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Depression is one of the most prevalent and debilitating psychiatric disorders worldwide. Recently, we showed that both relatively short and relatively long cytosine–adenine–guanine (CAG) repeats in the huntingtin gene (HTT) are associated with an increased risk of lifetime depression. However, to what extent the variations in CAG repeat length in the other eight polyglutamine disease-associated genes (PDAGs) are associated with depression is still unknown. We determined the CAG repeat sizes of ATXN1, ATXN2, ATXN3, CACNA1A, ATXN7, TBP, ATN1 and AR in two well-characterized Dutch cohorts—the Netherlands Study of Depression and Anxiety and the Netherlands Study of Depression in Older Persons—including 2165 depressed and 1058 non-depressed individuals—aged 18–93 years. The association between PDAG CAG repeat size and the risk for depression was assessed via binary logistic regression. We found that the odds ratio (OR) for lifetime depression was significantly higher for individuals with >10, compared with subjects with ≤10, CAG repeats in both ATXN7 alleles (OR = 1.90, confidence interval (CI) 1.26–2.85). For TBP we found a similar association: A CAG repeat length exceeding the median in both alleles was associated with an increased risk for lifetime depression (OR = 1.33, CI 1.00–1.76). In conclusion, we observed that carriers of either ATXN7 or TBP alleles with relatively large CAG repeat sizes in both alleles had a substantially increased risk of lifetime depression. Our findings provide critical evidence for the notion that repeat polymorphisms can act as complex genetic modifiers of depression.
repeat expansion in exon 1 of the huntingtin (HTT) gene.\textsuperscript{13,14} Recently, we demonstrated that both relatively short and relatively large CAG repeats in the longer HTT allele are associated with lifetime depression, suggesting that repeat polymorphisms could also act as complex genetic modifiers of depression and account for part of its ‘missing heritability.’\textsuperscript{15}

Apart from Huntington disease, eight other polyglutamine disorders, all of which are neurodegenerative disorders, are frequently associated with considerable neuropsychiatric impairment (Table 1).\textsuperscript{16–35} These rare disorders result from relatively large repeat expansions in polyglutamine disease-associated genes (PDAGs). However, to what extent more common repeat length variations in these other PDAGs to depression is unknown. Hence, here we aimed to assess the contribution of CAG repeat length variations in these other PDAGs to depression susceptibility using data from two well-de

### MATERIALS AND METHODS

We genotyped eight PDAGs (ATXN1, ATXN2, ATXN3, CACNA1A, ATXN7, TBP, ATN1 and AR) in all participants with sufficient amounts of DNA available from blood samples of two well-characterized Dutch cohorts: The Netherlands Study of Depression and Anxiety (NESDA) and the Netherlands Study of Depression in Old Persons (NESDO).

#### Cohort 1

The NESDA is a cohort study among 2981 participants aged 18–65 years.\textsuperscript{36} The participants were recruited from the general population, general practices and mental health-care institutes. The sample included 378 depressed individuals (360 with MDD) and 132 healthy controls. The same methods for diagnosing depression were used as in the NESDA.\textsuperscript{38}

#### Genotyping

A polymerase chain reaction (PCR) was performed in a TProfessional thermocycler (Biometra, Westburg, Leusden, the Netherlands) with labelled primers flanking the CAG stretch of the PDAGs (Biolegio, Nijmegen, the Netherlands; Supplementary Table 1). The PCR was performed using 10 ng of genomic DNA, 1 × OneTaq mastermix (New England Biolabs, Ipswich, MA, USA, OneTaq Hot start with GC Buffer mastermix), 1 μl of primer Mix A or B (Supplementary Table 1) and Aqua B. Braun water to a final volume of 10 μl. The PCR was run with 27 cycles of 30 s, denaturation at 94 °C, 1 min of annealing at 60 °C and 2 min elongation at 68 °C, preceded by 5 min of initial denaturation at 94 °C. Final elongation was performed at 69 °C for 5 min. Every PCR included a negative control without genomic DNA and a reference sample of CEPH 1347-02 genomic DNA. The PCR products were run on an ABI 3730 automatic DNA sequencer (Applied Biosystems, Foster City, CA, USA) and analysed using the GeneMarker software version 2.4.0. (SoftGenetics, State College, PA, USA). For every analysis, we included three controls with known CAG repeat lengths for each PDAG to assure that every run was performed reliably. All assessments were made with cases and controls randomized on plates and blinding with respect to disease status information.

