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Parent-of-Origin Effect on the Age at Symptom Onset in Myotonic Dystrophy Type 2

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Abstract

Background and Objectives

The existence of clinical anticipation, congenital form, and parent-of-origin effect in myotonic dystrophy type 2 (DM2) remains uncertain. Here, we aimed at investigating whether there is a parent-of-origin effect on the age at the first DM2-related clinical manifestation.

Methods

We identified patients with genetically confirmed DM2 with known parental inheritance from (1) the electronic medical records of our institutions and (2) a systematic review of the literature following the PRISMA 2020 guidelines and recorded their age at and type of first disease-related symptom. We also interrogated the Myotonic Dystrophy Foundation Family Registry (MDFFR) for patients with DM2 who completed a survey including questions about parental inheritance and age at the first medical problem which they related to their DM2 diagnosis.

Results

A total of 26 patients with DM2 from 18 families were identified at our institutions as having maternal (n = 14) or paternal (n = 12) inheritance of the disease, whereas our systematic review of the literature rendered a total of 61 patients with DM2 from 41 families reported by 24 eligible articles as having maternal (n = 40) or paternal (n = 21) inheritance of the disease. Both cohorts were combined for downstream analyses. Up to 61% and 58% of patients had muscle-related symptoms as the first disease manifestation in maternally and paternally inherited DM2 subgroups, respectively. Four patients developed hypotonia at birth and/or delayed motor milestones early in life, and 7 had nonmuscular presentations (2 had cardiac events within the second decade of life and 5 had cataracts), all of them with maternal inheritance. A maternal inheritance was associated with an earlier (within the first 3 decades of life) age at symptom onset relative to a paternal inheritance in this combined cohort, and this association was independent of the patient's sex (OR [95% CI] = 4.245 [1.429–13.820], $p = 0.0117$). However, this association was not observed in the MDFFR DM2 cohort (n = 127), possibly because age at onset was self-reported, and the information about the type of first symptom or medical problem that patients related to DM2 was lacking.

Discussion

A maternal inheritance may increase the risk of an early DM2 onset and of cataracts and cardiovascular events as first DM2 manifestations.

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Glossary

CNBP = cellular nucleic acid–binding protein; **DM1** = dystrophy type 1; **DM2** = dystrophy type 2; **MDFFR** = Myotonic Dystrophy Foundation Family Registry; **MGB** = Mass General Brigham; **ZNF9** = zinc finger protein 9.

The term *proximal myotonic myopathy* (PROMM) was introduced in 1995.[1,2] Three years later, the disease locus was mapped to Chr.3q-21.3.[3,4] In 2001, an intronic CCTG tetranucleotide expansion within intron 1 of cellular nucleic acid–binding protein (CNBP) gene, formerly called zinc finger protein 9 (ZNF9), was identified as the genetic basis of PROMM or myotonic dystrophy type 2 (DM2), which were concluded to be the same disease.[5] DM2 is probably underdiagnosed and its prevalence, although lower than that of myotonic dystrophy type 1 (DM1) in most studies, has been reported to be as high as 1 in 1,830 in the Finnish population.[6] Unlike DM1, in DM2, muscle weakness affects predominantly proximal muscles and the multisystem manifestations (cognitive impairment, daytime sleepiness, respiratory involvement, abnormal cardiac rhythm, etc.) are less severe and more variable.[7,8]

DM1 exhibits clinical anticipation and parent-of-origin effect (differences in phenotype depending on whether the pathogenic allele is maternally or paternally inherited) and has a congenital form; however, whether these 3 characteristics apply to DM2 remains uncertain. Some studies have considered the possibility of anticipation phenomenon and even the existence of a congenital form in PROMM/DM2.[9-13] However, in the absence of a molecular correlate (such as longer repeat expansions in the offspring than in affected parent), it is difficult to ascribe self-reported symptoms by DM2 carriers within the first decades of life to the first disease manifestation. While in DM1, the exact number of trinucleotide repeats within the 3′ UTR of *DMPK* gene is often known and it is well-established that longer CTG expansions are associated with both an earlier symptom onset and a more severe phenotype, the number of tetranucleotide repeats in DM2 is technically challenging to determine because expansions are usually much longer (up to ~11,000 CCTG repeats). That is why the identification of an expanded allele containing >75 CCTG repeats was established to be sufficient for DM2 genetic confirmation by most laboratories and, consequently, why whether such a genotype-phenotype correlation exists in this disease form remains elusive. Furthermore, while the congenital form of DM1 is clearly associated with maternal inheritance, the existence of a congenital form in DM2 remains an open question.

Here, we aimed at determining whether there is a parent-of-origin effect in DM2, specifically, whether the age at symptom onset and the type of first symptom differ in maternally vs paternally inherited DM2. We reasoned that, if demonstrated, a parent-of-origin effect in DM2 would further expand our understanding of the phenotypic spectrum of DM2 and prompt investigations on the underlying molecular mechanisms accounting for such effect.

Methods

Participants/Pedigrees

The electronic medical records at the Mass General Brigham (MGB) Health System were searched for the terms "myotonic dystrophy" and "muscular dystrophy" to identify patients with genetically confirmed DM2 seen at our institutions from 2000 through 2020. In addition, a systematic review of the literature was performed following the PRISMA 2020 guidelines[14,15] on June 22, 2022, using "myotonic dystrophy type 2 [Title/Abstract] OR proximal myotonic myopathy [Title/Abstract] OR CNBP [Title/Abstract] OR ZNF9 [Title/Abstract]" as search strategy to identify DM2 pedigrees published in PubMed since January 1, 2000, that were informative for the purpose of this study. Both MGB and literature cohorts were grouped for downstream analyses. Finally, an independent analysis was performed using data from the Myotonic Dystrophy Foundation DM2 Family Registry (MDFFR), which served as a third cohort.

