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Neurocognitive Features of Motor Premanifest Individuals With Myotonic Dystrophy Type 1

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Neurol Genet 2021;7:e577. doi:10.1212/NXG.0000000000000577

Abstract

Objective

The goal of the study was to identify brain and functional features associated with premanifest phases of adult-onset myotonic dystrophy type 1 (i.e., PreDM1).

Methods

This cross-sectional study included 68 healthy adults (mean age = 43.4 years, SD = 12.9), 13 individuals with PreDM1 (mean age: 47.4 years, SD = 16.3), and 37 individuals with manifest DM1 (mean age = 45.2 years, SD = 9.3). The primary outcome measures included fractional anisotropy (FA), motor measures (Muscle Impairment Rating Scale, Grooved Pegboard, Finger-Tapping Test, and grip force), general cognitive abilities (Wechsler Adult Intelligence Scales), sleep quality (Scales for Outcomes in Parkinson's Disease–Sleep), and apathy (Apathy Evaluation Scale).

Results

Individuals with PreDM1 exhibited an intermediate level of white matter FA abnormality, where whole-brain FA was lower relative to healthy controls (difference of the estimated marginal mean [$EMM_{difference}$] = 0.02, 95% confidence interval (CI) 0.01–0.03, $p < 0.001$), but the PreDM1 group had significantly higher FA than did individuals with manifest DM1 ($EMM_{difference}$ = 0.02, 95% CI 0.009–0.03, $p < 0.001$). Individuals with PreDM1 exhibited reduced performance on the finger-tapping task relative to control peers ($EMM_{difference}$ = 5.70, 95% CI 0.51–11.00, $p = 0.03$), but performance of the PreDM1 group was better than that of the manifest DM1 group ($EMM_{difference}$ = 5.60, 95% CI 0.11–11.00, $p = 0.05$). Hypersomnolence in PreDM1 was intermediate between controls ($EMM_{difference}$ = −1.70, 95% CI −3.10–0.35, $p = 0.01$) and manifest DM1 ($EMM_{difference}$ = −2.10, 95% CI −3.50–0.60, $p = 0.006$).

Conclusions

Our findings highlight key CNS and functional deficits associated with PreDM1, offering insight in early disease course.

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Go to Neurology.org/NG for full disclosures. Funding information is provided at the end of the article.

The Article Processing Charge was funded by the NIH.

Glossary

AES = Apathy Evaluation Scale; **DM1** = myotonic dystrophy type 1; **EMM** = estimated marginal mean; **ePAL** = estimated progenitor allele length; **FA** = fractional anisotropy; **FDR** = false discovery rate; **HD** = Huntington disease; **MIRS** = Muscle Impairment Rating Scale; **PreDM1** = presymptomatic phase of DM1; **SP-PCR** = small-pool PCR; **WM** = white matter.

Myotonic dystrophy type 1 (DM1) is an autosomal dominant trinucleotide repeat disorder caused by a CTG repeat expansion in the *DMPK* gene. Symptom manifestation of adult-onset DM1 may be preceded by a prodromal phase, similar to Huntington disease (HD) where motor manifestation is preceded by changes in brain morphology, cognition, behavior, and motor function.[1–3] Formulas that include age and trinucleotide repeat length have been developed for the presymptomatic phases of HD to determine proximity to disease onset and progression. Proximity to HD onset is correlated with reduced striatal volume, the most sensitive MRI measure of HD motor onset.[3–8] A Dutch group introduced the notion that some carriers of the DM1 mutation lacked diagnostic signs.[9] Several studies have subsequently evaluated swallowing[10] and eye movement[11] in presymptomatic patients with DM1. Collectively, little is known about the presymptomatic phase of DM1 (PreDM1), particularly regarding brain morphology, or the potential utility of an age by CTG product for estimating disease burden.

Several key features require exploration in the context of PreDM1. Reduced white matter (WM) fractional anisotropy (FA) in patients with DM1 relative to controls is a prominent feature of CNS abnormality.[12–21] Cognitive challenges are also prevalent in adult-onset DM1[22] and encompass mild to moderate intellectual impairment, executive dysfunction, and visuospatial difficulty.[23] Apathy is substantially more prevalent in adults with DM1 than unaffected adults.[24] Finally, hypersomnolence is evident in approximately 30%–60% of patients, making it one of the most frequent nonmuscular symptoms.[25]

First, we identified brain WM FA and functional measures—including motor skill, general cognitive abilities, somnolence, and apathy—associated with PreDM1. Second, we evaluated the utility of a CTG by age product to approximate disease burden in regard to brain imaging measures.

Methods

Participants

Individuals with DM1 were recruited consecutively to participate in the Iowa DM1–Brain and Muscle study in Iowa City, Iowa, via advertisements through the advocacy group The Myotonic Dystrophy Foundation and word of mouth. Healthy control participants were recruited from the Iowa City area via advertisements or as a spouse/partner of participants with DM1. Exclusion criteria for all participants included MRI contraindication, a history of serious head injury, or a chronic neurologic disorder other than DM1. Control participants were additionally required to be without history of substance abuse, psychiatric disease, or major medical disease. Recruitment was targeted to adult-onset DM1 only (onset after age 18 years). Individuals who reported disease onset DM1 before age 18 years were excluded. The groups consisted of 61 controls, 45 subjects who had been genetically confirmed to have the gene expansion (CTG ≥50) for DM1, and 12 with a family history of DM1 without confirmative testing (i.e., at risk). These at-risk participants underwent genetic testing for research purposes only. At-risk individuals who were determined to have CTG repeat length ≥50 were included in the DM1 group (N = 5); the remainder were included in the control group (N = 7). The final sample included 118 individuals (68 controls and 50 DM1). Recruitment took place between March 2016 and February 2020.

