Increased risk for recurrent major depression in DYT1 dystonia mutation carriers

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Abstract—*Background:* Prior studies suggest that dystonia is comorbid with affective disorders. This comorbidity could be a reaction to a chronic debilitating disorder or expression of a predisposing gene. The authors took advantage of the identification of a gene for dystonia, DYT1, to test these alternative explanations. *Methods:* The authors administered a standardized psychiatric interview to members of families with an identified DYT1 mutation. The authors classified family members into three groups: mutation carriers with dystonia (manifesting carriers; n = 96), mutation carriers without dystonia (non-manifesting carriers; n = 60), and noncarriers (n = 65). *Results:* The risk for recurrent major depressive disorder was increased in both non-manifesting carriers (RR = 4.95, CI = 1.72 to 14.29) and manifesting carriers (RR = 3.62, CI = 1.00 to 10.53) compared with noncarriers. Mutation carriers also had earlier age at onset of recurrent major depressive disorder than noncarriers. The severity of motor signs was not associated with the likelihood of recurrent depression. Mutation carriers did not have an increased risk for other affective disorders, such as single major depression or bipolar disorder. *Conclusions:* Early-onset recurrent major depression is associated with the DYT1 GAG mutation and this association is independent of motor manifestations of dystonia. These findings suggest that early-onset recurrent depression is a clinical expression of the DYT1 gene mutation.

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The DYT1 gene on chromosome 9q34 is a major cause of childhood and adolescent onset primary dystonia.[1] A single mutation, a GAG deletion resulting in the loss of a glutamic acid residue in the encoded protein, TorsinA,[1] accounts for all reported DYT1 associated primary dystonia.[2] The clinical manifestations of this mutation range from mild focal dystonia usually affecting an arm to generalized dystonia involving limbs, axial, and even cranial muscles.[3] Penetrance is estimated at only 30%; thus most mutation carriers are clinically normal, or at least unaffected with overt signs of dystonia.[4,5] Previous studies in individuals with dystonia have reported an increase of psychiatric symptoms, particularly affective disorders.[6-9] The cause of this association is unknown; it could be a reaction to a chronic debilitating disorder or an expression of a predisposing gene. We took advantage of the identification of the DYT1 gene to determine if affective disorders are another manifestation of the mutation. We assessed whether affective disorders occurred more commonly in carriers, including carriers not manifesting dystonia, compared to noncarriers by examining these disorders in members of DYT1 families.

Subjects and methods. *Participants.* Subjects were recruited from families participating in previous genetic studies of dystonia and found to harbor the DYT1 GAG deletion.[5,10] The study was approved by institutional review boards; all subjects gave informed consent to participate. The methods for recruitment have been described previously.[5] Each subject was classified as having definite dystonia, probable dystonia, possible dystonia, no dystonia, or unrateable. These classifications were made blinded to genotype.[4,11] Subjects were classified as manifesting dystonia if they had definite or probable dystonia. We included probable because this category includes signs consistent with mild dystonia that could be symptomatic. Non-manifesting dystonia included possible and no dystonia. We classified individuals with possible dystonia as unaffected (noncarriers or non-manifesting) because muscle contractions were only remotely suggestive of dystonia and not producing symptoms, e.g., unusual hand grip with mild excess hand tension but normal flowing handwriting, increased blinking with no flurries or sustained contractions.[11]

For the present study, we excluded subjects younger than 18 years and those categorized as unrateable. Only at risk family members were included (i.e., none were married-in and all were mutation carriers or first-degree noncarrier relatives of mutation carriers). We divided the sample into manifesting carriers (MC),