Data Collected

Age at symptom onset (or age at the first disease manifestation), type of first symptom (or first disease manifestation), sex, maternal or paternal inheritance, DM2 genetic confirmation (i.e., >75 CCTG repeats), and the presence of additional genetic variants in *CLCN1* or *SCNA4A* genes as possible phenotype modifiers were collected when available. To minimize ascertainment bias in age at symptom onset, we categorized this variable in decades of life and defined "early onset" when the first symptom (or disease manifestation) occurred within the first 3 decades of a patient's life and "late onset" when occurred in the fourth or following decades. Although DM2 is a multiorgan disease and other clinical features may have been unrecognized manifestations of this muscular dystrophy, in this study, we considered not age-related cataracts, symptomatic heart disease, and muscle symptoms (myotonia, muscle stiffness, myalgias, and muscle weakness) as the only DM2-related symptoms to minimize the possibility of including unrelated, nonspecific symptoms as clinical manifestations of DM2. Similarly, only symptomatic cardiac events were included because asymptomatic cardiac rhythm abnormalities—although possibly a consequence of DM2—could also be interpreted as incidental findings on cardiac tests (e.g., ST segment and T-wave abnormalities on ECG), often performed for unrelated reasons (e.g., prior to surgery, well-being screening, etc). Hypotonia at birth and/or a delay in motor milestones were considered first manifestation of the disease when reported in the literature[10,12,13] or considered as such by the clinician taking care of the patient. Lack of information in patients' medical records regarding age at symptom onset, absence of

confirmatory genetic testing (except for those reported families with PROMM phenotype prior to identification of gene defect), and unknown parental inheritance were exclusion criteria. For asymptomatic DM2 carriers, we collected the last known decade of life in which they remained asymptomatic. The information collected from the MDFFR was based on the answers of patients with DM2 to a survey which included the following questions pertinent to our study: (1) At what age did the first medical problems occur that may be related to your myotonic dystrophy? (2) Please, indicate which family members are also known to have myotonic dystrophy, and (3) Were you the first person in your family given the diagnosis? Unlike the MGB and literature DM2 cohorts, patients' sex, type of first symptom or disease manifestation, and genetic modifiers were not available.

Statistical Analyses

Univariate analyses comparing proportions of categorical variables (parental inheritance, sex, type of symptom at onset) were conducted with the Fisher exact test. To determine whether parental inheritance is associated with age at symptom onset independently of patient's sex, we built a logistic regression model with age at symptom onset (dichotomized in early vs late as described above) as dependent variable and parental inheritance (paternal vs maternal) and patient's sex as independent variables. Asymptomatic DM2 carriers were excluded from analyses addressing age at onset or type of clinical manifestation/symptom. Statistical significance was set at a p-value <0.05. All analyses were run in GraphPad Prism version 9 (GraphPad Inc. La Jolla, CA).

Standard Protocol Approvals

This study was conducted following institutional review board approval.

Data Availability

Deidentified participants' data may be made available to qualified investigators on request.

Results

Mass General Brigham DM2 Cohort

There were 70 genetically confirmed patients with DM2 in the Mass General Brigham (MGB) cohort, of whom information about parental inheritance was available for 26 patients from 18 families. Fourteen of these 26 patients with DM2 had maternal inheritance and 12 had paternal inheritance. Table 1 shows the clinical characteristics and parental inheritance of these 26 patients with DM2, and Figure 1 shows the pedigrees of the 6 families with more than 1 patient with DM2 evaluated in our clinics. Of note, in these 6 families, affected members from younger generations developed the first manifestation of the disease earlier than affected members from older generations, and 5 of the 6 patients with early onset (i.e., within the first 3 decades of life) had maternal inheritance. Using this age cut-off criterion, all except 1 patient with maternal inheritance (13/14, 93%) had early-onset DM2. Furthermore, the 2 patients with maternal inheritance who developed symptoms during the first decade of life presumably had a congenital form of the disease and deserved a more detailed description:

Family 2, participant II:1: An adult man who experienced breathing difficulties and multiple respiratory tract infections within the first weeks of his life. He was born at full-term from a vaginal delivery. His examination revealed generalized hypotonia, neck flexion weakness, and areflexia. His CK was reported to be mildly elevated at birth. An EMG did not reveal electrical myotonia, and a muscle biopsy was reported as normal. He started to walk at the age 2 years and needed assistance with walker and wheelchair during his childhood. He also reported cramps and pain in back, neck, and hips—symptoms also present in his mom, who carried a DM2 diagnosis. He eventually underwent genetic testing, which confirmed the DM2 diagnosis. A second EMG at the age 24 years did not show electrical myotonia and was considered normal. His CK at that time was also normal (125 IU/L, normal range: 39–308).

Family 3, participant II:1: A teenager girl who was noticed to have delay in motor milestones. She walked without support after age 2 years, and her CK was 183 IU/L (normal range: 40–150). She underwent genetic testing for DM2 because her family history of this muscular dystrophy raised suspicion about these symptoms being due to DM2, and the test was confirmatory.

Conversely, only 2 of the 12 patients with paternal inheritance (16.7%) in the MGB cohort experienced their first symptom during the first 3 decades of life, and none of them did within the first decade of life. In fact, 6 (50%) remained asymptomatic at least by the third decade, and 4 had a late onset.

Intriguingly, 4 women in this cohort experienced their first disease-related symptom, specifically skeletal muscle symptoms, during a pregnancy; III:1 (family 6) and II:1 (family 7) both had maternally inherited DM2 in the third decade of life, whereas II:1 (family 13) and I:1 (family 3) had paternally inherited DM2 with onset in the third and fourth decade of life, respectively.

In addition, noteworthy, not age-related cataract was the first disease manifestation in 2 patients with maternal inheritance whereas it was not identified as presenting manifestation in any patient with paternal inheritance. Finally, symptomatic cardiac manifestations were not observed as presenting symptom in any patient of the MGB cohort.

Literature DM2 Cohort

The flowchart in Figure 2 summarizes the results of our systematic review. A total of 571 articles were identified using the aforementioned search terms as potentially containing DM2 pedigrees of interest for the purpose of this study. By applying automation tools to include "English/Spanish" written reports since "2000/1/1" related to "Humans," 190 of these 571 articles were filtered out. Then, PG-P reviewed the title and

