ORIGINAL ARTICLE

Survival patterns and cancer determinants in families with myotonic dystrophy type 1

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Background and purpose: Research indicates that patients with myotonic dystrophy type 1 (DM1) are at increased risk of cancer and early death. Family data may provide insights given DM1 phenotypic heterogeneity, the broad range of non-muscular manifestations and the usual delays in the diagnosis of DM1.

Method: Family history data were collected from 397 genetically and/or clinically confirmed DM1 patients (respondents) enrolled in the US or UK myotonic dystrophy registries. Standardized mortality ratios were calculated for DM1 first-degree relatives (parents, siblings and offspring) by their reported DM1 status (affected, unaffected or unknown). For cancer-related analyses, mixed effects logistic regression models were used to evaluate factors associated with cancer development in DM1 families, including familial clustering.

Results: A total of 467 deaths and 337 cancers were reported amongst 1737 first-degree DM1 relatives. Mortality risk amongst relatives reported as DM1-unaffected was comparable to that of the general population [standardized mortality ratio (SMR) 0.82, $P = 0.06$], whilst significantly higher mortality risks were noted in DM1-affected relatives (SMR = 2.47, $P < 0.0001$) and in those whose DM1 status was unknown (SMR = 1.60, $P < 0.0001$). In cancer risk analyses, risk was higher amongst families in which the DM1 respondent had cancer (odds ratio 1.95, $P = 0.0001$). Unknown DM1 status in the siblings (odds ratio 2.59, $P = 0.004$) was associated with higher cancer risk.

Conclusion: There is an increased risk of death, and probably cancer, in relatives with DM1 and in those whose DM1 status is unknown. This suggests a need to perform a careful history and physical examination, supplemented by genetic testing, to identify family members at risk for DM1 and who might benefit from disease-specific clinical care and surveillance.

Introduction

Myotonic dystrophy type 1 (DM1; OMIM 160900) is an autosomal dominant multisystem disorder characterized by progressive muscle weakness and myotonia [1]. The disease is caused by unstable CTG nucleotide repeat expansions in the 3′ untranslated region of the *dystrophia myotonica protein kinase* (*DMPK*) gene on chromosome 19q13 [2–4] and characterized by genetic anticipation, in which offspring present at earlier ages and with more severe phenotypes than their parents [5].

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Common, non-muscular clinical manifestations of DM1 include cataracts, cardiac conduction defects, respiratory insufficiency, sleep disturbances, central nervous system involvement, and endocrine and gastrointestinal abnormalities [1,6]. Life expectancy in DM1 patients is significantly reduced; median age at death is early to late 50s, with respiratory and cardiac complications followed by malignancy comprising the main causes [7,8]. Diagnostic delays and misdiagnosis are common occurrences in DM1, particularly in patients with mild or atypical clinical presentations; a recent study reported average diagnostic delays of 7 years [9].

Recent studies have provided evidence that DM1 patients are at high risk of certain cancers. The evidence is strongest for cancers of the endometrium, cutaneous melanoma and thyroid [10–14], followed by cancers of the ovary, brain [10,13], testis [11,12] and possibly basal cell carcinoma of the skin [15]. Despite reports of the high relative risks associated with these cancers, their absolute risks are relatively modest [8,16]. It has been suggested that cancer incidence in DM1 patients is obscured by the high competing death rates from non-cancer causes [8]. The risk factors and molecular mechanisms of DM1 carcinogenesis are largely unexplored but are hypothesized to result from a genetic predisposition to cancer that is driven by specific aspects of DM1 pathophysiology [17].

Family studies in extended DM1 pedigrees are limited despite their potential to better characterize the full disease phenotype. Such studies may be of particular importance for severe non-muscular phenotypes that may appear prior to diagnosis. For example, cancer incidence studies in DM1 patients showed a high frequency of cancers prior to disease diagnosis [10,16]. Similarly, a nationwide study from Denmark showed that the first year after DM1 diagnosis carried the highest risk of a new cardiac diagnosis suggesting that pre-existing prevalent conditions may be detected during the DM1 workup [18]. Also, the high risk of sudden death noted in patients with DM1 [19] has recently been shown to be associated with a family history of sudden death [20].

In this study, the risk of all-cause mortality was evaluated and determinants of cancer development in first-degree relatives of respondents were assessed in a large DM1 cohort.