PreDM1 was operationally defined by the absence of detectable motor symptoms as determined by a clinical examination by neuromuscular neurologist using the Muscle Impairment Rating Scale (MIRS). The MIRS ranges from 1 (normal, no symptoms) to 5 (severe symptoms). We chose this definition to operationalize our analysis; however, we understand that the onset of DM1 is not always clear. Some patients may have, for example, cataracts, sleepiness, or apathy, but no motor symptoms. Some patients may also have mild motor symptoms subjectively that do not manifest by a clinical examination.[26] From our sample of 50 subjects with DM1, 13 of them had an MIRS = 1 and were therefore defined as preDM1, with the remaining 37 subjects defined as manifest DM1.

Standard Protocol Approvals, Registrations, and Patient Consents

All data were deidentified, and all participants consented to nondisclosure of genetic results obtained as part of the study. All participants gave written informed consent before enrolling in the protocol. The study was approved by the University of Iowa Institutional Review Board.

Genetics: Estimated Progenitor Allele Length and Detection of Variant Repeats

Genotyping of pre- and manifest DM1 participants was completed by small-pool PCR (SP-PCR).[27] For each participant, 4 reactions were completed, each using 300 pg genomic DNA template derived from blood leukocytes. The primers used were (forward) DM-C (5′ AACGGGGCTCGAAGGGTCCT 3′) and (reverse) DM-DR (5′ CAGGCCTGCAGTTTGCCCATC 3′). CTG repeat lengths were estimated by comparison

Table 1 Sample Characteristics

	Healthy adults (N = 68)	PreDM1 (N = 13)	DM1 (N = 37)
Sex, n (%)			
Female	45 (66.2)	7 (53.8)	26 (70.3)
Male	23 (33.8)	6 (46.2)	11 (29.7)
Age, y			
Mean (SD)	43.4 (12.9)	47.4 (16.3)	45.2 (9.27)
Median [min, max]	43.7 [18.3, 63.4]	53.3 [19.2, 64.0]	44.1 [30.3, 62.2]
Age of symptom onset, y			
Mean (SD)	—	—	32.7 (10.1)
Median [min, max]	—	—	32.0 [16.0[c], 52.0]
Education, y			
Mean (SD)	16.1 (2.07)	15.8 (1.83)	15.8 (2.24)
Median [min, max]	16.0 [12.0, 20.0]	16.0 [13.0, 20.0]	16.0 [12.0, 20.0]
ePAL[a]			
Mean (SD)	13.9 (6.13)	102 (59.1)	180 (97.4)
Median [min, max]	13.0 [5.00, 43.0]	85.0 [55.0, 276]	146 [67.0, 501]
Missing, n (%)	1 (1.5)	0 (0)	1 (2.7)
Variant repeats, n (%)[b]			
Controls	68 (100)	0 (0)	0 (0)
Pure	0 (0)	12 (92.3)	33 (89.2)
Variant	0 (0)	1 (7.7)	4 (10.8)
Muscle Impairment Rating Scale, n (%)			
1	0 (0)	13 (100)	0 (0)
2	0 (0)	0 (0)	25 (67.6)
3	0 (0)	0 (0)	9 (24.3)
4	0 (0)	0 (0)	2 (5.4)

Abbreviations: DM1 = myotonic dystrophy type 1; ePAL = estimated progenitor allele length; PreDM1 = presymptomatic phase of DM1.
[a] For alleles <50, the value represents the absolute length of the longest inherited allele.
[b] Refers to naturally occurring interruptions in the CTG repeat tract that has been associated with a milder phenotype.
[c] One individual reported mild hand myotonia at age 16 years, but no other symptoms.

against DNA fragments of known length and molecular weight markers, using CLIQS software (TotalLabs UK Ltd., Newcastle upon Tyne, United Kingdom). The lower boundary of the expanded molecules in SP-PCR was used to estimate the progenitor (or inherited) allele length (ePAL).[28] Patients with CCG interruptions (referred to as variant repeats) have been shown to have a substantially milder form of DM1 compared with patients with pure repeats.[29] Therefore, we also evaluated small-pool PCR products from all participants for AciI sensitivity (New England BioLabs UK Ltd., Hitchin, United Kingdom; restriction site 5′CCGC-3′) allowing identification of participants with variant repeats, as previously described.[30] For patients with variant repeats, as for those with pure CTG repeat expansions, ePAL was defined as the total length of triplet repeats (whether CTG, CCG, or other triplet motifs) as determined from the lower boundary of bands on the SP-PCR blot. This estimate was used because AciI sensitivity alone cannot be used to infer the precise number or location of variant repeats or to determine the length of the longest stretch of pure CTG repeats present.

Genetics: Determination of CTG Repeat Length in Control Participants

CTG repeat length was estimated by MiSeq sequencing, essentially as described for HD alleles,[31] substituting DM1-for HD-specific primers, and using reference sequences

comprising 0 to 100 CTG repeats and 5′- and 3′-flanking sequence to the primer binding sites.