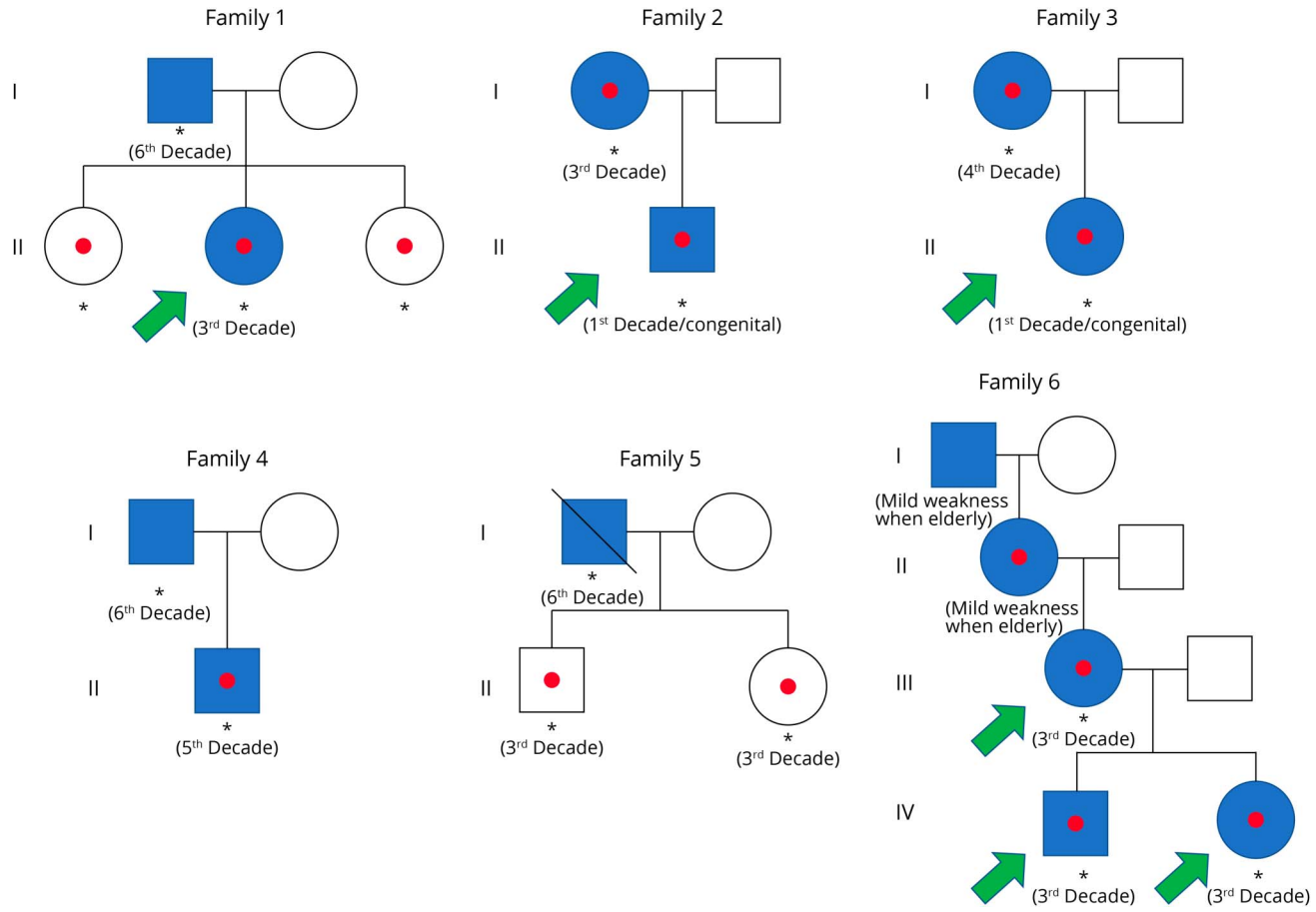
Table 1 Mass General Brigham DM2 Cohort With Known Parental Inheritance (n = 26)

Family	Participant	Sex	Decade of symptom onset	First symptom	Inheritance
Family 2	I:1	F	Third	Muscle pain and stiffness of lower extremities	Maternal
Family 2	II:1	M	First (congenital)	Hypotonia at birth, delay in motor milestones (walked after age 2 years), lower body muscle pain	Maternal
Family 3	II:1	F	First (congenital)	Hypotonia at birth, delay in motor milestones (walked after age 2 years), cerebellar astrocytoma	Maternal
Family 6	III:1	F	Third	Muscle pain and weakness of lower extremities during pregnancy	Maternal
Family 6	IV:1	M	Third	Muscle pain and weakness of lower extremities	Maternal
Family 6	IV:2	F	Third	Unknown	Maternal
Family 7	II:1	F	Third	Muscle stiffness during pregnancy	Maternal
Family 8	II:1	F	Third	Proximal muscle weakness	Maternal
Family 9	II:1	M	Second	Muscle weakness	Maternal
Family 10	II:1	F	Second	Cataracts removed at age 18 years as only manifestation	Maternal
Family 11	II:1	F	Third	Myotonia	Maternal
Family 14	II:1	M	Sixth	Exercise intolerance	Maternal
Family 16	II:1	M	Third	Muscle pain and weakness of lower extremities	Maternal
Family 17	II:1	F	Second	Cataracts removed at age 20 years	Maternal
Family 1	II:1	F	N/A	Asymptomatic by fourth decade	Paternal
Family 1	II:2	F	Third	Muscle pain and stiffness of lower extremities	Paternal
Family 1	II:3	F	N/A	Asymptomatic by fourth decade	Paternal
Family 3	I:1	F	Fourth	Muscle pain and weakness of lower body during pregnancy	Paternal
Family 4	II:1	M	Fifth	Muscle pain and lower extremity weakness	Paternal
Family 5	II:1	M	N/A	Asymptomatic by third decade	Paternal
Family 5	II:2	F	N/A	Asymptomatic by third decade	Paternal
Family 6	II:1	F	Seventh	Mild weakness of lower extremities	Paternal
Family 12	II:1	F	Fifth	Cramps, muscle pain	Paternal
Family 13	II:1	F	Third	Myotonia, muscle pain during pregnancy	Paternal
Family 15	II:1	M	N/A	Asymptomatic by fourth decade	Paternal
Family 18	II:1	M	N/A	Asymptomatic by sixth decade	Paternal

abstract of the remaining 381 articles and excluded 257 because they did not contain information of interest to address the aim of our study. After full reading of the remaining 124 articles, 1 additional article was excluded for the same reason.[16] Of these 123 articles, 96 were excluded because they did not contain pedigree or symptom onset information for any of the reported patients with DM2, 1 article because it was a commentary on another included article, 1 because of a discrepancy in patient's sex between the text and the pedigree figure which could affect our study findings, and 1 because a genetic defect different from DM2 could not be entirely ruled out as the culprit for the atypical DM2 phenotype of the patient described.[10,17,18] Of note, 3 articles published between 2000 and 2002 describing the history, examination, EMG, and/or muscle biopsy of 8 patients with typical PROMM phenotype were included despite lacking confirmatory genetic testing for DM2.[19-21]

A total of 61 patients with DM2 from 41 families were identified in the final 24 eligible articles[11,12,19-40] of whom 40 had maternal inheritance and 21 paternal inheritance. Table 2 shows the clinical characteristics of these patients with DM2 with maternal or paternal inheritance. Five patients presented during the first decade of life, 4 of whom had maternal inheritance, and 2 of these 4 exhibited hypotonia and delayed developmental milestones suggestive of a presumed DM2 congenital form.[11,12,32] Only 1 patient with PROMM phenotype who developed symptoms during the first decade of life appeared to have paternal inheritance (his father suffered sudden death at age 42

Figure 1 Pedigrees From 6 DM2 Families From the Mass General Brigham Cohort Included in This Study



Five of the 6 patients with DM2 who developed first symptom within the first 3 decades of life (green arrow) had a maternal inheritance of the disease. Symbols: * positive for CCTG expansion within *CNBP*; ( ) decade at symptom onset or presumed first manifestation of the disease; blank square or circle: asymptomatic participant; filled square or circle: symptomatic subject; red dot: included in the study because age at symptom onset and parental inheritance were known.

years whereas his mother did not have clinical or electrical evidence of the disease); however, the results of the genetic testing were not reported for either proband or parents likely because DM2 genetic testing was not available at that time.[21] All patients who became symptomatic within the first decade of life had skeletal muscle manifestations.

