Title

Serum miRNAs as potential monitoring and prognostic biomarkers of muscle wasting progression in Myotonic Dystrophy type I.

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Background: Myotonic Dystrophy type I (DM1) is a progressive neuromuscular disorder characterized by variable muscle wasting. Reliable and minimally invasive biomarkers for disease monitoring remain an unmet need in DM1. We previously reported that circulating muscle-specific miRNAs, miR-1, miR-133a, miR-133b and miR-206, reflect disease progression in cross-sectional analyses of DM1 patients. In this study, we investigated their longitudinal behaviour and identified additional miRNAs with potential prognostic value.

Method: Serum samples were collected from DM1 patients that participated in 'PhenoDM1' study (Newcastle, UCLH, UK). Each patient provided yearly blood samples at two or three clinical visits. Patients were classified as stable or progressive based on clinical examination at blood collection. Circulating levels of the four miRNAs were quantified by real-time PCR and analysed for their association with longitudinal clinical progression. To identify prognostic biomarkers, small RNA sequencing was performed on samples collected one year before the appearance of clinical symptoms from initially stable patients who either remained stable or subsequently became progressive. Candidate miRNAs were selected through bioinformatic analysis and validated by real-time PCR.

Results: Longitudinal analyses showed that stable DM1 patients displayed stable or decreased levels of muscle-specific miRNAs over time, whereas progressive patients demonstrated increases. Within-patient analyses confirmed that increased miRNA levels corresponded to clinical deterioration, while stable or declining levels reflected clinical stability. Furthermore, small RNA sequencing identified candidate miRNAs with altered levels prior to the onset of clinical progression, including two miRNAs increased in patients who subsequently deteriorated, and two miRNAs associated with continued clinical stability

Conclusion: Our findings demonstrated that circulating muscle-specific miRNAs reflect disease progression in DM1 and support their use as minimally invasive longitudinal biomarkers for monitoring disease progression and therapeutic responses. Moreover, the identification of miRNAs altered before clinical deterioration suggests their potential use as prognostic biomarkers for muscle wasting progression in DM1.