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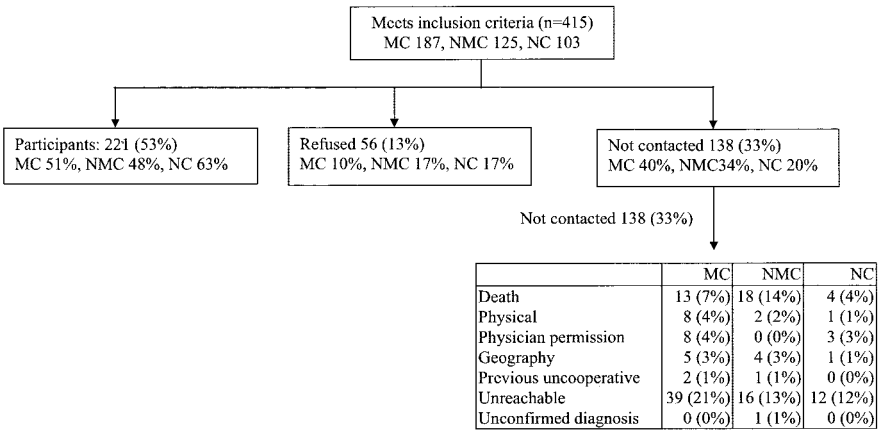

	MC	NMC	NC
Death	13 (7%)	18 (14%)	4 (4%)
Physical	8 (4%)	2 (2%)	1 (1%)
Physician permission	8 (4%)	0 (0%)	3 (3%)
Geography	5 (3%)	4 (3%)	1 (1%)
Previous uncooperative	2 (1%)	1 (1%)	0 (0%)
Unreachable	39 (21%)	16 (13%)	12 (12%)
Unconfirmed diagnosis	0 (0%)	1 (1%)	0 (0%)

Figure 1. Breakdown of recruitment categories by the three carrier groups. MC = manifesting carriers; NMC = non-manifesting carriers; NC = noncarriers.

non-manifesting carriers (NMC), and noncarriers (NC) of the DYT1 mutation. Among MC, we rated dystonia as severe if it was generalized or multifocal in distribution and mild if it was segmental or focal.[3] All NC were non-manifesting as none of them had probable or definite dystonia.

A total of 415 individuals met criteria for inclusion in this study (187 MC, 125 NMC, and 103 NC). These individuals were re-contacted by telephone and asked to participate. Individuals who consented to participate were asked if they had undergone genetic testing and whether they knew their carrier status, and were then scheduled for a telephone interview. We attempted to reach each individual at least seven times, at different times of the day and weekends, and if we could not locate them, searched telephone and internet databases for new addresses and phone numbers. The interviewers were blind to genetic status and to study hypotheses.

Measures. Independent variable. To determine DYT1 mutation carrier status, DNA was extracted from whole blood following standard protocols. We used published primers, 6418 and 6419,[1] for PCR amplification across the critical region of the DYT1 mutation. PCR products were resolved in a denaturing 6% polyacrylamide gel and visualized by silver staining.

Dependent variables. Trained interviewers, blind to the individual's position in the pedigree and carrier status, administered the computerized version of the Composite International Diagnostic Interview (CIDI)–WHO version (http://wwwlive.who.ch/msa/cidi/computerizedcidi.htm) via telephone. The CIDI is a comprehensive, fully standardized diagnostic interview used to assess psychiatric symptomatology in epidemiologic studies[12,13] and versions have been administered over the telephone.[14,15]

Affective disorders. We used the lifetime version of the CIDI to assess whether an individual's symptoms ever met Diagnostic and Statistical Manual of Mental Disorders–IV criteria for various affective disorders. Five categories of lifetime prevalence of affective disorders were included: any affective disorder (defined as any major depressive disorder, dysthymia, or bipolar disorder), any major depressive disorder (any MDD) (defined as single episode or recurrent MDD), single episode MDD, recurrent MDD (defined as having more than one episode of depression), and bipolar disorder. We analyzed recurrent MDD separately because evidence suggests it is more familial.[16,17]

Analysis. We first compared carriers (both MC and NMC) with NC. Next, to exclude a difference related to symptoms of dystonia, we separately analyzed NMC with NC, restricting the comparison to individuals without dystonic symptoms. Last, we analyzed MC with NC including an examination of potential confounding by severity. Analyses were conducted using a clustered Cox proportional hazards model using STATA statistical software.[18] We used the cluster option because of potential clustering of the data by family membership, because more than one member of a family was included.[19-21]