Of interest in the literature DM2 cohort, all 5 female patients who developed the first disease symptom during or after their pregnancy—occurring within the second or third decade of life in all 5—had paternal inheritance and belong to the same family.[23] All of them presented with skeletal muscle symptoms. Three patients developed not age-related cataracts and 2 suffered early cardiovascular events as the first disease manifestation, all of them had maternal inheritance.[19,20,25,29] By contrast, none of the paternally inherited patients with DM2 presented with cataract or symptomatic cardiac disease.

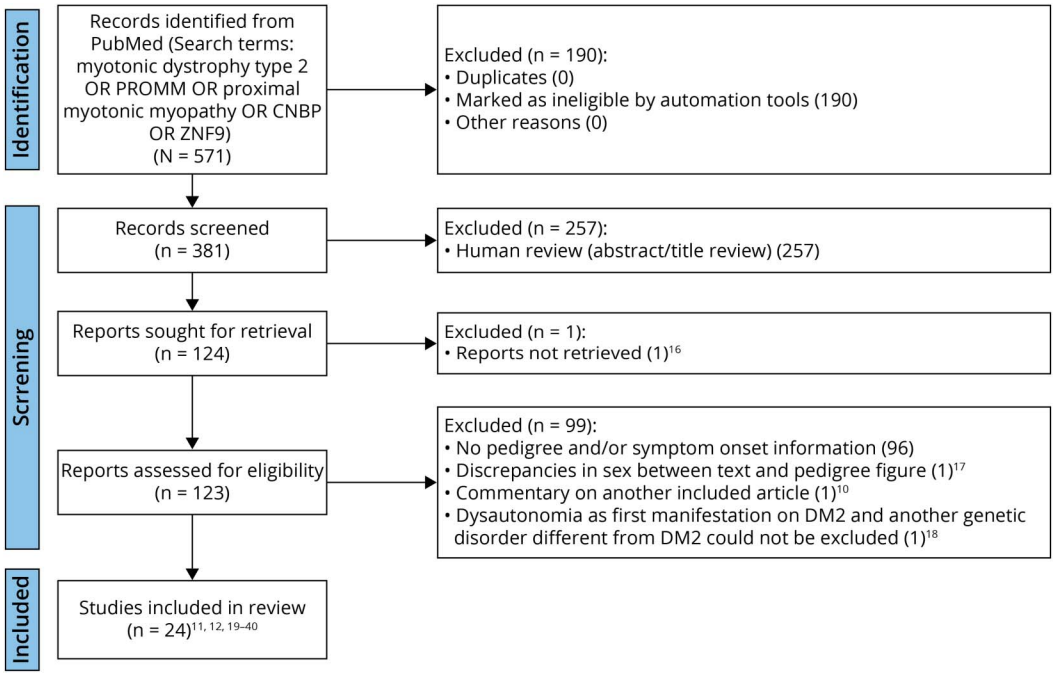
Combined MGB Literature DM2 Cohort for Downstream Analyses

A total of 87 patients from 59 families were included in downstream analyses, 54 with maternal inheritance and 33 with paternal inheritance. We investigated differences in sex, age at onset, and type of presenting symptom or manifestation. Regarding sex, within the maternally inherited DM2 group, there were 29 female patients, 25 male patients, and 1 patient with unknown sex. Within the paternally inherited DM2 group, there were 24 female patients, 7 male patients, and 2 patients with unknown sex. Excluding patients with unknown sex, we observed a female predominance in the paternally inherited cohort (OR [95% CI] = 2.956 [1.136–7.426], p = 0.0374, Fisher exact test).

Regarding age at onset, excluding 7 maternally inherited and 7 paternally inherited asymptomatic carriers, logistic regression analysis revealed that a maternal inheritance is associated with an earlier (within the first 3 decades of life) age at symptom onset relative to a paternal inheritance (OR [95% CI] = 3.214 [1.178–8.240], p = 0.0258) and that this association is independent of patient's sex (OR [95% CI] = 4.245 [1.429–13.820], p = 0.0117) (Figure 3).

Skeletal muscle–related symptoms were the most frequent first disease manifestation in both maternally and paternally inherited patients with DM2, with no statistically significant

Figure 2 Flow Chart of the Systematic Review Following the PRISMA 2020 Guidelines



difference between them (OR [95% CI] = 1.158 [0.5000–2.875], $p = 0.8231$, Fisher exact test). Although differences did not reach statistical significance, presumed congenital/very early-onset (first decade) symptoms, cataracts, and cardiovascular disease presentations were exclusive of patients with DM2 with maternal inheritance ($p = 0.2928$, 0.1518, and 0.5237, respectively). Within the group of female patients with DM2, those with paternally inherited DM2 were more likely to develop muscle symptoms as first DM2 manifestation during or after a pregnancy than those with maternally inherited DM2 although differences did not reach statistical significance (7/24 [29.2%] vs 2/29 [6.9%], OR [95% CI] = 5.559 [1.193–28.02], $p = 0.0623$, Fisher exact test). Finally, the proportion of asymptomatic carriers by at least the third decade of life was not statistically different in maternally (6/54, 11.1%) vs paternally inherited (7/33, 21.2%) DM2 groups (OR [95% CI] = 0.4643 [0.1316–1.462], $p = 0.2267$, Fisher exact test) (Figure 4).

Influence of *CLCN1* or *SCN4A* Genetic Variants

A summary of patients with DM2 with either *CLCN1* (chloride voltage-gated channel 1) or *SCN4A* (sodium channel, voltage-gated, type IV, alpha subunit) genetic variants is presented in Table 3. Two patients from the MGB cohort were found to have heterozygous likely pathogenic variants in *CLCN1*: p.Phe167Leu in a patient who developed symptoms during pregnancy within the third decade of life and inherited the disease maternally, and p.Arg894X in another woman who presented with muscle stiffness during her childhood; however, she was not included in our final cohort because of unknown parental inheritance.

