

BLOOD-BASED TRANSCRIPTIONAL BIOMARKERS OF MACHADO-JOSEPH DISEASE

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Whereas Machado-Joseph disease (MJD) remains an untreatable disorder, disease-modifying compounds have begun being tested in the context of clinical trials; their success is dependent on the sensitivity of the methods used to measure subtle therapeutic benefits. Thus, efforts are being made to propose a battery of potential outcome measures, including molecular biomarkers (MBs), which remain to be identified. MBs are particularly pertinent if trials are expected to enrol preclinical subjects. Our group has been investigating MJD-specific expression patterns, with the aim to identify novel MBs, studying patients in distinct stages of disease severity, as well as asymptomatic and preclinical subjects. Results of an exploratory whole-genome expression microarray allowed us to identify a set of genes whose expression was deregulated in patients blood samples (Raposo *et al.*, 2015). Data from this array was combined with information from the literature concerning molecules whose levels were described as altered in the presence of mutated ataxin-3. In this candidate study we were able to confirm, using quantitative real-time PCR, that levels of *HSPB1* and *BCL2* were found to be significantly deregulated. We have further performed a pilot longitudinal study, using patient's samples collected at two moments of disease progression. *BCL2* and *DNAJB14* adjusted mRNA levels were found to be significantly different between the baseline and the second moment. In an additional microarray experiment, in which different stages of disease progression were included, a set of deregulated genes, currently being analysed, was identified. Candidate MBs will have to be further tested by analysing independent cohorts of patients and evidencing the correlation with clinical as well as imaging data.