Results. *Study group.* A total of 221 of 415 (53.3%) individuals meeting criteria participated (96 MC, 60 NMC, and 65 NC). The nonparticipants included 56 (13%) who refused to participate, and 138 (33%) who could not be contacted (see figure 1 for recruitment rates by comparison group). The 138 individuals who could not be contacted included several subgroups: unreachable (48.6%), death since previous participation, physical limitation, denial of permission to contact from physician, residence overseas (geography), previous refusal to participate, unconfirmed diagnosis.

The three comparison groups did not differ significantly in refusal rates or in the proportion unreachable after numerous attempts, although a somewhat higher proportion of MC was unreachable and a lower proportion refused. Compared to participants, subjects who refused were less likely to be female (47.2% nonparticipants vs 54.3% participants) or Jewish (56.6% nonparticipants vs 63.3% participants), and were older (mean age nonparticipants 53 years vs participants 48 years), but none of these differences was significant.

Table 1 shows the demographic characteristics of the participating groups. Compared with NC, the NMC were older, more likely to be Jewish, less likely to have a college education, and had smaller families with fewer affected family members. The MC also had smaller families and fewer family members with dystonia than the NC. Carrier status was not related either to sex or to genetic distance from an affected relative.

Tests of hypotheses. *All carriers and NC.* Our first analysis compared all carriers (n = 156) with NC (n = 65). Only two subjects, one NMC and one NC, met criteria for bipolar disorder. Therefore, bipolar disorder was not included as a separate diagnostic category, but was included as part of any affective disorder. In the univariate analysis (table 2), the risks were not increased in carriers compared with NC for any affective disorder, any MDD, or single MDD. The risk for recurrent MDD was three times higher in carriers compared to NC, although this increased risk did not reach significance. In the multivariate analysis, adjusting for potential confounders including ethnicity, age, number of affected family members, and family size, singly or in combination, did not appreciably affect the risks for any affective disorder, any MDD, or single MDD. However, for recurrent MDD (table 3), adjustment for the number of affected family members led to increased risk. Additional adjustment for ethnicity, age, education, and family size did not appreciably alter the relative risks. Adding a variable to the model indicating whether a subject manifested dystonia (manifesting vs non-manifesting)

Table 1 *Comparison of demographic variables among manifesting carriers, non-manifesting carriers, and noncarriers*

Characteristics	Manifesting carriers, n = 96	Non-manifesting carriers, n = 60	Noncarriers, n = 65
Sex			
Male	49 (51.0)	24 (40.0)	28 (43.1)
Female	47 (49.0)	36 (60.0)	37 (56.9)
Ethnicity			
Jewish	59 (61.5)	44 (73.3)*	37 (56.9)
Non-Jewish	37 (38.5)	16 (26.7)	28 (43.1)
Education			
<College graduate	47 (49.0)	35 (58.3)*	31 (47.7)
College graduate	49 (51.0)	25 (47.7)	34 (52.3)
Genetic distance from affected relative			
>1st degree relative		11 (18.3)	9 (13.8)
1st degree relative		49 (81.7)	56 (86.2)
Age at interview, y†			
<49	52 (54.2)	22 (36.7)*	38 (58.5)
≥49	44 (45.8)	38 (63.3)	27 (41.5)
Number affected in family†			
<5 affected members	67 (69.8)*	39 (65.0)*	33 (50.8)
≥5 affected members	29 (30.2)	21 (35.0)	32 (49.2)
Family size*			
<7 members	62 (64.6)*	34 (56.7)*	25 (38.5)
≥7 members	34 (35.4)	26 (43.3)	40 (61.5)

Values are n (%).