A total of 7 patients with DM2 from 2 families in the literature cohort were identified as having heterozygous likely pathogenic *CLCN1* variants; all presented with muscle symptoms during the first 3 decades of life except 1 who remained asymptomatic by at least the second decade.[23,37] The only 3 patients with *CLCN1* variants who had paternally inherited DM2 were female patients, and all of them presented their first symptom during or after a pregnancy within the third decade of life, whereas the remaining patients had maternal inheritance and all except 1 developed symptoms even earlier (second decade of life) outside of a pregnancy. Finally, 2 patients with likely pathogenic variants in *SCNA4* also had maternally inherited DM2 and developed muscle symptoms as the first disease manifestation during the second decade of life.[28,34]

Myotonic Dystrophy Foundation Family Registry DM2 Cohort

The answers to the 3 aforementioned questions included in the Myotonic Dystrophy Foundation Family Registry (MDFFR) survey were retrieved from 139 patients with DM2. Twelve of these 139 were excluded because they did not know the age of their first DM2-related medical problem (n = 5), did not have any symptoms at the time of the survey (n = 5), or reported having both maternal and paternal family members affected (n = 2). Thus, a total of 127 patients were included for final analyses, 66 and 61 with maternally and paternally inherited DM2, respectively. No statistically significant differences were found in the age at the first medical problem self-reported as "may be related" to DM2 in those with maternal vs paternal inheritance (eTable 1, links.lww.com/NXG/A599). Of interest, 7 patients reported their first DM2-related medical problem within the first decade of life and 3 of those within the first year of life (2 reported maternal and 1 reported paternal inheritance). Of note, none of the 46 patients with DM2 who

Table 2 Literature DM2 Cohort With Known Parental Inheritance (n = 61)

Author/Year	Country	Sex	Age at symptom onset	First symptom	Inheritance
Roy et al. 2021[22]	US	F	Fifth decade	Leg stiffness, proximal lower extremity weakness	Maternal
Roy et al. 2021[22]	US	F	N/A	Asymptomatic by 4th decade	Maternal
Roy et al. 2021[22]	US	M	Sixth decade	Cramps, pain	Maternal
Sun et al. 2011[23]	Norway	M	N/A	Asymptomatic by 3rd decade	Maternal
Sun et al. 2011[23]	Norway	M	N/A	Asymptomatic by 2nd decade	Maternal
Sun et al. 2011[23]	Norway	M	Second decade	Muscle stiffness	Maternal
Leonardis, 2017[24]	Slovenia	M	Third decade	Muscle stiffness	Maternal
Gelibter et al. 2020[25]	Italy	F	Second decade	Type 2 second degree A-V block and structural cardiac abnormalities	Maternal
Papadimas et al. 2015[26]	Greece	M	Sixth decade	Proximal muscle weakness	Maternal
Papadimas et al. 2015[26]	Greece	F	Sixth decade	Proximal muscle weakness	Maternal
Papadimas et al. 2015[26]	Greece	F	Seventh decade	Proximal muscle weakness, ptosis	Maternal
Papadimas et al. 2015[26]	Greece	M	N/A	Asymptomatic by 5th decade	Maternal
Papadimas et al. 2015[26]	Greece	M	N/A	Asymptomatic by 5th decade	Maternal
Papadimas et al. 2015[26]	Greece	F	N/A	Asymptomatic by 4th decade	Maternal
Dabby et al. 2011[27]	Israel	F	Third decade of life	Myotonia or weakness or muscle pain	Maternal
Binda et al. 2018[28]	Italy	M	Second decade	Muscle stiffness and myotonia	Maternal
Renard et al. 2010[12]	France	F	First decade/Congenital	Congenital pes equinovarus	Maternal
Kruse et al. 2008[32]	Germany	M	First decade/Congenital	Pes equinus (reduced fetal movements in uterus), hypotonia, delayed motor milestones	Maternal
Finsterer et al. 2015[29]	Austria	M	Fourth decade	Cataracts	Maternal
Finsterer et al. 2015[29]	Austria	F	Fifth decade	Cataracts	Maternal
Schneider et al. 2000[20]	Germany	F	Third decade	Cataracts	Maternal
Schneider et al. 2000[20]	Germany	F	Third decade	Proximal muscle weakness	Maternal
Schneider et al. 2000[20]	Germany	M	N/A	Asymptomatic by 3rd decade	Maternal
Schoser et al. 2004[30]	Afghanistan	?	Second decade	Proximal weakness, myalgias, hyperhidrosis	Maternal
Milone et al. 2009[33]	US	F	Fourth decade	Hand stiffness after swimming in the pool	Maternal
Bugiardini et al. 2015[34]	Italy	F	Second decade	Hand cramping and difficulties relaxing hands	Maternal
Ehler et al. 2012[35]	Czech Republic	F	Fourth decade	Hand weakness and fatigue	Maternal
Rudnik et al. 2011[36]	Germany	M	Fourth decade	Hand myotonia and fatigue	Maternal
Rudnik et al. 2011[36]	Germany	M	Third decade	Muscle stiffness and myotonia	Maternal
Lucchiari et al. 2008[11]	Italy	M	First decade	Difficulties initiating leg movements at onset of physical activity	Maternal
Lucchiari et al. 2008[11]	Italy	F	First decade	Leg weakness and myalgias	Maternal
Cardani et al. 2012[37]	Italy	F	Second decade	Grip myotonia, difficulties with leg movements, symptoms improved with repetition	Maternal
Cardani et al. 2012[37]	Italy	F	Second decade	Grip myotonia	Maternal
Kohler et al. 2000[19]	Switzerland	M	Fourth decade	Difficulties climbing stairs and getting up from chair	Maternal
Kohler et al. 2000[19]	Switzerland	F	Sixth decade	Pain in lower extremities	Maternal
Kohler et al. 2000[19]	Switzerland	M	Second decade	Occlusion left central retinal artery (possibly secondary to cardiac-related event), then myotonia.	Maternal

Continued

Table 2 Literature DM2 Cohort With Known Parental Inheritance (n = 61) *(continued)*

Author/Year	Country	Sex	Age at symptom onset	First symptom	Inheritance
Kohler et al. 2000[19]	Switzerland	M	Fourth decade	Weakness in lower legs	Maternal
Toth et al. 2007[40]	Poland	M	Third decade	Difficulties initiating leg kick and leg movements, "muscle freezing"	Maternal
Auvinen et al. 2008[31]	Finland	F	Second decade	Muscle stiffness	Maternal
Auvinen et al. 2008[31]	Finland	F	Second decade	Muscle stiffness	Maternal