MRI

Participants who participated before June 2016 (N = 52, 24 controls, 28 DM1) were scanned using a 3T Siemens TrioTIM scanner. Those who participated after June 2016 (N = 66, 34 controls, 22 DM1) were scanned using a 3T General Electric Discovery MR750w scanner.

Batch effects in diffusion-weighted images associated with scanner versions were normalized using ComBat harmonization (see figure e-1, links.lww.com/NXG/A406).[32] Diffusion-weighted images were collected using echo planar recovery magnitude sequences collected in the axial plane with either a single shell (B1000, 64 directions), multishell (B1000 and B2000, 29–30 directions per shell), or both (details provided in table e-1, links.lww.com/NXG/A406).

White Matter FA

Diffusion-weighted images were processed using standard procedures of the FMRIB Diffusion toolbox from the FSL software package (fmrib.ox.ac.uk/fsl), where phase encoding distortion and eddy current artifacts were removed.[33,34] Diffusion tensor models were generated using dtifit, and diffusivity measures, including FA, were calculated. To normalize scalars to a common space, the following registrations were performed using rigid, affine, and nonlinear (symmetric normalization) components using Advanced Normalization Tools[35]: (1) B0 images (after encoding distortion and artifacts are removed) were registered to T2w images in native space (not to T1w images, since B0 and T2w images have similar intensity distributions by tissue type, which improves registration accuracy). (2) For more accurate anatomic registrations, T2w images were coregistered to T1w images in native, individual space. Finally, (3) for accurate normalization, both T1w and T2w coregistered images were registered simultaneously to coregistered, same-modality images in template space. These transformations were applied to FA maps in a single linear interpolation step to prevent compounding interpolation errors.

Motor Function

The MIRS is an expert rating tool established in accordance with the clinically recognized distal to proximal progression of muscle impairment in DM1.[36]

Fine motor skills were measured with the finger-tapping and the grooved Pegboard tests (Lafayette Instruments, Lafayette, LA). Participants completed 5 consecutive 10 second tap trials. The dependent variable was the average number of taps using the dominant hand. The Grooved Pegboard test requires participants to insert keyed pegs into slots. The outcome measure of interest was time in seconds, to completion using the dominant hand. The Lafayette Instruments dynamometer was used to assess grip force in kilogram force. The dependent variable represents the average grip force of the dominant hand across 3 trials.

General Cognitive Abilities

Participants completed the Wechsler Adult Intelligence Scale IV to estimate verbal comprehension, perceptual reasoning, working memory, and processing speed.[37]

Sleep Quality

The Scales for Outcomes in Parkinson's Disease–Sleep survey was used to assess sleep quality.[38] The self-report scale includes 5 nighttime sleep quality items and 6 hypersomnolence items, which were summed to calculate total sleep quality and hypersomnolence scores.

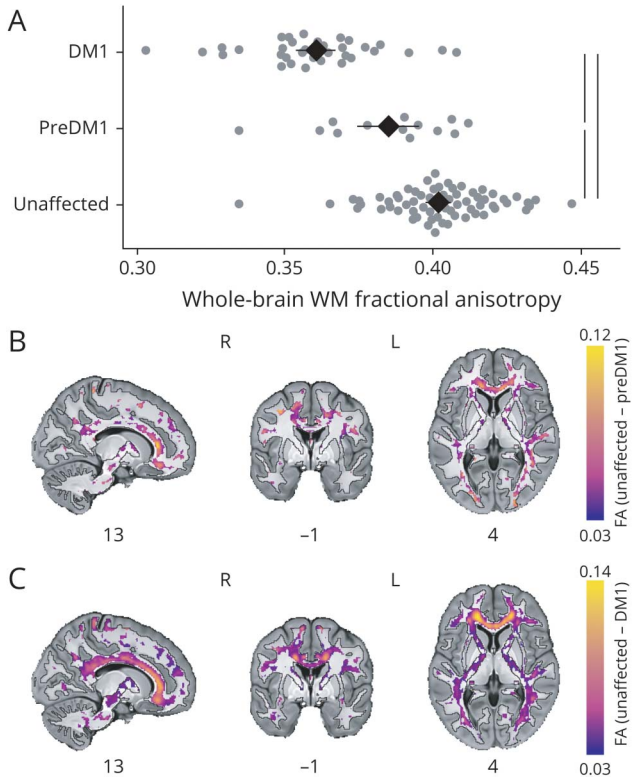
Apathy

The Apathy Evaluation Scale (AES) was used to determine self-reported degree of apathy.[39] The AES includes 18 items that are rated on a 4-point Likert scale. Items were summed to create a total score, where higher scores represent increased apathy.