* Significantly different from noncarrier group ($p < 0.05$, from logistic regression).
† Variables categorized as bivariate for table clarity but are included as continuous in analyses.

showed that the increase in recurrent MDD was due to the DYT1 mutation (adjusted RR = 3.23, CI = 1.21 to 8.62) rather than the presence of dystonic symptoms (adjusted RR = 1.07, CI = 0.43 to 2.68).

NMC and NC. Our second analysis compared NMC (n = 60) with NC (n = 65). In the univariate analysis (see table 2), the risk was not increased in NMC compared with NC for any affective disorder, any MDD, or single MDD. As in the analyses comparing all carriers to NC, the risk for recurrent MDD was increased in NMC. In the multivariate analysis the risk for recurrent MDD (see table 3), but not other diagnoses, increased after adjusting for the number of family members with dystonia. Additional adjustment for ethnicity, age, education, and family size did not appreciably alter the relative risks.

MC and NC. Our third analysis compared MC (n = 96) with NC (n = 65). The pattern of association between the DYT1 mutation and various affective disorders in MC was comparable in magnitude to those in the above analyses. In the univariate analysis, the risk was not increased in MC compared with NC for any affective disorder, any MDD, or single MDD but was increased for recurrent

Table 2 *Comparison of unadjusted lifetime prevalence of DSM-IV affective disorders in carriers and noncarriers*

Disorders	Manifesting carriers, n = 96	Non-manifesting carriers, n = 60	Noncarriers, n = 65	All carriers vs noncarriers	Manifesting carriers vs noncarriers	Non-manifesting carriers vs noncarriers
Any affective disorder	26 (27.1)	18 (30.0)	14 (21.5)	1.04 (0.69–1.57)	1.07 (0.64–1.79)	0.90 (0.48–1.67)
Any major depression	26 (27.1)	17 (28.3)	11 (16.9)	1.30 (0.81–2.09)	1.38 (0.78–2.47)	1.08 (0.56–2.08)
Single major depression	13 (13.5)	9 (15.0)	8 (12.3)	0.68 (0.34–1.36)	0.74 (0.30–1.82)	0.58 (0.25–1.32)
Recurrent major depression	13 (13.5)	8 (13.3)	3 (4.6)	3.04 (0.97–9.50)	3.18 (0.89–11.40)	2.64 (0.84–8.29)

Values are n (%) or relative risk (95% CI), computed by Cox proportional hazards model adjusted for clustering by family.

DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, 4th ed.

Table 3 *Comparison of lifetime prevalence of recurrent major affective disorder in carriers and noncarriers*

Adjusted for	All carriers vs noncarriers	Manifesting carriers vs noncarriers	Non-manifesting carriers vs noncarriers
Sex	3.04 (0.97–9.53)	3.17 (0.89–11.32)	2.65 (0.84–8.36)
Ethnicity	3.15 (1.08–9.14)	3.17 (0.89–11.32)	3.56 (1.37–9.25)
Education	3.00 (0.98–9.15)	3.20 (0.94–10.89)	2.50 (0.78–8.05)
Number affected	3.37 (1.28–8.82)	3.22 (0.98–10.55)	4.95 (1.72–14.29)
Family size	3.05 (1.12–8.30)	3.10 (0.95–10.17)	3.12 (1.18–8.24)
Number affected and ethnicity	3.38 (1.30–8.78)	3.29 (1.01–10.72)	5.11 (1.79–14.59)
Number affected and education	3.28 (1.22–8.81)	3.04 (0.93–9.96)	5.11 (1.59–16.40)
Number affected and family size	3.21 (1.26–8.15)	3.08 (0.95–9.96)	4.84 (1.69–13.84)
Sex, ethnicity, education, number affected, family size	3.12 (1.20–8.10)	2.97 (0.95–9.29)	5.13 (1.65–15.93)

Values are relative risk (95% CI), computed by Cox proportional hazards model adjusted for clustering by family.

MDD (see table 2). This effect for recurrent MDD increased after adjusting for the number of family members with dystonia and ethnicity (see table 3). Also, there was no difference between MC and NMC in the risk for recurrent MDD (RR = 1.10, CI = 0.48 to 2.50).