Author/Article	Country	Family/ Participant	Sex	Decade of symptom onset	First symptom	Inheritance
Roy et al. 2021[22]	US	F5-13	?	Fourth	Proximal lower extremity weakness	Paternal
Roy et al. 2021[22]	US	F6-16	F	NA	Asymptomatic by fourth decade	Paternal
Roy et al. 2021[22]	US	F6-17	F	Third	Cramp	Paternal
Sun et al. 2011[23]	Norway	F-III:2	F	Third	Stiffness of fingers, weakness lower extremity, myalgias	Paternal
Sun et al. 2011[23]	Norway	F-III:5	F	Third	Muscle stiffness, generalized weakness, myalgias	Paternal
Sun et al. 2011[23]	Norway	F-III:6	F	Third	Myotonia and muscle stiffness following pregnancy	Paternal
Sun et al. 2011[23]	Norway	F-III:7	F	Third	Myotonia and muscle stiffness following pregnancy	Paternal
Sun et al. 2011[23]	Norway	F-III:9	F	Third	Myotonia, muscle stiffness, and myalgia following pregnancy	Paternal
Sun et al. 2011[23]	Norway	F-III:10	F	Third	Cold-induced myotonia, muscle stiffness, myalgias, proximal lower extremity weakness following pregnancy	Paternal
Sun et al. 2011[23]	Norway	F-III:11	F	Second	Myotonia, muscle stiffness and myalgias following pregnancy	Paternal
Papadimas et al. 2015[26]	Greece	Pt 1	F	Sixth	Proximal muscle weakness, myalgias	Paternal
Papadimas et al. 2015[26]	Greece	Pt 9	F	Fourth	Proximal muscle weakness	Paternal
Papadimas et al. 2015[26]	Greece	Pt 10	F	Fourth	Myalgias, fatigue	Paternal
Papadimas et al. 2015[26]	Greece	Pt 11	F	Fourth	Myotonia	Paternal
Papadimas et al. 2015[26]	Greece	Pt 14	F	Fifth	Myotonia	Paternal
Papadimas et al. 2015[26]	Greece	Pt 16	M	Fifth	Myalgias	Paternal
Dabby et al. 2011[27]	Israel	Pt 9	F	Sixth	Myotonia or weakness or muscle pain	Paternal
Dabby et al. 2011[27]	Israel	Pt 10	M	Sixth	Myotonia or weakness or muscle pain	Paternal
Sicurelli et al. 2011[38]	Italy	Pt	F	Fifth	Fluctuating muscle weakness, pain, and stiffness	Paternal
Wahbi et al. 2008[39]	France	Pt	M	Fourth	Hand myotonia and lower extremity weakness	Paternal
Schneider et al. 2002[21]	Germany	Pt	?	First	Stiffness in leg muscles	Paternal

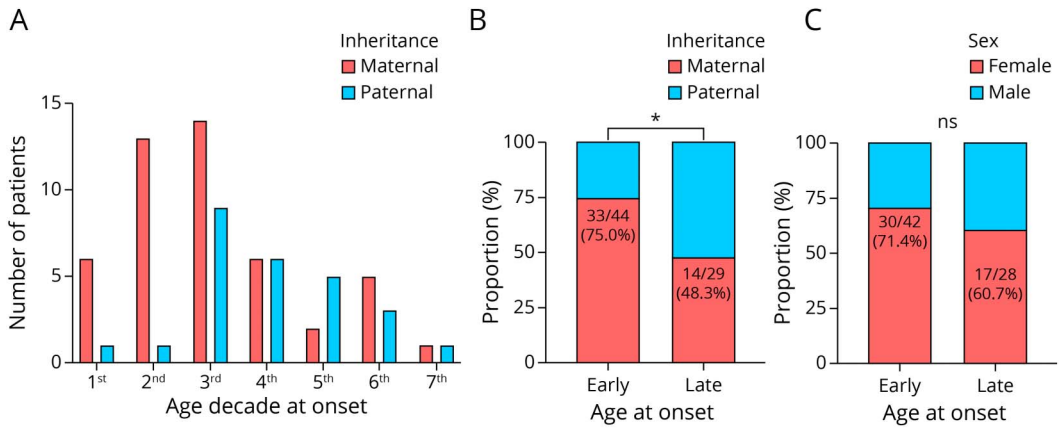
reported to be the first member of the family receiving a diagnosis of DM2 stated that the first possibly DM2-related medical problem occurred within the first decade of their life.

Discussion

Our study systematically investigated the existence of a parent-of-origin effect on symptom onset in DM2 after the identification of its genetic defect in 2001.[5] Using data collected by expert clinicians (MGB and literature cohorts) and highly specific clinical manifestations (skeletal muscles, heart, and cataracts), we found that an earlier symptom onset (≤third decade of life) is associated with a maternal inheritance and that this association is independent of the patient's sex.

While the median age at symptom onset in DM2 was reported to be within the fifth decade of life,[8] our study emphasizes the importance of considering this muscular dystrophy in patients who present muscle symptoms within the first 3 decades of

Figure 3 Symptom Onset in Maternally vs Paternally Inherited DM2



D Age at onset ~ sex + inheritance (late as reference)

Variable	OR	95% CI	*p* value
Sex			
Male	Reference	---	---
Female	2.525	(0.828, 8.251)	0.1103
Inheritance			
Paternal	Reference	---	---
Maternal	4.245	(1.429, 13.820)	0.0117

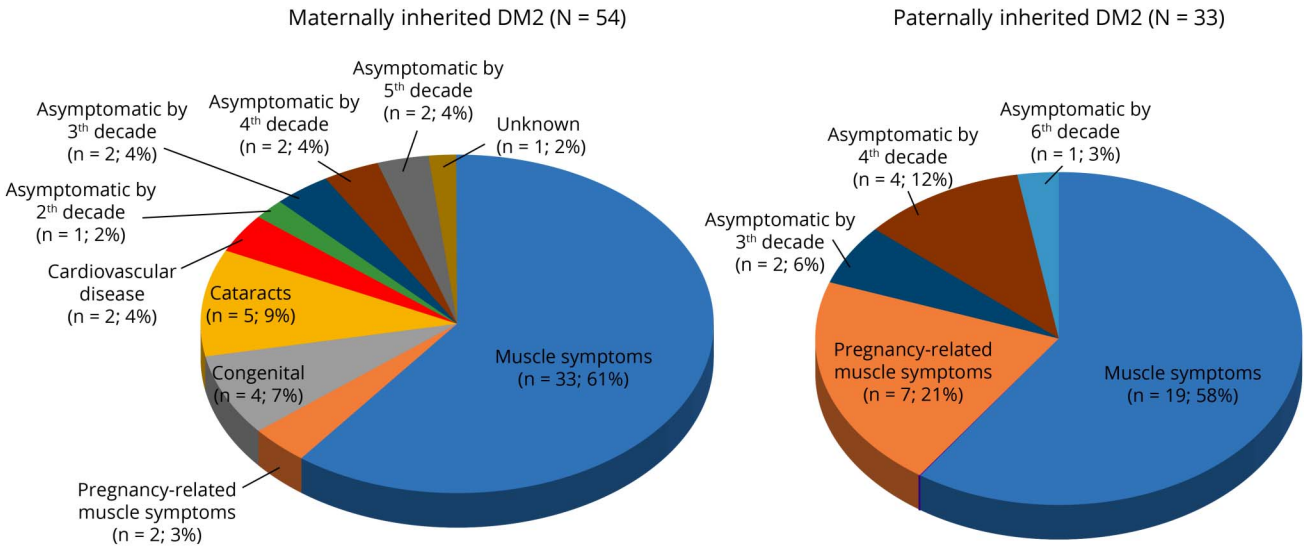
(A) Bar plot shows the number of both maternally (red) and paternally (blue) inherited patients with DM2 (y axis) by age decade at first symptom from first through seventh (x axis). A total of 73 patients with DM2 were represented (asymptomatic carriers were excluded). Note that the graph is shifted to the left likely because of selection bias as parental inheritance is more frequently known in patients who developed symptoms early in life. (B) Patients with DM2 with maternal inheritance experience the first disease symptom within the first 3 decades of life (early onset DM2) more often than those with paternal inheritance; differences were statistically significant (OR [95% CI] = 3.214 [1.178–8.240], $p = 0.0258$). (C) There were no differences in sex between patients with DM2 with early vs late onset of the disease (OR [95% CI] = 1.618 [0.625–4.152], $p = 0.4381$). (D) Logistic regression analysis showed that maternal inheritance associates with early-onset DM2 independently of patient's sex ($p = 0.0117$).