Statistical Analysis

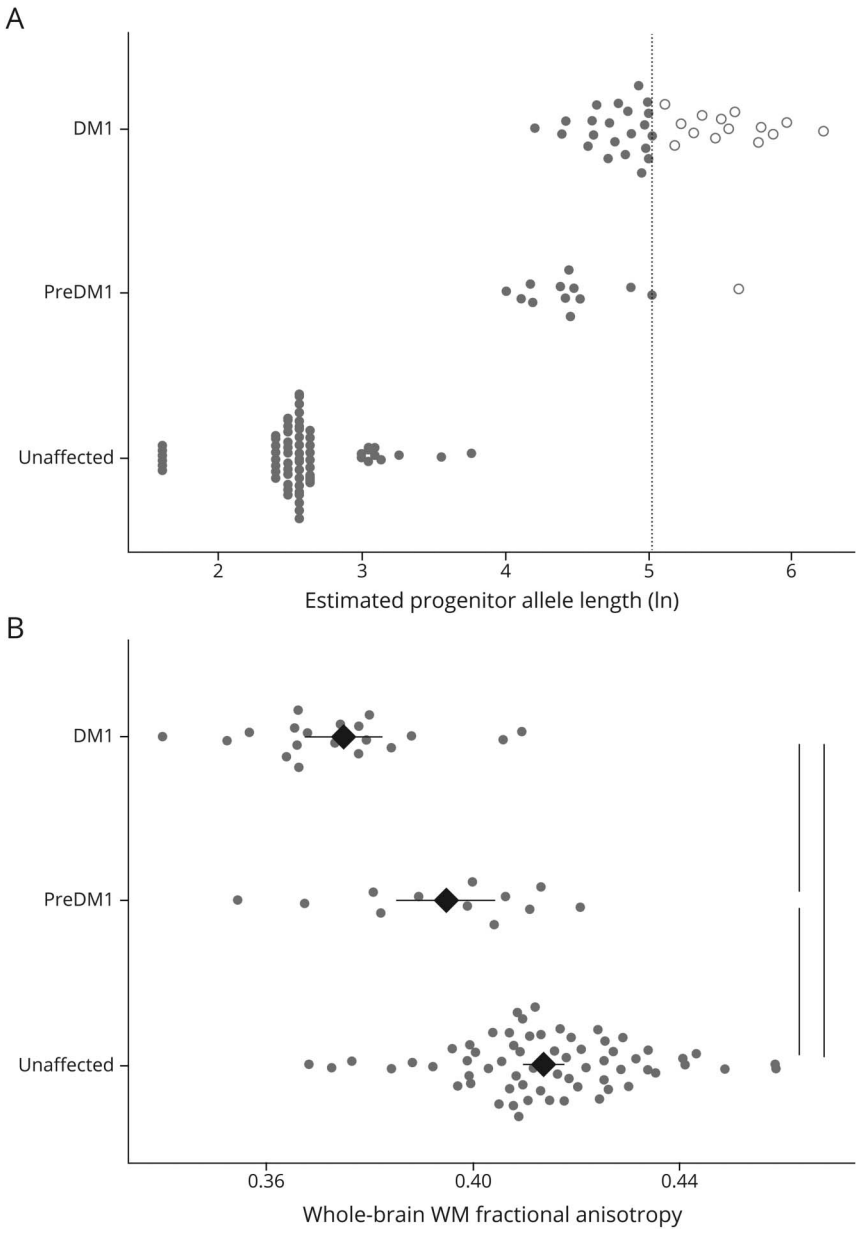
Demographic characteristics of the DM1 group and the control group were summarized with descriptive statistics.

Figure 1 WM FA Across Groups



Panel A shows that whole-brain WM FA is shown on the x-axis across groups (controls, PreDM1, and manifest DM1). Estimated marginal means are represented as diamonds with associated 95% confidence limits. Small circles represent individual observations. Significant differences between groups at $p < 0.05$ are marked with black, vertical bars. Whole-brain WM FA in PreDM1 was intermediate between that of control individuals and patients with manifest DM1. Panel B shows a voxel-wise map of FA differences between the control group and PreDM1 group. Panel C shows FA differences between the control group and the manifest DM1 group. DM1 = myotonic dystrophy type 1; FA = fractional anisotropy; PreDM1 = presymptomatic phase of DM1; WM = white matter.

Figure 2 ePAL Characteristics of Subset of Patients With DM1



Panel A shows the distribution of the natural log of ePAL (x-axis) across groups (y-axis). Individuals with ePAL (estimated progenitor allele length) greater than 125 repeats were excluded (manifest DM1 = 14; PreDM1 = 1), resulting in a group of 12 individuals with PreDM1 and 22 individuals with manifest DM1with comparable ePAL repeats. The dotted, vertical line represents the cutoff for creating subgroups with comparable ePAL. The open circles represent observations that were excluded from the subset analysis. Panel B shows whole-brain WM FA on the x-axis and group on the y-axis. Estimated marginal means are shown as diamonds with associated 95% confidence limits. The analyses included participants with DM1 with comparable ePAL repeats. The findings recapitulate those of the full sample: cerebral FA of the PreDM1 group is intermediate between that of controls and individuals with manifest DM1. The vertical bars highlight pairwise comparisons that were statistically significant at $p < 0.05$. DM1 = myotonic dystrophy type 1; ePAL = estimated progenitor allele length; PreDM1 = presymptomatic phase of DM1; WM = white matter.

Group differences in functional outcomes and WM FA values were examined using a linear mixed effects framework, where the random effect of family and fixed effects of group controls vs PreDM1 vs manifest DM1, age, and sex were included in each model. Wald tests were applied to assess effects of grouping variables with more than 2 levels, and the false discovery rate (FDR) was applied to account for multiple comparisons.[40] Results were displayed as estimated marginal means (EMMs) or as the difference in EMM ($EMM_{difference}$). The age*ePAL product was computed and examined in relationship to whole-brain WM FA within individuals with PreDM1 and in DM1.

Data Availability

Data can be shared on reasonable request.