Methods

Data collection and study participants

This study is a collaboration between the Clinical Genetics Branch, US National Cancer Institute, the University of Rochester and Newcastle University. Detailed study design and patient characteristics have been reported [21,22]. Briefly, study questionnaires were delivered to genetically and/or clinically confirmed DM patients from the US National Registry of Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Patients and Family Members [23] (US DM Registry; $N = 850$) and the UK DM Registry ($N = 409$) [24]; a follow-up mail survey was sent to non-responders from both registries. The questionnaire collected personal history of benign and malignant tumors, selected lifestyle factors and selected family history information. A total of 541 DM subjects responded to the questionnaire (USA, 280; UK, 261). Patients with DM2 and those who did not complete either the family history or personal cancer history questionnaire were excluded, to ensure high-quality data. The analysis included 397 DM1 patients (genetically confirmed 193; 48.6%) reporting on 1737 first-degree relatives. Figure 1 represents a flowchart illustrating the patient selection process.

The family history questionnaire collected the following information from study participants regarding their first-degree relatives (parents, siblings and offspring): year of birth, sex, DM1 status (affected, unaffected, unknown), history of cancer/tumor diagnosis (yes, no), cancer site and age at diagnosis, vital status, and year of death, if applicable. Tumor reports were reviewed, and only malignant tumors were included in this analysis.

The study was approved by the Ethics Committees of the University of Rochester, Newcastle University and the National Institutes of Health Office of Human Subjects Research. All patients provided informed consent prior to their participation.

Statistical analysis

Characteristics of the US and UK DM1 patients included in this study were compared using the Fisher's exact and Wilcoxon rank sum tests.

Survival estimates were compared with population life tables published by the US Centers for Disease Control available at (https://www.cdc.gov/nchs/data/nvsr/nvsr66/nvsr66_03.pdf) and the UK Office for National Statistics available at (https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetableunitedkingdomreferencetables).

All analyses were conducted using R statistical software [25]. Standardized mortality ratios (SMRs), with corresponding 95% confidence intervals (CIs), were calculated using the package 'ems', version 1.0.0 [26]. Survival analyses were conducted using the 'survival'

package, version 2.38 [27]. Generalized linear mixed models were fitted using the 'lme4' package, version 1.1-15 [28]. Expected numbers of deaths amongst first-degree relatives were obtained using the published age- and country-specific life tables cited above.

All estimates were stratified by reported DM1 status (affected, unaffected or unknown). In parental dyads with one parent reported as DM1-affected and the other as DM1-unknown ($n = 16$), the second parent was designated as DM1-unaffected, due to the population rarity of DM1 mutations. In parents both reported as DM1-unknown ($n = 65$) or DM1-unaffected ($n = 43$), both parents were assigned DM1-unknown status. The DM1 status of siblings and offspring was used as reported.

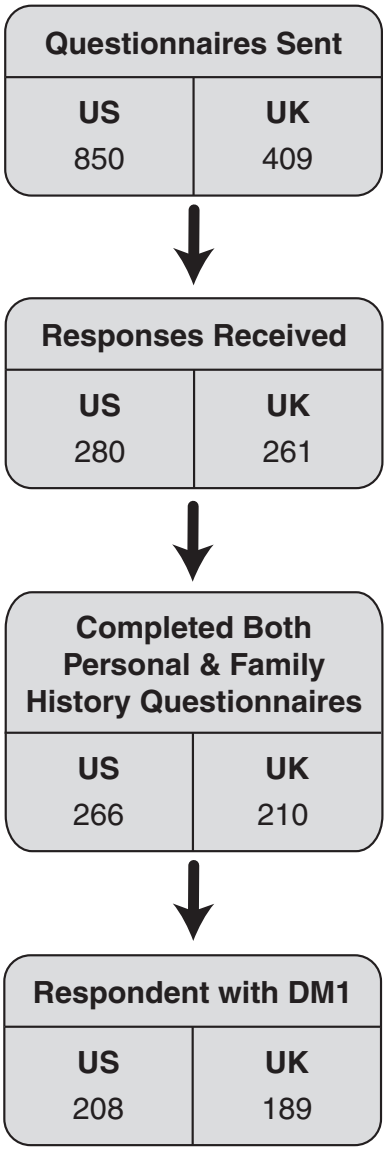

Figure 1 Flowchart of patient study inclusion.

