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# Relative Risks for Comorbidities Associated with Myotonic Dystrophy: A Population-Based Analysis

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## Abstract

**Introduction—**The relative risk, at a population-level, for comorbidities associated with myotonic dystrophy are not reported.

**Methods—**This study utilized the Utah Population Database to identify patients with myotonic dystrophy in Utah by ICD-9 code. Comorbidities listed in the medical record were compared in cases to those of the Utah population.

**Results—**Individuals with myotonic dystrophy possess an increased risk of central and obstructive sleep apnea, hypothyroidism, and intellectual disability. The risk of cardiac conduction disorder is 60 times the population risk.

**Discussion—**This study provides a population level relative risk of comorbidities in myotonic dystrophy. This allows for improved counseling of patients regarding these increased risks.

### Search terms

myotonic dystrophy; relative risk; genetic epidemiology; neuromuscular disease; Utah Population Database; sleep apnea; hypothyroidism

## Introduction

The myotonic dystrophies (DM) are autosomal dominant, multisystem disorders caused by gene repeat expansions. Myotonic dystrophy type-1 (DM1) is due to a $CTG_n$ expansion in

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the *DMPK* gene, and myotonic dystrophy type-2 (DM2) is due to a $CCTG_n$ expansion in the *CNBP* gene.[1,2] Both DM1 and DM2 lead to progressive muscle weakness, early onset cataracts, and myotonia (delayed muscle relaxation).[3] In addition, both disorders are characterized by their multisystem nature, causing fatigue, central nervous system dysfunction, cardiac arrhythmias, and irritable bowel symptoms.[3]

The prevalence of DM1 is 1:8000 individuals, and the prevalence of DM2 is unknown, though it may be as high as 1:5000 individuals.[4,5] Given the varied age of onset and protean nature of the symptom constellation, both disorders are thought to be underdiagnosed and likely have a higher prevalence. The symptoms associated with DM can vary between individuals. Currently, there are no data about the risks of known complications (e.g., cardiac arrhythmias) in myotonic dystrophy patients.

This study utilized the Utah Population Database (UPDB) to clarify the relative risk for common comorbidities in DM patients.

## Methods

The UPDB is a computerized genealogical resource consisting of Utah genealogy data linked to records from electronic medical records from the University of Utah Health Sciences Center (UUHSC) and other health data for the state. Patients were identified with the ICD-9 code for myotonic dystrophy (359.21), which includes both myotonic dystrophy type-1 and type-2. In order to identify risk of comorbidities among individuals with DM in our data, all DM patients who had ancestors in the genealogy were used to calculate relative risks (RR) of 1- different comorbidities: intellectual disabilities, ADHD, chronic fatigue syndrome, cardiac conduction disorder, central sleep apnea, obstructive sleep apnea, chronic respiratory failure, hypothyroidism, cataracts (myotonic and other), and diabetes mellitus. The procedure used to estimate RR in cases is a well-established approach for analyzing genealogical data within the UPDB.[6] Expected numbers of DM cases with specific co-morbid conditions were estimated internally in the UPDB based on rates calculated in cohorts of all UUHSC patients determined by gender, birth-state (Utah or not), birth-county (urban or rural), and year of birth (5-year cohorts). The cohort-specific rate for each comorbid condition was estimated as the number of individuals with the co-morbidity of interest in each cohort divided by the total number of individuals in the cohort who have at least 3 generations of genealogy and UUHSC linked data. The expected number of DM patients with the comorbid condition was obtained by multiplying the number of DM patients in each cohort times the cohort-specific rate for the comorbid condition, and then summing across cohorts. We tested the null hypothesis of $RR \leq 1$ for each comorbid condition, assuming that the number of observed cases follows a Poisson random variable with a mean equal to the expected number of cases. For the myotonic dystrophy patients, the age at which co-morbid ICD-9 diagnoses initially appear in the medical record was abstracted and analyzed descriptively.

## Results

This study identified 80 patients diagnosed with DM who also had genealogy data. The mean age of the DM patients was 39.7 years (SD 17.9, range 0–82 years). Among these patients, the average age of death was 54 years. Primary causes of death (n=20) in DM cases with linked Utah death certificate data included unspecified (n=6), cardiac arrhythmias or heart failure (n=6), infection (n=4), neoplasms (n=2), and stroke (n=2); we did not examine RRs for cause of death. Among the 80 patients with DM, there was a significantly increased risk of cardiac arrhythmias, central and obstructive sleep apnea, cataracts, intellectual disabilities, and hypothyroidism (Table 1). When evaluating the age at which many of these diagnoses appear in the medical record, many were seen in patients as young as 18–20 years (Table 1).

## Discussion

DM is a multisystem disorder that affects skeletal muscle, heart, brain, eye, and GI tract, among others. Though many of the symptoms associated with DM are previously described, this study examines, at a population level, the risk for common comorbidities in patients with DM. Notably, the significantly increased risk of cardiac conduction abnormalities must be appreciated.

There are limitations to this study. This is a de-identified study, and affected individuals and the diagnosis of comorbid conditions were identified through ICD9 diagnosis coding in the medical record. It is possible that additional cases of DM were censored, either because they were not diagnosed or coded properly, because they did not link appropriately to genealogy data, or because their data were not present in the UUHSC time period available (1994 to present). Comorbidities that were coded poorly in the medical records (e.g., respiratory failure, GI issues) were not included in the analysis. In addition, because of the use of the ICD-9 code, both DM1 and DM2 were considered together in the analysis. It is possible that 1 form of DM may contribute more substantially to the overall relative risk. Finally, the ages provided for each ICD-9 code were based on when these diagnoses were coded in the medical record and may not represent when the actual event occurred.

Overall, this study provides estimates of risk for commonly diagnosed comorbidities in DM. The results provide additional information useful to clinicians when counseling patients on these comorbidities.

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**Table 1**

Relative Risk of comorbidities in Myotonic Dystrophy

| Co-morbidity | Number Observed | Number Expected | *P*-value | Relative Risk | Mean Age at Diagnosis of Comorbidity[1] (years) (SD; range) |
|---|---|---|---|---|---|
| Cardiac Conduction Disorder | 8 | 0.13 | 2.154E-12 | 60.2 (29.9, 108.6) | 39.6 (11.3; 18–48 years) |
| Obstructive Sleep Apnea | 12 | 1.23 | 8.042E-9 | 9.8 (5.6, 15.8) | 45.4 (13.4; 22–74) |
| Central Sleep Apnea | * | * | 4.486E-4 | 66.1 (11.7, 208.1) | * |
| Intellectual Disabilities | * | * | 0.0212 | 9.0 (1.6, 28.4) | * |
| Hypothyroidism | 6 | 2.32 | 0.0309 | 2.6 (1.1, 5.1) | 51.5 (21.8; 27–79) |
| Myotonic Cataract | * | * | 8.927E-4 | 1119.7 (57.6, 5311.4) | * |
| Any Cataract | 19 | 3.05 | 7.203E-10 | 6.23 (4.08, 9.15) | 41.3 (12.4; 20–59) |

[*] -- indicates that the exact number is below 5 and cannot be reported due to data confidentiality

[1] Mean age at diagnosis refers to the age at which the ICD-9 code for the comorbidity is used in the medical record for those individuals with myotonic dystrophy.

Abbreviations: Myotonic Dystrophy (DM), Myotonic Dystrophy type-1 (DM1), Myotonic Dystrophy type-2 (DM2), Utah Population Database (UPDB), University of Utah Health Sciences Center (UUHSC)