Results

Sample

The sample included 68 control individuals (33.8% male), 13 individuals with PreDM1 (46.2% male), and 37 individuals with manifest DM1 (29.7% male; table 1). There were fewer males than females ($\chi^2_{(1)} = 12.237$, $p = 0.0005$); however, the sex distribution was similar across groups ($\chi^2_{(2)} = 1.159$, $p = 0.560$). Age at evaluation and education were also comparable across groups ($F_{(2,115)} = 0.66$, $p = 0.519$; $F_{(2,115)} = 0.27$, $p = 0.766$, respectively). ePAL was significantly longer in the manifest DM1 group relative to the PreDM1 group ($X_{(2)}^2 = 86.98$, $p = 7.9 \times 10^{-5}$). One individual with PreDM1 and 4 individuals with DM1 were identified as having a variant repeat.

Table 2 Functional Outcomes Across Groups

	Main group effect[a]			Controls–PreDM1		Controls–DM1		PreDM1–DM1	
	$\chi^2_{(2)}$	*p* Value	p_{FDR} Value	EMM_{diff}	95% CI	EMM_{diff}	95% CI	EMM_{diff}	95% CI
WRAT—Scaled Score	9.59	0.008	0.05	3.10	−3.30 to 9.50	7.60	2.60 to 13.00	4.50	−1.30 to 10.00
Apathy Self-Score	25.70	<0.001	<0.001	−1.50	−4.90 to 2.00	−6.10	−8.60 to 3.70	−4.70	−8.20 to 1.10
Verbal comprehension	9.84	0.007	0.05	1.90	−4.50 to 8.20	7.30	2.60 to 12.00	5.40	−0.98 to 12.00
Perceptual reasoning	30.90	<0.001	<0.001	−3.90	−11.00 to 3.40	13.00	7.60 to 18.00	17.00	8.80 to 24.00
Working memory	16.04	0.0003	0.002	4.60	−3.60 to 13.00	11.00	5.70 to 17.00	6.60	−2.10 to 15.00
Processing speed	18.93	<0.001	0.0005	0.43	−7.40 to 8.20	12.00	6.10 to 17.00	11.00	2.90 to 19.00
Full-Scale IQ	29.36	<0.001	<0.001	1.10	−5.90 to 8.00	13.00	8.00 to 18.00	12.00	4.50 to 19.00
Pegboard	16.61	<0.001	0.001	−2.30	−11.00 to 6.50	−12.00	−18.00 to 6.30	−10.00	−19.00 to 0.68
Finger tapping	40.48	<0.001	<0.001	5.70	0.51 to 11.00	11.00	7.80 to 15.00	5.60	0.11 to 11.00
Grip strength	41.99	<0.001	<0.001	4.80	−1.90 to 11.00	15.00	10.00 to 19.00	9.90	2.80 to 17.00
Sleep quality	1.78	0.41	1	−0.61	−2.20 to 1.00	−0.71	−1.80 to 0.40	−0.10	−1.80 to 1.60
Hypersomnolence	64.07	<0.001	<0.001	−1.70	−3.10 to 0.35	−3.80	−4.80 to 2.90	−2.10	−3.50 to 0.60

Abbreviations: CI = confidence interval; DM1 = myotonic dystrophy type 1; EMM_{diff} = difference of estimated marginal mean; FDR = false discovery rate; PreDM1 = presymptomatic phase of DM1; WRAT = Wide Range Achievement Test.
[a] Represents summary statistics for group coefficient in the model.

White Matter FA

The PreDM1 group exhibited an intermediate level of WM FA abnormality: whole-brain FA was lower relative to controls (EMM_{PreDM1} = 0.39, $EMM_{control}$ = 0.42, $EMM_{difference}$ = 0.02, $p < 0.001$), but the PreDM1 group had significantly higher FA than did individuals with manifest DM1 (EMM_{DM1} = 0.37, $EMM_{difference}$ = 0.02, $p < 0.001$; figure 1A). On average, whole-brain WM FA in the PreDM1 group was ∼6% lower than that of the control group and ∼5% higher than the manifest DM1 group. Figure 1B highlights voxel-wise FA differences between the control group and PreDM1 and between manifest DM1 and controls (figure 1C). The pattern for both is widespread changes with the greatest changes being in frontal regions. Group differences between regional WM FA are shown in figure e-2 (links.lww.com/NXG/A406). Similar to the voxel-wide analysis, most regions are affected with the anterior aspects of the corpus callosum (genu) having the highest level of abnormality.

Note that removal of the 5 individuals (PreDM1 = 1; DM1 = 4) with variant repeats did not result in significant changes (controls vs PreDM1: $EMM_{difference}$ = 0.02, controls vs DM1 = 0.04, PreDM1 vs DM1 = 0.02).

To explore the potential impact of differences in ePAL between PreDM1 and manifest DM1, analyses were repeated in a subset of patients with DM1 with comparable ePAL (figure 2A; PreDM1 = 12 [mean age = 49.55 years, SD = 14.99]; manifest DM1 = 22 [mean age = 47.95 years, SD = 9.26]). As with the full sample, the PreDM1 group exhibited lower whole-brain WM FA than the control group ($EMM_{difference}$ = 0.019, 95%, $p < 0.001$) and higher whole-brain WM FA than the manifest DM1 group ($EMM_{difference}$ = 0.020, p = 0.002; figure 2B).