Multivariable mixed effects logistic regression was used for cancer risk models, clustering on family groups. The analysis focused on first reported cancer modeled as a dichotomous response (yes/no). Final models included country of data collection, reported DM1 status, sex of the relative, relationship status to the respondents, and cancer history in the respondent. Analyses were conducted for all family members combined and were also stratified by relationship to the respondent. A P value of <0.05 was considered statistically significant for this study.

Results

The study included 208 US and 189 UK patients reporting on 693 parents, 656 siblings and 388 offspring. US and UK DM1 patients were comparable for age at questionnaire completion, DM1 paternal transmission, ages at DM1 onset and diagnosis, and sex (Table 1). More US DM1 patients with a history of cancer responded to the questionnaire versus the UK (USA, $N = 62$, 30%; UK, $N = 11$, 6%; P Fisher's exact < 0.0001). US participants had more children ($P = 0.004$, Wilcoxon rank sum) and siblings ($P < 0.0001$, Wilcoxon) than did UK respondents (Table 1). Amongst family members, 640 were reported to be DM1-affected (219 parents, 262 siblings

Table 1 Description of characteristics of the US and UK myotonic dystrophy type 1 (DM1) study participants

	US cohort	UK cohort
Number of participants with DM1	208	189
Age at interview [years; median (IQR)]	53 (18.0)	47 (19.5)
DM inheritance		
Maternal	47 (23%)	35 (19%)
Paternal	71 (34%)	83 (44%)
Unknown	90 (43%)	71 (38%)
Age at onset [years; median (IQR)]	25.5 (23.0)	27.0 (20.5)
Age at diagnosis [years; median (IQR)]	33.0 (23)	33.0 (18)
Sex (% female)	115 (55%)	98 (52%)
Personal history of cancer (n/% yes)	62 (30%)	11 (6%)
Personal history of benign tumor (n/% yes)	34 (16%)	17 (9%)
Number of children		
0	99 (48%)	106 (56%)
1	34 (16%)	28 (15%)
2	42 (20%)	37 (20%)
≥3	32 (15%)	18 (10%)
Number of siblings		
0	18 (9%)	41 (22%)
1	62 (30%)	73 (39%)
2	58 (28%)	52 (28%)
3	35 (17%)	9 (5%)
≥4	35 (17%)	7 (4%)

IQR, interquartile range, defined as the difference between the 75th and 25th percentiles of the observed quantity.

and 159 offspring), 651 unaffected (214 parents, 300 siblings and 137 offspring) and 446 with DM1-unknown status (260 parents, 94 siblings and 92 offspring).

Survival probability in first-degree relatives of DM1 patients

Four hundred and sixty-seven deaths were reported in patients' first-degree relatives (296 in parents, 150 in siblings and 21 in offspring). Figure 2 summarizes survival estimates in DM1 relatives by their reported DM1 status compared with corresponding general population estimates. There was no statistically significant difference in overall survival of DM1-unaffected relatives versus the general population (SMR = 0.82, 95% CI 0.76–1.01, $P = 0.06$). Relatives reported as DM1-affected or DM1-unknown were at increased mortality risk relative to the general population (SMR = 2.47, 95% CI 2.29–2.67, $P < 0.0001$ in DM1-affected relatives; SMR = 1.60, 95% CI 1.48–1.74, $P < 0.0001$ in relatives with DM1-unknown status). For DM1-affected relatives, mortality risk increased in subsequent generations (parents, SMR = 2.1, 95% CI 1.90–2.31; siblings, SMR = 3.11, 95% CI 2.69–3.59; offspring, SMR = 5.53, 95% CI 4.53–6.75). Detailed risk estimates by relationship and country of data collection are summarized in Table 2.

