Repeat Instability and Splicing Abnormalities in a novel DM2 BAC Transgenic Mouse Model

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Myotonic Dystrophy type 2 (DM2) is a multisystemic disease caused by an intronic CCTG•CAGG repeat expansion in *CNBP*. There are no mouse models available for DM2. A mouse model that recapitulates the molecular and phenotypic features of DM2 will provide a better understanding of the molecular mechanisms of disease and aid in therapeutic testing. We used a human bacterial artificial chromosome (BAC) to generate two lines of DM2 BAC transgenic mice containing a single copy of the entire human *CNBP* gene with initial repeat lengths of ~750 CCTGs. Selective breeding and the model's substantial intergenerational repeat instability has led to mice with repeat lengths ranging from ~300 to 7,000 CCTGs. We are currently breeding mice with ~6,000 CCTGs to generate cohorts of longer repeat mice, as DM2 patients have repeats ranging from 75-11,000 CCTGs. DM2 mice exhibit somatic instability, with differing patterns of repeat expansion and contraction between tissues. RNA-FISH of DM2 BAC mice shows RNA foci accumulation in skeletal muscle, cardiac tissue, and the brain. RNA analysis via RT-PCR reveals alternative splicing changes found in patients in DM2 BAC mice with repeats ranging from 3,000-6,000 CCTGs in skeletal muscle, cardiac, and brain tissue. In conclusion, we have generated a DM2 BAC transgenic mouse model that shows substantial somatic and intergenerational repeat instability, RNA foci, and splicing abnormalities, all features of disease in DM2 patients. This model will improve our understanding of the molecular mechanisms of DM2, potentially becoming a powerful tool for testing new therapeutic approaches.

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