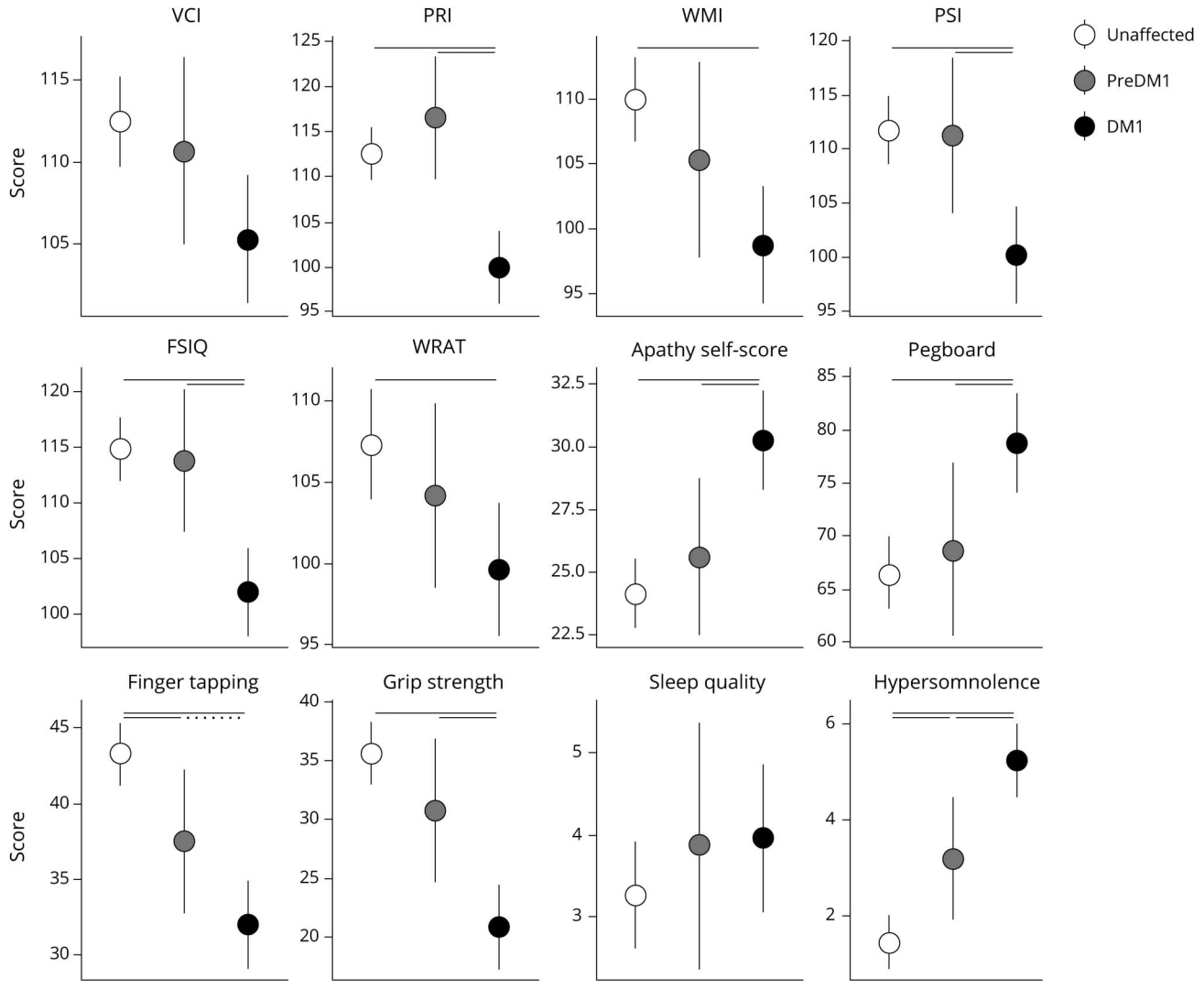
Functional Outcomes

Group differences were significant for all measures, except verbal comprehension and sleep quality (all, $p_{FDR} < 0.05$; table 2). In general, the PreDM1 group was intermediate between the control group and manifest DM1 (figure 3). Significant differences between PreDM1 and controls were noted for finger tapping ($EMM_{difference}$ = 5.70, p = 0.03) and hypersomnolence ($EMM_{difference}$ = −1.70, p = 0.01). Differences between PreDM1 and manifest DM1 were statistically significant for finger tapping ($EMM_{difference}$ = 5.60, p = 0.05) and hypersomnolence ($EMM_{difference}$ = −2.10, p = 0.006). Comparisons between the PreDM1 and the manifest DM1 group also showed significant differences on other functional measures (table 2), including apathy, Perceptual Reasoning Index scores, Processing Speed Index scores, Full-Scale IQ, Pegboard, and grip strength. The manifest DM1 consistently had poorer outcomes than did the PreDM1 group. Differences between controls and individuals with manifest DM1 were all significant (all, $p < 0.01$), except for sleep quality (p = 0.91; table 2 and figure 3).

Association Between WM FA and Proxy for Disease Burden

The age*ePAL product was computed as a proxy for disease burden, and its association with whole-brain WM FA was explored within individuals with PreDM1 and in DM1.

Figure 3 Functional Outcomes Across Groups



Each panel lists the functional measure at the top, with scores on the y-axis for controls (white), PreDM1 (gray), and manifest DM1 (black). Estimated marginal means and associated 95% confidence limits are shown. The horizontal lines highlight pairwise comparisons that were statistically different at $p < 0.05$. DM1 = myotonic dystrophy type 1; FSIQ = Full-Scale IQ; PreDM1 = presymptomatic phase of DM1; PRI = perceptual Reasoning Index; PSI = Processing Speed Index; VCI = Verbal Comprehension Index; WMI = Working Memory Index; WRAT = Wide Range Achievement Test.