Because recurrent MDD may be confounded by the severity of dystonia symptoms and signs, we assessed whether the risk of recurrent MDD differed among three groups with severe, mild, and probable dystonia. Severity was not related to risk for recurrent MDD (RR = 0.86, CI = 0.73 to 1.01 for each unit increase in severity).

Age at onset of MDD. The age at onset of recurrent MDD exhibited a bimodal distribution (early-onset $\leq$ 30 and late-onset $>$ 45 years). The prevalence of early-onset recurrent MDD was 11.5% (18/156) in carriers (12.5% in MC, 10.0% in NMC) and 1.5% (1/65) in NC. The prevalence of late-onset recurrent MDD was 1.9% (3/156) in carriers (1.0% in MC, 3.3% in NMC) and 3.1% (2/65) in NC. This bimodality is illustrated in figure 2.

Additional confirmatory analyses. Adjustment for the number of family members with dystonia increased the RR for recurrent MDD. We conducted further analyses to explore the reasons for this confounding. Initially we included this variable in the model because we hypothesized that families with more affected members might have greater psychological burden, resulting in increased risk of depression. This hypothesis proved to be incorrect. Table 4 shows the distribution of families by the total number of affected members they contained. Confounding by number of affected family members results from inclusion of a single family (Family Z), which contained a greater proportion of individuals who are NC and a greater proportion of individuals with recurrent MDD than do the other families. In Family Z, 15 individuals had dystonia. Among participating members, 3 were NMC and 11 NC. Four of the 14 participating family members (2 NMC/2 NC) had recurrent MDD (29%), while in all other families 6% of participating family members had recurrent MDD. Inclusion of this family reduces the association with recurrent MDD because the proportion of NC with recurrent MDD is higher in this family (2/11, 18%) than in the other noncarriers in the sample (n = 1/54, 2%). When Family Z is removed from the analysis, the univariate RR for recurrent MDD in the comparison of NMC with NC increases to 5.6 (95% CI = 0.65 to 47.13).

We classified subjects with possible dystonia (n = 29, 19 NMC, 10 NC) as non-manifesting in the present study. However, we questioned whether even these nonspecific asymptomatic features could influence the risk of recurrent MDD. Including this classification as a variable in the model (i.e., possible/unaffected) did not change the RR for recurrent MDD in the comparison of NMC to NC (4.63, 95% CI = 1.39 to 15.44).

Because 30% of the total sample is derived from three large families, we assessed whether the effect of the DYT1 mutation on recurrent MDD was restricted to the larger families (see table 4). In the comparison of NMC to NC, the magnitude of the association of the DYT1 mutation with recurrent MDD was elevated both in the three large families (univariate RR = 2.68, CI = 1.47 to 4.88; adjusted RR = 8.34, CI = 7.29 to 9.54) and the remaining 37 smaller families (univariate RR = 4.14, CI = 0.48 to 36.04; adjusted RR = 4.19, CI = 0.48 to 36.63). Next, to minimize the effect of the large families, we separated all of the

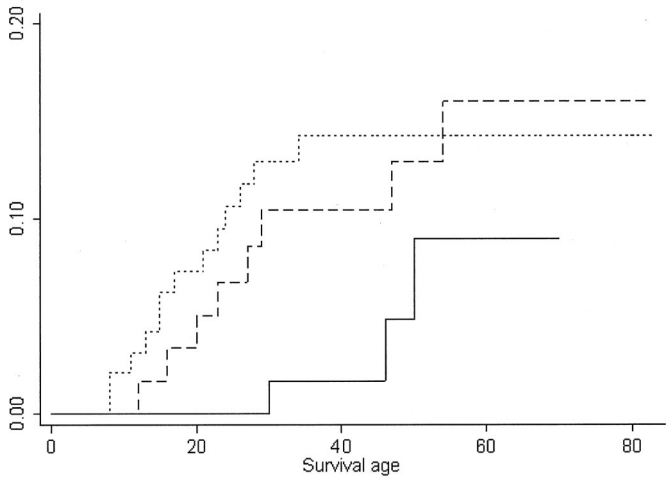

Figure 2. Kaplan Meier cumulative incidence estimates. Solid line = noncarrier; dotted line = manifesting carrier; dashed line = non-manifesting carrier.

