

Genetic determinants of disease severity in the myotonic dystrophy type 1 OPTIMISTIC cohort

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Study objective and summary result

This study investigated the role of genetic variation at the *DMPK* locus in creating symptomatic diversity in adults with myotonic dystrophy type 1 (DM1), and it found that estimated progenitor allele length (ePAL) and variant repeats within the CTG repeat expansion explain much of the clinical variability of such patients.

What is known and what this paper adds

Greater CTG repeat lengths in the *DMPK* gene are associated with greater disease severity and earlier age at onset in patients with DM1, but the relationship is complicated by factors such as the instability of CTG repeat expansions in the soma. This investigation elucidates the details of the relationship.

Participants and setting

The investigators reviewed data from 250 ambulant adults with genetically proven DM1 and severe fatigue (i.e., Checklist Individual Strength–Fatigue scores ≥ 35) who participated in the OPTIMISTIC trial. Participants were recruited for this trial through 4 centers in France, Germany, the Netherlands, and the UK between April 2014 and May 2015.

Design, size, and duration

The OPTIMISTIC participants self-reported their ages at DM1 onset. Venous blood samples were collected at baseline for genetic testing. PALs were estimated with a small-pool PCR method that corrects for age-at-sampling biases in measuring CTG lengths. *Acil* digests and repeat-primed PCR were used to test for variant repeats within CTG repeat expansions. Linear regression analyses were used to test genetic variables for the ability to explain variation in ages at onset and 22 progressive DM1 phenotypes collected as part of the OPTIMISTIC protocol.

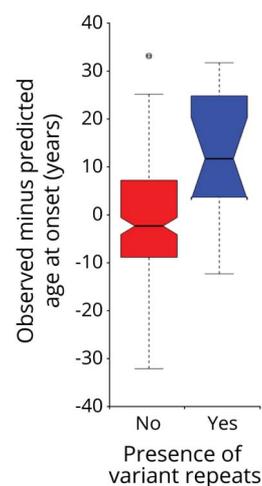
Primary outcome measures

The primary outcomes were genetic variables that could explain variation in ages at onset.

Main results and the role of chance

The factors associated with earlier ages at onset included greater ePAL ($p < 10^{-10}$), the absence of variant repeats ($p = 0.0019$) and greater rates of somatic expansion of the CTG

Figure Influence of variant repeats on ages at onset



$p = 0.002$.

repeat ($p = 0.00029$). These same factors also contributed to multiple progressive muscle and cognitive phenotypes.

Bias, confounding, and other reasons for caution

Very mild and very severe patients were excluded from the study. The regression models might have been affected by residual confounding.

Generalizability to other populations

This investigation's reliance on data from individuals recruited in northern Europe may limit the international generalizability of the results.

Study funding/potential competing interests

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A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.

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