Whole-brain WM FA was significantly predicted by age*ePAL in the PreDM1 group ($t_{(10)} = -2.87$, $p = 0.02$), suggesting that a large age*ePAL product was significantly associated with lower whole-brain WM FA (figure 4). In contrast, the age*ePAL product did not significantly predict whole-brain WM FA among individuals with DM1 ($t_{(29)} = -1.22$, $p = 0.2$; figure 4).

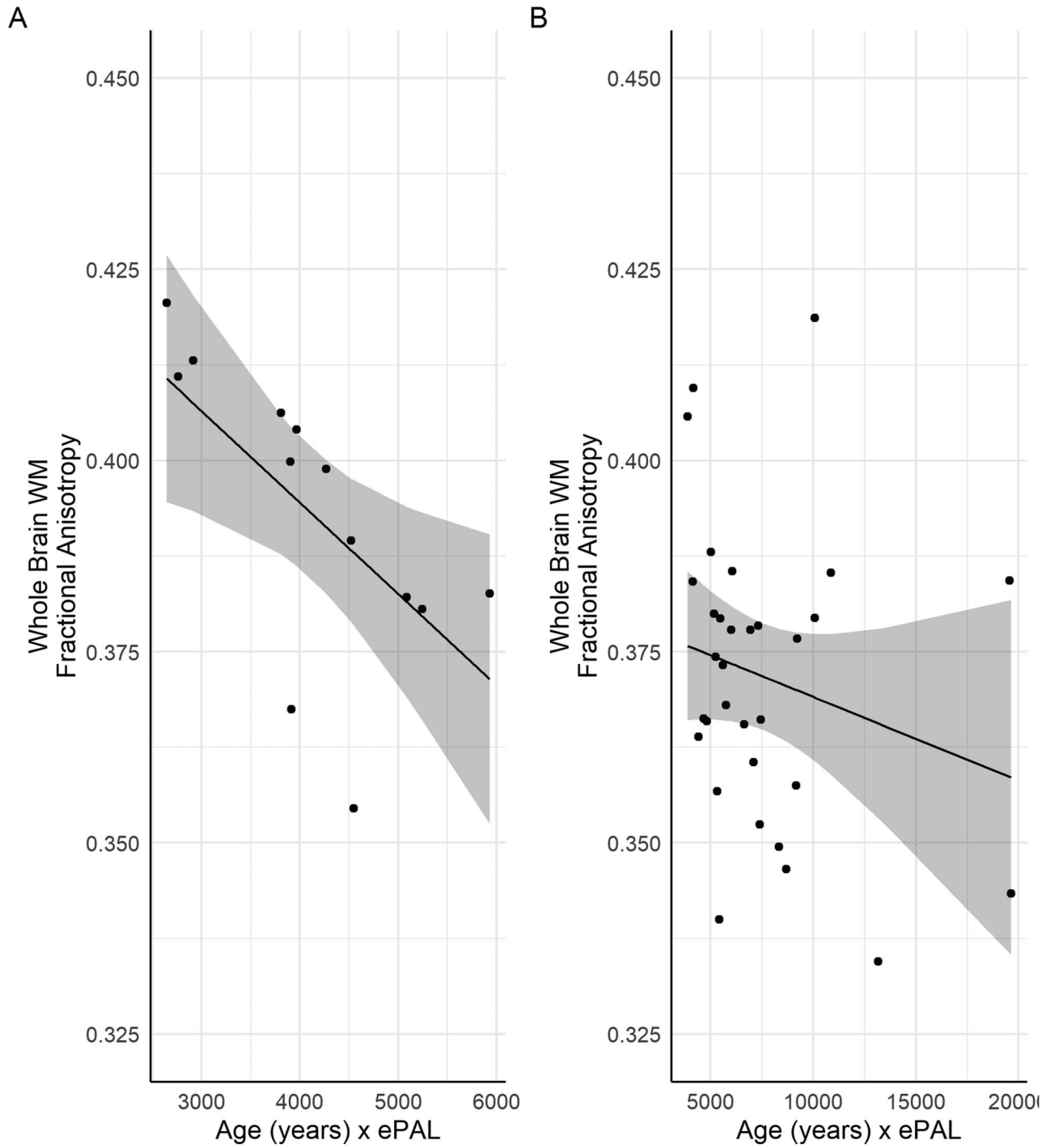
Discussion

In almost all measures, we found that the PreDM1 group was generally intermediate between healthy controls and individuals with manifest DM1. In particular, compared with controls, subjects with PreDM1 had significantly (1) lower brain FA; (2) poorer finger-tapping scores; and (3) higher self-ratings of hypersomnolence. These findings support the notion that among DM1 mutation carriers, changes in the brain, fine motor skills, and sleep may precede the onset of the classic clinical motor signs.

Premanifest DM1 was defined based on the absence of motor signs and symptoms as measured with the MIRS, which is commonly used for monitoring DM1 stage and progression. Although our definition did not encompass nonmuscular symptoms that are known to be associated with DM1 (e.g., cataracts),[41] a precise definition of disease manifestation in DM1 is challenging given the multisystemic nature of the disease. Nonetheless, muscle impairment remains a key defining feature of DM1, making MIRS a useful proxy for disease manifestation.