Table 4 *Distribution of families by total number of family members with dystonia by carrier status irrespective of whether the affected individual participated in the present study*

No. affected in family	No. of families	MC	NMC	NC
1	19	13	9	6
2	20	21	13	14
3	10	15	9	4
4	6	18	8	9
5	2	4	5	5
7	1	2	3	3
9	2	14	10	13
15	1	9	3	11
Total	61	96	60	65

MC = manifesting carriers; NMC = non-manifesting carriers; NC = noncarriers.

families into sibships and analyzed the subset of sibships containing at least one NMC and at least one NC. This subset included 19 sibships that comprised 47 individuals from 10 families. In this analysis, the clustering was by sibship rather than family membership. In the comparison of NMC to NC, the association with recurrent MDD was not diminished either in univariate analysis (RR = 3.95, CI = 0.83 to 18.70) or after adjustment for the number of family members with dystonia (RR = 5.82, CI = 1.46 to 23.22).

One possible explanation for the increased risk of recurrent MDD in NMC than NC is that individuals knew their carrier status, and that this knowledge caused depression in NMC more than NC. However, in the comparison of NMC with NC, the effect of the DYT1 mutation on recurrent MDD was not reduced when we included as a variable whether the subject had undergone genetic testing (RR = 6.27, CI = 1.23 to 31.81) or by additionally including a variable indicating whether the subject was an obligate carrier (i.e., having both a parent or sibling and a child with dystonia) (RR = 6.69, CI = 1.31 to 34.17). Moreover, removing subjects who had undergone testing did not diminish the association with recurrent MDD either in univariate analysis (RR = 5.90, CI = 0.56 to 62.14) or after adjustment for the number of family members with dystonia (RR = 10.63, CI = 0.49 to 231.96).

Discussion. The findings of this study support the hypothesis that recurrent MDD is an independent expression of the DYT1 dystonia mutation and is not a result of having a chronic and stigmatizing illness. In an analysis in which no one exhibited symptoms of dystonia (i.e., comparing NMC and NC), NMC were over four times more likely than noncarriers to exhibit recurrent MDD. This association remained after adjustment for multiple factors that might influence risk for depression, including knowledge of genetic status. We also found that MC had the same increased risk of recurrent MDD as NMC and recurrent MDD was not more frequent in those with severe disease than in those with milder signs of dystonia. The finding of similar risks for recurrent MDD regardless of motor signs suggests that gene expression for psychiatric and motor symptomatology is independent and that depression is not a harbinger or consequence of motor manifestations.

A different gene predisposing to early-onset recurrent MDD is unlikely to explain the results of this study. This would occur only if DYT1 were closely linked to the other locus, and if the high-risk alleles at the two loci were associated in the population (i.e., in linkage disequilibrium). We found an increased risk of recurrent MDD in DYT1 carriers vs noncarriers in both Jewish (RR = 4.62, CI = 0.70 to 30.64) and non-Jewish (RR = 2.90, CI = 1.10 to 7.60) families. If the increased risk of recurrent MDD were due to a different gene, the risk-raising allele of this gene would be in linkage disequilibrium with the DYT1 mutation in both Jewish and non-Jewish families. In Jewish families, almost all DYT1 mutation carriers share a common haplotype around DYT1 on chromosome 9, so in that group, the haplotype could include a depression-causing allele at another locus. However, in non-Jews (and in the non-Jewish families included in this study) no common haplotype is found[1,22]; hence we would not expect to see linkage disequilibrium between a depression-causing allele and the DYT1 mutation.