life (early-onset DM2). Indeed, 9.6%, 19.2%, and 31.5% of the patients with DM2 in the combined symptomatic cohort (n = 73) and 5.5%, 11.8%, and 22% in the MDFFR cohort (n = 127) developed their first clinical manifestation (or presumed first DM2-related medical problem) within the first, second, and third decade of life, respectively. Although the existence of a congenital DM2 form remains uncertain, all patients with DM2 who presumably developed the first disease manifestation within the first year of their life (n = 7, including the 2 patients in our MGB cohort) had maternal inheritance,[10-13] except for 1 MDFFR patient who reported a paternal inheritance. Of note, participant II:1 (family 2) from our MGB cohort underwent EMG during childhood and at age 24 years, and neither study revealed electrical myotonia; thus, if a congenital DM2 form in fact exists, clinical or electrical myotonia may be absent, similar to congenital DM1.[12,32] Investigations of a second genetic disorder to account for symptoms within first year of life in DM2 carriers will be necessary before attributing them to a true congenital form.

Skeletal muscle symptoms (muscle weakness, myalgias, muscle stiffness, or myotonia) were the most common symptom at presentation in both paternally and maternally inherited DM2, whereas other presenting manifestations such as cataracts and cardiovascular events were much less frequent and only observed in the maternally inherited group. Therefore, DM2 maternal inheritance may predispose to an earlier involvement of organs other than skeletal muscles.

Pregnancy is known to either exacerbate or trigger first skeletal muscle symptoms such as myotonia, muscle pain, or muscle stiffness in mothers with DM2. Up to 21% of women developed their first DM2 symptoms during a pregnancy as reported in a study.[41] Hence, pregnancy contributes to anticipate the age at symptom onset in female patients with DM2. Seven of the 9 female patients who developed first DM2 symptoms during pregnancy in this study had DM2 paternal inheritance, 6 within the second or third decade of life and 1 within the fourth decade of life. Furthermore, there was a clear female predominance within the paternally inherited cohort reported herein; 24 (72.7%) were female patients, 7 (21.2%) were male patients, and 2 unknown, whereas sex distribution was more evenly distributed within the maternally inherited cohort, with 29 (53.7%) female patients, 24 (44.4%) male patients, and 1 unknown. This observation together with the findings that maternal inheritance is associated with an earlier symptom onset independently of patient's sex and that male patients and female patients were similarly represented in early-onset vs late-onset DM2 (Figure 3) suggest that pregnancy is a risk factor for clinical presentation in paternally inherited female patients with DM2, whereas female patients who inherited disease from their mom are predisposed to develop

Figure 4 Type of First Symptom in Maternally vs Paternally Inherited Patients With DM2



Muscle-related symptoms (myalgias, muscle stiffness, myotonia, and muscle weakness) were the most frequent first disease manifestation in both maternally and paternally inherited DM2. Congenital forms, cataracts, and cardiac disease were the first manifestation of the disease only in patients with DM2 with maternal inheritance.

early-onset DM2 independently of pregnancy occurrence and, in some cases, even before reaching childbearing age.

The parent-of-origin effect shown here raises questions about the underlying mechanism. The DM2-linked CCTG expanded repeat within the intron 1 of the *CNBP* gene is part of a complex repetitive motif (TG)n(TCTG)n(CCTG)n. This repeat tract is generally interrupted in healthy nonexpanded alleles by 1 or more GCTG, TCTG, or ACTG motifs and postulated to be typically uninterrupted in expanded alleles although this requires further investigation.[42] If so, whether maternally inherited expanded alleles are more prone to miss these "stabilizers" motifs should be studied. We also considered a possible implication of known genetic modifiers. Likely pathogenic variants in the *CLCN1* gene located in chromosome 7q35 cause 2 types of nondystrophic myotonia congenita: Becker disease (autosomal recessive) and Thomsen disease (autosomal dominant). In 1998, a family with PROMM phenotype who was later confirmed to carry a CCTG expansion in the *CNBP* gene was reported to have a likely pathogenic variant (p.R894X) in *CLCN1* in some of the affected members.[43,44] At the 84th ENMC Workshop, a role of *CLCN1* as genetic modifier of DM2 phenotype was debated.[45] Subsequent studies reported a higher than expected prevalence of *CLCN1* variants in patients with DM2.[46,47] Likely pathogenic variants in the *SCN4A* gene located in chromosome 17q23-25 have been linked with paramyotonia congenita, sodium channel myotonia, hyperkalemic periodic paralysis, and hypokalemic periodic paralysis, all of them autosomal dominantly inherited disorders.[48,49] These *SCN4A* variants have also been described in patients with DM2 and associated with an earlier onset and more severe phenotype of this muscular dystrophy.[28,34] Of note, in our combined MGB literature cohort, all 9 patients with symptomatic DM2 with either *CLCN1* or *SCN4A* genetic variants had early-onset DM2; 6 had a maternal inheritance, and the 3 patients with paternal inheritance were female patients who developed their first symptom during or immediately after a pregnancy (Table 3). These findings raise the possibility that an as yet unknown protective factor delays symptom onset when DM2 is paternally inherited but may be lost when there is a second pathogenic variant in either *CLCN1* or *SCN4A* genes, or with pregnancy, or with a combination of both. It is also important to recognize that the proportion of patients with DM2 remaining asymptomatic after the third decade of life did not statistically differ between the maternally inherited and paternally inherited DM2 groups. Therefore, although maternal inheritance may increase the risk for early onset DM2, there is still a subgroup of patients who remain asymptomatic by midadulthood. Whether and which genetic modifiers account for these differences in symptom onset within the maternally inherited DM2 group remains to be determined.