Cancer risk and determinants in first-degree relatives of DM1 patients

Cancer was reported in 337 relatives (233 parents, 81 siblings, 23 offspring). Relatives affected with DM1 and those reported as having unknown DM1 status developed cancers more frequently than those reported

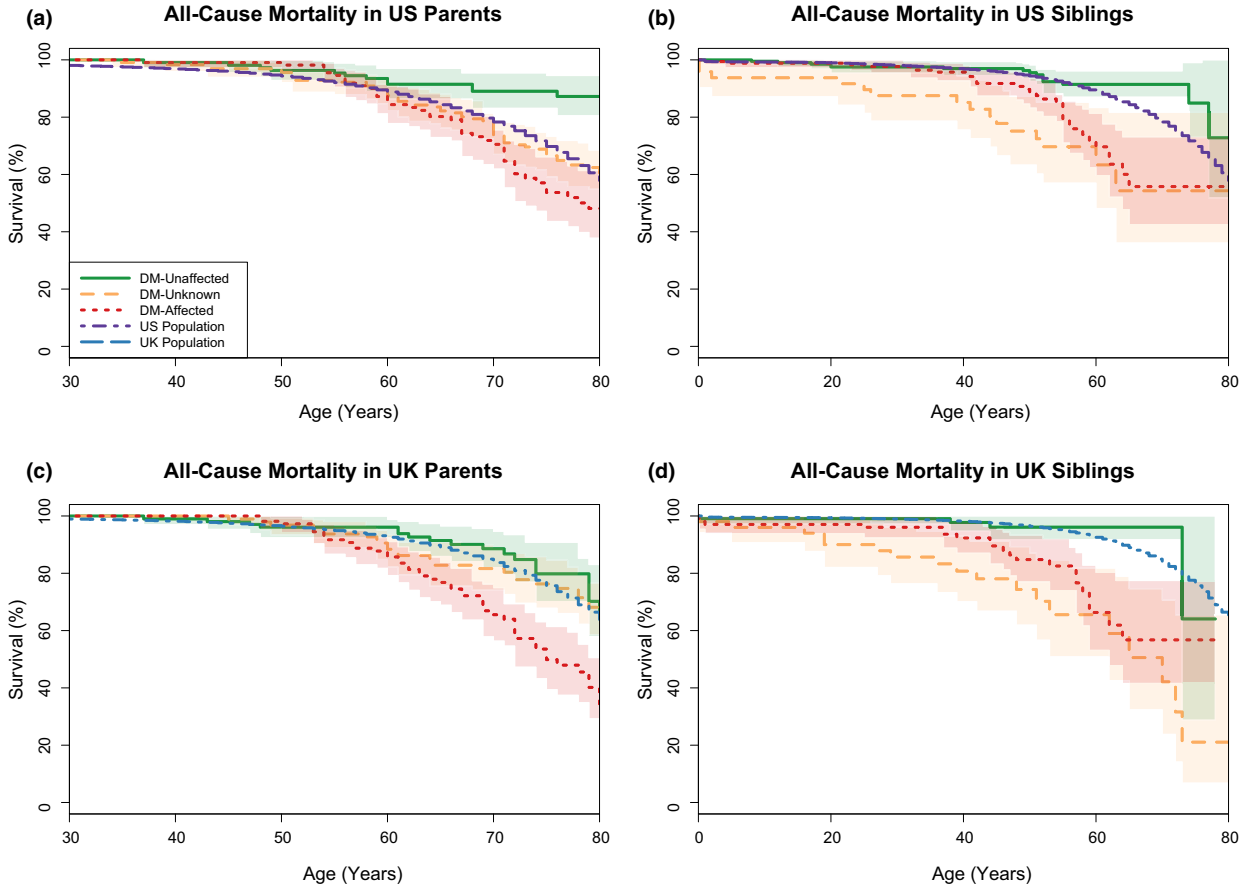

Figure 2 Overall survival in parents (a, c) and siblings (b, d) of DM1 respondents, by country (a, b, USA; c, d, UK) and reported DM1 status, with overall population survival. Amongst siblings, green solid curves display survival amongst family members reported as DM-unaffected, orange dashed for family members reported as DM-unknown and red dotted for family members reported as DM-affected. Amongst parents, red curves correspond to parents reported as DM-affected, green curves to parents reported as DM-unaffected and orange curves to parents from pairs in which both parents were reported as DM-unknown or DM-unaffected. General population survival in the USA is depicted as a dashed purple line and in the UK is depicted as a dashed blue line. [Color figure can be viewed at wileyonlinelibrary.com]