Reduced WM FA is one of the most reproducible findings in the DM1 literature,[12] and we showed that reductions in WM

Figure 4 Relationship Between ePAL*Age Product and Whole-Brain WM FA Among Individuals With DM1 and PreMD1



Panel A shows the relationship between age*ePAL product (x-axis) and whole-brain WM FA (y-axis) for the PreDM1 group, and panel B shows the same relationship for individuals with manifest DM1. DM1 = myotonic dystrophy type 1; ePAL = estimated progenitor allele length; FA = fractional anisotropy; PreDM1 = presymptomatic phase of DM1; WM = white matter.

FA precede clinical motor signs and symptoms associated with DM1. Moreover, we noted that an estimate of disease burden, age*ePAL product, was highly predictive of FA measures in the PreDM1 sample—those with the highest disease burden (a proxy to time to onset) had the lowest FA values. These results suggest that WM FA may be useful in tracking disease progress before clinical symptoms parallel to the way striatal volume tracks and predicts motor onset in HD.[42] The age*ePAL did not predict FA in the manifest phase, which could mean that by the time of motor onset, FA has declined so far that there may be a floor effect for predicting further change using this index. The present sample of

manifest DM1 had a median MIRS score of 2, indicating that as a group, these patients were very early in the course of disease, yet their WM FA was a full 10% lower than healthy controls. Our novel estimate of disease burden requires further investigation to establish its utility in predicting disease onset.

Individuals with PreDM1 exhibited significantly more difficulty with the finger-tapping test than did controls, suggesting that this quantitative measure of fine motor skill may be quite sensitive to early brain changes in addition to primary muscle dysfunction. Abnormalities in similar finger-tapping tasks also are reported as some of the earliest changes in individuals with PreHD and speeded finger-tapping paradigms appear particularly useful in detecting such changes in motor function.[43] Evaluation of fine motor skills among individuals in premanifest stages of DM1 will be important in determining markers of disease progression.

Hypersomnolence also appeared to precede muscle impairment. Although this is a self-reported measure and not a quantitative assessment, excessive daytime sleepiness has been considered one of the most troublesome and disabling features of the disease. Future studies might involve monitoring of objective measures of wakefulness such as using monitors that track movement/activity or direct assessment of EEG.

Our findings should be considered with several limitations. As noted previously, our definition of PreDM1 is limited to clinical motor signs and symptoms. Some subtle manifestations of clinical symptoms may not have been detected with the clinical examination we used to determine a patient's status. Second, the sample included a small number of premanifest individuals with DM1, limiting statistical power. DM1 being a rare disorder, it is challenging to recruit a large sample at a single institute. Multisite efforts are required to gain insight into CNS involvement in DM1. Third, ePAL differed significantly between the PreDM1 group and the manifest DM1 group. This difference could be related to participation bias, where patients who are healthy enough to participate in research are also likely less affected by the disease. Limiting the analyses to DM1 groups with comparable ePAL recapitulated the pattern observed in the entire sample, suggesting that the observed differences between PreDM1 and manifest DM1 were not explained by ePAL differences alone. Fourth, our study design was cross-sectional, and longitudinal studies evaluating changes in brain structure and function are essential for understanding disease progression. Longitudinal assessment will be particularly important in establishing if FA, speeded finger tapping, and hypersomnolence are useful in predicting motor onset among premanifest patients.

The present study identified brain and functional changes in premanifest DM1 as defined by the absence of clinically determined motor symptoms. Further studies are needed to replicate and extend our findings.

Disclosure

E. van der Plas, T.R. Koscik, V. Magnotta, and S.A. Cumming declare no competing interests. D. Monckton: within the last 3 years, D. Monckton has been a scientific consultant and/or received an honoraria/stock options from AMO Pharma, Charles River, Vertex Pharmaceuticals, Triplet Therapeutics, LoQus23, and Small Molecule RNA. D. Monckton also had/has research contracts with AMO Pharma and Vertex Pharmaceuticals. L. Gutmann and P. Nopoulos declare no competing interests. Go to Neurology.org/NG for full disclosures.

Study Funding

This work was supported by the NINDS (R01 NS094387, P. Nopoulos). The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Publication History

Received by *Neurology: Genetics* September 1, 2020. Accepted in final form January 22, 2021.

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Name	Location	Contribution
Ellen van der Plas, PhD	University of Iowa Hospital & Clinics	Contributed to data preparation; analyzed the data; and drafted the manuscript
Timothy R. Koscik, PhD	University of Iowa Hospital & Clinics	Conducted statistical analyses and prepared tables and figures
Vincent Magnotta, PhD	University of Iowa Hospital & Clinics	Implemented MRI acquisition protocol and supervised the technologists who scanned participants
Sarah A. Cumming, PhD	University of Glasgow, United Kingdom	Conducted the genetic analyses and reviewed the manuscript and provided critical revisions
Darren Monckton, PhD	University of Glasgow, United Kingdom	Supervised the genetic analyses and reviewed the manuscript and provided critical revisions
Laurie Gutmann, MD	University of Iowa Hospital & Clinics	Conceptualized the study and reviewed the manuscript and provided critical revisions
Peggy Nopoulos, MD	University of Iowa Hospital & Clinics	Conceptualized the study and reviewed the manuscript and provided critical revisions

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Neurol Genet 2021;7;
DOI 10.1212/NXG.0000000000000577