Cardiac rhythm abnormalities are one of the most feared complications in patients with DM because they can be life-threatening events leading to sudden death. Thus, performing periodic heart rhythm monitoring in all DM carriers and providing genetic counseling to their family members are key to prevent this cardiac mortality. While these cardiac events are often the first disease manifestation in DM1 (i.e., a positive family history of sudden death is not uncommon), they are less obvious as DM2 presenting symptom, likely because of its more variable and underdiagnosed phenotype, and possibly because of the under-recognized manifestations in the pediatric population. The authors of a study described a DM2 female patient who developed a type 2 second-degree atrioventricular block and

Table 3 *CNCL1* and *SCN4A* Genetic Variants in the DM2 Cohorts

Study/Cohort	Country	Participant/Family	Sex	Symptom onset	Type of first symptom	Inheritance	*CLCN1*	*SCN4A*
MGB cohort	US	II:1 (family 7)	F	Third decade	Muscle stiffness during pregnancy	Maternal	c.501 C>G, p.Phe167Leu (ht)	—
MGB cohort*	US	II:1 (family 19)	F	First decade	Myotonia in hands	Unknown	c.2680 C>T, p.Arg894X (ht)	—
Sun et al. Clin Genet. 2011[23]	Norway	F-IV:4	M	N/A	Asymptomatic by 2nd decade	Maternal	c.1238 C>G, p.Phe413Cys (ht)	—
Sun et al. Clin Genet. 2011[23]	Norway	F-IV:5	M	Second decade	Muscle stiffness	Maternal	c.1238 C>G, p.Phe413Cys (ht)	—
Binda et al. Sci Rep. 2018[28]	Italy	Patient	M	Second decade	Muscle stiffness and myotonia	Maternal	—	c.2717G>C, p.Ser906Thr (ht) (Polymorphism)
Cardani et al. J Neurol. 2012[35]	Italy	II:1	F	Second decade	Grip myotonia and difficulties in starting leg movements, symptoms improved with repetition	Maternal	c.501C>G, p.Phe167Leu (ht)	—
Cardani et al. J Neurol. 2012[37]	Italy	I:1	F	Second decade	Grip myotonia	Maternal	c.501C>G, p.Phe167Leu (ht)	—
Sun et al. Clin Genet. 2011[23]	Norway	F-III:7	F	Third decade	Myotonia and muscle stiffness after pregnancy	Paternal	c.1238 C>G, p.Phe413Cys (ht)	—
Sun et al. Clin Genet. 2011[23]	Norway	F-III:9	F	Third decade	Myotonia, muscle stiffness, and myalgia after pregnancy	Paternal	c.1238 C>G, p.Phe413Cys (ht)	—
Sun et al. Clin Genet. 2011[23]	Norway	F-III:10	F	Third decade	Severe and cold-induced myotonia, muscle stiffness, myalgia, proximal lower-extremity weakness after pregnancy	Paternal	c.1238 C>G, p.Phe413Cys (ht)	—
Bugiardini et al. 2015[34]	US	Patient	F	Second decade	Hand cramps and myotonia	Maternal	—	c.215C>T p.Pro72Leu (ht)

structural cardiac abnormalities within the second decade of life presumably as first disease manifestation; she inherited the disease from her mom, who was the proband.[25] The authors of another study reported a genetically unconfirmed patient with PROMM phenotype who suffered a vascular event (occlusion of the central retinal artery) within the second decade of life and who also inherited the disease maternally.[19] These data prompt to consider the indication of genetic counseling and testing in the offspring of patients with DM2 who are within the pediatric age range (0–17 years) and, if a pathogenic DM2 expansion is demonstrated, to recommend periodic cardiac monitoring (e.g., ECG) in these young DM2 carriers. Whereas consensus-based care recommendations for congenital and childhood-onset DM1 include a cardiac management protocol,[50] similar guidelines for pediatric DM2 carriers are currently lacking.

Some limitations of our study should be acknowledged. A selection bias is inherent to the inclusion criterion of known parental inheritance. Patients with DM2 with known parental inheritance are more likely to be younger individuals for whom their affected parent sought medical attention. On the other hand, patients with DM2 with the most common age at symptom onset (i.e., fourth decade of life and later) are more likely to have an unknown parental inheritance and, therefore, to be excluded from the study. This limitation likely explains the shift toward the left (early-onset) in the age frequency distribution of the combined symptomatic cohort. In addition, an ascertainment bias should also be considered. Because most patients were known to have an affected parent at the time of their diagnosis, it is possible that symptoms that would not have otherwise triggered seeking medical attention in an individual without known family history, did prompt these patients to seek medical evaluation, thereby leading to overestimate the causal link between the DM2 diagnosis and the patient's symptom at a younger age. While this potential limitation is known to affect the assessment of the anticipation phenomenon, it is very unlikely to affect the maternally and paternally inherited DM2 groups to a different extent and, therefore, to explain the findings of this study. Finally, it should also be noted that we could not replicate our findings in the MDFFR DM2 cohort. Several caveats could explain this discrepancy such as the self-reported vs expert clinician ascertainment of the age at onset and the lack of information about the type of first manifestation (or medical problem) related to DM2 in the MDFFR survey, which could have attributed symptoms that are unrelated to DM2.

Although its recognition is more straightforward when there is a positive family history of the disease, DM2 is likely underdiagnosed in both adult and pediatric populations. This is likely because our understanding of the DM2 phenotypic variability is limited and mainly based on adult-onset patients with classic phenotype, who may actually only represent the "tip of the DM2 iceberg." This study highlights that the first manifestation of the disease may occur within the first 3 decades of life (early-onset DM2) in a sizable proportion of patients and that this occurs more often when the disease is maternally inherited at least in clinician-reporting cohorts. Thus, considering the possibility of DM2 in an index pediatric patient and providing genetic counseling and testing in the young offspring of an affected parent (especially if this parent is the mother) may optimize the care of these patients who could benefit from upcoming disease-modifying therapies which might be more effective at early stages.

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Vincent Picher-Martel, MD, PhD	Department of Neurology, Massachusetts General Hospital, Harvard Medical School; Department of Neurology, Brigham Women's Hospital, Harvard Medical School, Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data

Appendix *(continued)*

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William S. David, MD, PhD	Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
Anthony A. Amato, MD	Department of Neurology, Brigham Women's Hospital, Harvard Medical School, Boston, MA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data

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