as DM1-unaffected (21.8% vs. 15.4%, $P < 0.001$). In analyses adjusted for country of data collection, cancer risks in DM1-affected relatives or those with unknown status were modestly but not significantly elevated [odds ratio (OR) 1.28 and 1.26, respectively]. Risk was significantly higher in parents (OR = 8.4, 95% CI 5.25–13.46, $P < 0.0001$) and siblings (OR = 2.39, 95% CI 1.47–3.91, $P = 0.0004$) than offspring, and in families whose DM respondent had cancer (OR = 1.95, 95% CI 1.39–2.73, $P = 0.0001$; Table 3). In analyses stratified by relationship, excess cancer risks in the DM1-unknown family members were noted in siblings (OR = 2.59, 95% CI 1.37–4.88, $P = 0.004$) and probably offspring (OR = 2.68, 95% CI 0.81–8.86, $P = 0.1$) but not in parents (OR = 1.15, 95% CI 0.77–1.7, $P = 0.5$). The cancer risks were elevated amongst parents of DM1 respondents with cancer (OR = 2.65, 95% CI 1.76–4.01, $P < 0.0001$) and possibly siblings (OR = 1.43, 95% CI 0.80–2.54, $P = 0.2$) but not amongst offspring (OR = 0.77, 95% CI 0.26–2.28, $P = 0.6$; Table 3).

Discussion

In this study, mortality risk and cancer determinants in first-degree relatives of DM1 patients were evaluated. As expected, relatives who were themselves reported to have DM1 demonstrated higher mortality risk than the general population. For relatives with unknown DM1 status (most probably composed of a mixture of unaffected and affected individuals with an anticipated milder or atypical phenotype), mortality risks were comparable to or higher than those observed in DM1-affected individuals. Similarly, cancers were more frequently reported for DM1-affected and DM1-unknown relatives than for DM1-unaffected individuals, and risk was higher amongst families in which the DM1 respondent had cancer.

In agreement with previous literature [29,30], our study showed a higher mortality risk in DM1-affected individuals. The higher mortality risks in subsequent generations (SMR = 2.1 in parents, 3.1 in siblings and 5.5 in offspring) probably reflect the known genetic anticipation phenomenon in patients with DM1.

Table 2 Standardized mortality ratio for DM1-affected relatives by their reported DM1 status

	DM1-unaffected			DM1-affected			DM1-unknown		
	O	E	SMR (95% CI)	O	E	SMR (95% CI)	O	E	SMR (95% CI)
Parents									
US	29	38.27	0.76 (0.56, 1.02)	55	32.32	1.70 (1.47, 1.97)	85	64.47	1.32 (1.17, 1.48)
UK	25	23.02	1.09 (0.81, 1.46)	57	21.05	2.71 (2.38, 3.08)	45	31.59	1.42 (1.20, 1.69)
Total	54	61.29	0.88 (0.71, 1.09)	112	53.36	2.10 (1.90, 2.31)	130	96.06	1.35 (1.23, 1.49)
Siblings									
US	16	21.03	0.76 (0.46, 1.26)	32	12.14	2.64 (2.16, 3.22)	15	3.88	3.87 (3.06, 4.90)
UK	4	4.64	0.86 (0.32, 2.34)	20	4.58	4.37 (3.58, 5.34)	18	2.95	6.11 (5.18, 7.21)
Total	20	25.67	0.78 (0.50, 1.22)	52	16.72	3.11 (2.69, 3.59)	33	6.82	4.84 (4.21, 5.56)
Offspring									
US	0	2.27	–	6	2.22	2.70 (1.67, 4.36)	1	1.01	0.99 (0.14, 6.90)
UK	0	0.59	–	11	0.85	12.93 (10.98, 15.22)	3	0.38	7.87 (5.27, 11.76)
Total	0	2.86	–	17	3.07	5.53 (4.53, 6.75)	4	1.39	2.87 (1.62, 5.08)
Total	74	89.82	0.82 (0.67, 1.01)	181	73.16	2.47 (2.29, 2.67)	167	104.27	1.60 (1.48, 1.74)

CI, confidence interval; DM1, myotonic dystrophy type 1; E, expected; O, observed; SMR, standardized mortality ratio.