#### Statistical analysis

Binary logistic regression was used to assess whether CAG repeat sizes in the two alleles of each PDAG were associated with the risk of lifetime depression. For each PDAG, in an initial model, the presence of lifetime depression were used as in the NESDA.\textsuperscript{38}

### Table 1. Summary genotyped polyglutamine disease-associated genes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Disease</th>
<th>Protein</th>
<th>CAG repeat ranges</th>
<th>Allele</th>
<th>Mean</th>
<th>Median</th>
<th>N</th>
<th>Range</th>
<th>No. of intermediate</th>
<th>No. of pathological</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATXN1</td>
<td>SCA1</td>
<td>Ataxin-1</td>
<td>6–39</td>
<td>Short</td>
<td>29.22</td>
<td>29.00</td>
<td>3228</td>
<td>18–35</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Long</td>
<td>30.76</td>
<td>30.00</td>
<td>3228</td>
<td>26–39</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ATXN2</td>
<td>SCA2</td>
<td>Ataxin-2</td>
<td>14–32</td>
<td>Short</td>
<td>21.91</td>
<td>22.00</td>
<td>3236</td>
<td>14–24</td>
<td>0</td>
<td>0</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Long</td>
<td>22.35</td>
<td>22.00</td>
<td>3236</td>
<td>22–36</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ATXN3</td>
<td>SCA3</td>
<td>Ataxin-3</td>
<td>12–44</td>
<td>Short</td>
<td>18.96</td>
<td>20.00</td>
<td>3235</td>
<td>13–33</td>
<td>0</td>
<td>0</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Long</td>
<td>24.27</td>
<td>23.00</td>
<td>3235</td>
<td>13–49</td>
<td>1 (49)</td>
<td>0</td>
</tr>
<tr>
<td>CACNA1A</td>
<td>SCA6</td>
<td>CACNA1A</td>
<td>4–18</td>
<td>Short</td>
<td>10.52</td>
<td>11.00</td>
<td>3220</td>
<td>4–14</td>
<td>0</td>
<td>0</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Long</td>
<td>12.45</td>
<td>13.00</td>
<td>3220</td>
<td>4–22</td>
<td>0</td>
<td>1 (22)</td>
</tr>
<tr>
<td>ATXN7</td>
<td>SCA7</td>
<td>Ataxin-7</td>
<td>3–19</td>
<td>Short</td>
<td>10.04</td>
<td>10.00</td>
<td>2979</td>
<td>7–15</td>
<td>0</td>
<td>0</td>
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<td></td>
<td>Long</td>
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<td>2979</td>
<td>7–19</td>
<td>0</td>
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<tr>
<td>TBP</td>
<td>SCA17</td>
<td>TBP</td>
<td>25–43</td>
<td>Short</td>
<td>36.31</td>
<td>37.00</td>
<td>3238</td>
<td>27–39</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Long</td>
<td>37.89</td>
<td>38.00</td>
<td>3238</td>
<td>32–48</td>
<td>1 (44)</td>
<td>1 (48)</td>
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<tr>
<td>ATN1</td>
<td>DRPLA</td>
<td>Atrophin-1</td>
<td>3–38</td>
<td>Short</td>
<td>12.36</td>
<td>14.00</td>
<td>3228</td>
<td>5–22</td>
<td>0</td>
<td>0</td>
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<td></td>
<td>Long</td>
<td>15.47</td>
<td>15.00</td>
<td>3228</td>
<td>8–30</td>
<td>0</td>
<td>0</td>
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<tr>
<td>AR</td>
<td>SMBA</td>
<td>Androgen receptor</td>
<td>6–36</td>
<td>Short</td>
<td>20.80</td>
<td>21.00</td>
<td>3228</td>
<td>8–36</td>
<td>0</td>
<td>0</td>
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<td>Long</td>
<td>22.90</td>
<td>23.00</td>
<td>3228</td>
<td>8–36</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: CACNA1A, calcium channel, voltage-dependent P/Q type, α1A subunit; CAG, cytosine–adenine–guanine; DRPLA, dentatorubropallidoluysian atrophy; SBMA, spinal bulbar muscular atrophy; SCA, spinocerebellar ataxia; TBP, thymine-adenine-thymine-adenine (TATA) box-binding protein.
Table 2. The distribution of participants in three ATXN7 categories