Psychiatric expression of DYT1 appears to be limited to recurrent early-onset MDD. Carriers were not at increased risk for other affective disorders including bipolar disorder, single MDD, or a combination of any MDD, dysthymia, and bipolar disorder. An additional and unexpected finding was the early age at onset of recurrent MDD in mutation carriers. The early onset of MDD is entirely consistent with DYT1 expression where motor signs of dystonia also overwhelmingly begin by age 30 years.[3] It is also consistent with studies showing that the most familial (genetic) form of unipolar depression is early-onset recurrent MDD.[16,17]

The design of this study has a number of strengths. First it permitted us to distinguish between gene expression and reactive effects because we were able to compare psychiatric features in NMC and NC. In these groups no one exhibited signs of dystonia and all individuals were related to people with dystonia. Thus we could examine the effect of the mutation in two groups similarly exposed to the various factors that may lead to depression in DYT1 family members, e.g., survivor guilt, stress related to caring for affected family members, and embarrassment from public perception of the illness in their family. To exclude additional reactive effects resulting from knowledge of carrier status, we also repeated the analysis adjusting for knowledge of carrier status and excluding individuals who were aware of their carrier status. Second, this design, examining NMC and NC, eliminated the need to determine whether affective symptoms began before or after the onset of dystonia—an alternative, but difficult, approach to evaluating whether affective disor-

ders occur in response to having dystonia. Third, unlike the previous studies investigating the relationship between dystonia and psychopathology, this design only included individuals with one etiologic type of dystonia, the DYT1 mutation.

Our study also has limitations. Although our sample of DYT1 family members (221 total, 96 MC, 60 NMC, and 65 NC) is one of the largest described[23,24] it is only moderate in size. The comparison between NMC and NC included only 11 subjects (8 NMC/3 NC) with recurrent MDD. While statistically significant, these findings could be altered by misclassification of only a few people. However, the consistent finding of recurrent MDD in MC, the lack of relationship between dystonia severity and recurrent MDD, and differing age at onset of recurrent MDD in carriers vs noncarriers all strongly support the conclusion that this is an independent gene expression. We also had a relatively high nonparticipation rate. Roughly a third of the subjects meeting criteria for inclusion could not be contacted for various reasons including death, physical limitations, and residence overseas. Subjects who could not be reached after numerous attempts comprised the largest proportion, 49%, of this noncontacted group. However, the proportion in this group was similar with respect to gene status (21% MC; 13% NMC; 12% NC) suggesting that any potential bias would be toward the null hypothesis. Finally, because we restricted this study to families with DYT1 dystonia, the findings cannot be generalized to other dystonia subtypes.

The pathophysiologic mechanism by which the DYT1 mutation causes dystonia or recurrent MDD is unclear. TorsinA, the DYT1 protein product, shares sequence similarity with the functionally diverse AAA+ family of proteins that includes heat shock proteins, Clp proteases, and molecular chaperones.[1] Recent studies using models of alpha-synuclein[25] and polyglutamine aggregation[26] demonstrate that torsinA (or the *C elegans* related TOR-2) has suppressive effects on aggregation that are lost with mutated protein. TorsinA might work as a molecular chaperone in the management of protein misfolding, and the GAG deletion may alter neuronal response to stress induced changes in protein structure.[26] However, there is no evidence for degenerative brain changes in DYT1 and pathology, although limited, has detected only minor changes in striatal dopamine[27] and an increase in dopamine turnover.[28]

Studies of functional brain networks in DYT1 carriers are relevant to the current findings in supporting a broader view of DYT1 expression.[24] These studies found that DYT1 carriers, regardless of motor signs, have abnormal brain networks as detected by FDG PET with hypermetabolism of the lenticular nuclei, cerebellum, and SMA. This suggests a metabolic substrate that is associated with genotype regardless of clinical expression. Further, because neither dystonia, MDD, nor the combination is expressed in all mutation carriers, modifiers of DYT1 are implicated. Other genes or environmental effects may be interacting with DYT1 and its associated metabolic substrate to produce neurologic or psychiatric expression. Future studies may help identify the factors that contribute to DYT1 expression.

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