 significantly dysregulated miRNAs. Three selected miRNAs, miR-34a-5p, miR-338-3p and miR-350, were found upregulated in brain and heart tissues. Predicted targets involved in apoptosis, stress-signaling and mitochondrial function, were inversely found down-regulated. Functional analysis with miRNA mimics in cellular models confirmed these findings. miRNA profiling in plasma samples from neonatal PA patients and age-matched control individuals identified a set of differentially expressed miRNAs, several were coincident with those identified in the PA mouse, among them miR-34a-5p and miR-338-3p. These two miRNAs were also found dysregulated in childhood and adult PA patients' cohorts. Taken together, the results reveal miRNA signatures in PA useful to identify potential biomarkers, to refine the understanding of the molecular mechanisms of this rare disease and, eventually, to improve the management of patients.

microRNAs (miRNAs) are essential players in gene expression regulation. They are non-coding single-stranded RNAs of 20–24 nucleotides in length that act post-transcriptionally by base-pairing with the 3′ untranslated regions of target mRNAs. Typically, an 8-mer "seed" sequence located in the 5′ end of miRNAs directs the recognition of target mRNA and, consequently, gene silencing by degradation or translational repression, depending on whether the complementarity between miRNA and target mRNA sequence is perfect or not[1,2]. In some cases alternative modes of miRNA target recognition have been described, including G-bulge sites[3], imperfect centered sites[4] or sites centering on miRNA nucleotides 13-16 that compensate for seed mismatches or that supplement the seed region[5]. A single miRNA may control the expression of multiple targets and a particular mRNA can be targeted by several miRNAs, thus establishing miRNAs networks that govern many biological processes including cell differentiation, proliferation, cell death and metabolic control. Thereby, miRNA dysregulation may have a broad impact on cellular physiology contributing to disease development. In fact, alterations in miRNA function have been reported in many human disorders such as cancer[6], cardiovascular[7] and neurodegenerative diseases[8,9]. One of the most exciting developments in the field of miRNA research involves the efficient manipulation of miRNA function using antisense oligonucleotides acting as miRNA inhibitors or antagonists (antagomirs) or synthetic miRNAs (miRNA mimics) for restoring normal levels of a miRNA associated to a disease state. To date, there is a large interest in the potential of this approach which has already entered the clinical phase[10].

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