Table 3 Results of multivariable logistic regression models for probability of cancer in all relatives combined (a) and stratified by their relationship to the reporting respondent (b)–(d)

	(a) All first-degree relatives		(b) Parents		(c) Siblings		(d) Offspring	
Covariate	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
US versus UK	1.42	1.06, 1.91	1.09	0.77, 1.54	1.61	0.90, 2.90	2.51	0.83, 7.55
Proband cancer (yes versus no)	1.95	1.39, 2.73	2.65	1.76, 4.01	1.43	0.80, 2.54	0.77	0.26, 2.28
DM status (versus unaffected)								
Unknown	1.26	(0.90, 1.75)	1.15	0.77, 1.72	2.59	1.37, 4.88	2.68	0.81, 8.86
Affected	1.28	(0.94, 1.75)	1.11	0.72, 1.69	1.23	0.72, 2.12	1.71	0.53, 5.57
Male versus female	0.96	(0.74, 1.24)	1.44	1.03, 2.01	0.66	0.41, 1.08	0.36	0.13, 0.98

Data from DM1 relatives whose DM1 status was unknown to the family's respondent raise important questions related to the possible contribution of a non-muscular DM1-related phenotype in patient clinical outcome. The survival curve for parents of unknown DM1 status (when the DM1 status of one or both parents could not be determined) followed the expected Mendelian distribution of an equal mix of affected and unaffected (Fig. S1). This might be anticipated; however, these individuals were described as unknown DM1 status by their children, who may not have recognized a less severe or delayed onset of manifestations of DM1 in their parents. In untested siblings and offspring, those who were reported as unknown (possibly with a milder or atypical phenotype) had higher mortality risk than expected based on age- and country-specific survival data. Similarly, the risk of cancer was higher in siblings and offspring reported to have a DM1-unknown status than DM1-affected or DM1-unaffected. These findings highlight the importance of considering DM1 genetic testing amongst relatives to facilitate early diagnosis and proper clinical management for serious disease phenotypes that may appear before, or in the absence of, the classic clinical DM1 phenotype.

Results from the multivariable cancer risk models showed an association between cancer status in DM1 respondents and that of their first-degree relatives. This suggests familial aggregation of cancer in DM1 families, which one would expect if the cancer phenotype is caused by the DM1 genotype. Familial cancer clustering is one of the hallmarks of cancer predisposition syndromes [31]. However, the association in our study was seen only in parents and not in siblings or offspring. A previous large population-based study of cancer risk in family members of DM1 patients suggested that cancer risk in DM families (disease subtype was not available) was driven by individuals' DM status [32].

The strengths of the current study include its large sample size and broad representation of DM1 patients through analyzing extended family data. Several measures were implemented to ensure that possible differences between patients enrolled from different countries were controlled for, including use of the same questionnaire, harmonizing of variables that were added from individual registry databases, when needed, standardizing mortality rates to country-specific rates, and adjusting for country of data collection in our multivariable models. The study is limited by the self-reported nature of the cancer and DM1 diagnostic data available. To ensure better data quality and to minimize misclassification, the focus was on first-degree relatives, excluding family members of patients who did not report on their personal history of cancer, and all cancers combined rather than organ-specific cancers were evaluated. Our results showing no significant mortality differences between relatives reported as DM1-unaffected are consistent with valid, reliable death reporting for family members, but underreporting of family history of cancer is possible. A previous study evaluating the validity of population-based reporting of cancer family history concluded that reporting was not highly accurate, but higher validity for first-degree versus second-degree relatives was noted [33]. Patients included in this study may not be representative of the general DM1 patient population because of the voluntary enrollment nature of the registries. Similarly, the low response rate amongst the US registry members and moderate response rate amongst UK registry members may reduce the representativeness of our data, as seen by the oversampling of respondents with past cancer/tumor history in the US cohort. However, the focus of our analysis was on family members from at least two generations, which may minimize concerns regarding DM1 non-representativeness because of its intergenerational phenotypic variation.

Conclusions

Our study showed that family members reported as DM1-affected or DM1-unknown experienced increased mortality relative to the general population. The high risk of cancer and mortality in relatives with DM1-unknown status underscores the importance of a careful history and physical examination supplemented by genetic testing amongst unevaluated, first-degree relatives, to identify those individuals who might warrant DM1-related surveillance. Although such family members may not be readily recognized as classically affected due to their atypical syndromic presentation, their identification permits implementation of the appropriate medical surveillance required to prevent and manage other DM1-related disease manifestations.

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Disclosure of conflict of interests

The authors declare no financial or other conflict of interests.

Supporting Information

Additional Supporting Information may be found online in the supporting information section at the end of the article:

Figure S1. Comparison of observed and expected survival in DM1-unknown parents

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