<table>
<thead>
<tr>
<th>ATXN7 category</th>
<th>Allele</th>
<th>Mean</th>
<th>Range</th>
<th>Lifetime depression*</th>
<th>No lifetime depression*</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I^1</td>
<td>Short</td>
<td>9.94</td>
<td>7–10</td>
<td>1220</td>
<td>619</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>Long</td>
<td>10.00</td>
<td>7–10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Short</td>
<td>9.97</td>
<td>7–10</td>
<td>662</td>
<td>331</td>
<td>1.01 (0.86–1.20)</td>
</tr>
<tr>
<td></td>
<td>Long</td>
<td>12.18</td>
<td>11–19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Short</td>
<td>11.90</td>
<td>11–15</td>
<td>116</td>
<td>31</td>
<td>(1.26–2.85)^d</td>
</tr>
<tr>
<td></td>
<td>Long</td>
<td>12.54</td>
<td>11–18</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: I, both alleles of ATXN7 contain a CAG repeat number ≤ 10; II, the relatively longer ATXN7 allele contains a CAG repeat number > 10 and the relatively shorter allele contains a CAG repeat number ≤ 10; III, both alleles of ATXN7 contain a CAG repeat number > 10; CAG, cytosine–adenine–guanine; CI, confidence interval. ^Figures represent the number of subjects per ATXN7 category in the group with lifetime depression. †Figures represent the number of subjects per ATXN7 category in the group with no lifetime depression. *This category contains the largest number of subjects and was therefore chosen as the reference category for odds ratio calculation. ^dP < 0.01 by Fisher's exact test in comparison with the reference category.
Table 3. The distribution of participants in three TBP categories

<table>
<thead>
<tr>
<th>TBP category</th>
<th>Allele</th>
<th>Mean</th>
<th>Range</th>
<th>Lifetime depressiona</th>
<th>No lifetime depressionb</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Short</td>
<td>35.78</td>
<td>27–37</td>
<td>1462</td>
<td>716</td>
<td>1.00</td>
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<tr>
<td></td>
<td>Long</td>
<td>37.47</td>
<td>32–38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>Short</td>
<td>36.04</td>
<td>30–37</td>
<td>230</td>
<td>93</td>
<td>1.21 (0.94–1.57)</td>
</tr>
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<td></td>
<td>Long</td>
<td>39.30</td>
<td>39–48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Short</td>
<td>38.09</td>
<td>38–39</td>
<td>201</td>
<td>74</td>
<td>1.33 (1.00–1.76)</td>
</tr>
<tr>
<td></td>
<td>Long</td>
<td>39.28</td>
<td>39–44</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a, both TBP alleles contain a CAG repeat number < their median; b, the relatively longer TBP allele contains a CAG repeat number > the median and the relatively shorter TBP allele contains a CAG repeat number < the median; c, both TBP alleles contain a CAG repeat number = their median (median short allele = 37, median long allele = 38); d, figures represent the number of subjects per TBP category in the group with lifetime depression. e, this category contains the largest number of subjects and was therefore chosen as the reference category for odds ratio calculation. 

Figure 2. Odds ratio for lifetime depression per TBP category. The odds ratio for lifetime depression increases significantly when both the relatively shorter TBP allele and the relatively longer TBP allele exceed their median CAG repeat number (median short allele = 37, median long allele = 38). The group with both alleles being equal to or smaller than their medians was the largest and, therefore, is defined as the reference category. I, both TBP alleles contain a CAG repeat number < their median; II, the relatively longer TBP allele contains a CAG repeat number > the median and the relatively shorter TBP allele contains a CAG repeat number < the median; III, both TBP alleles contain a CAG repeat number = their median. Error bars indicate ± one s.e. *P < 0.05 by the Fisher’s exact test in comparison with the reference category. CAG repeat sizes in other PDAGs were not associated with risk of lifetime depression.

The number of CAG repeats in ATXN1, ATXN2, ATXN3, CACNA1A, ATN1 and AR were not associated with the risk of lifetime depression. Neither the main effect of the alleles, nor the interactions between the two alleles, or the quadratic terms, were significantly associated with the presence of lifetime depression in the combined cohort. As AR is located on the X-chromosome, we performed one analysis stratifying the data by gender and another analysis using only either the relatively short or the relatively long allele in the model. None of the two approaches demonstrated a significant association between CAG repeat number in AR and depression (Supplementary Table 3).

The effects of HTT, ATXN7 and TBP CAG repeat sizes are independent

In previous research, we demonstrated that both the main term of the longer HTT allele and the quadratic term of the longer HTT allele are also significantly associated with a diagnosis of lifetime depression. To assess the contribution of the CAG repeat polymorphisms in all PDAGs to depression risk, we examined the degree to which HTT, ATXN7 and TBP CAG repeat sizes explain depression heritability. To this end, we applied a multivariate model with the CAG repeat sizes in these three PDAGs as predictors. In addition, we adjusted for the effects of gender, age and education. We found that the parameter estimates as well as their associated statistical significances hardly changed, indicating that the effects of HTT, ATXN7 and TBP CAG repeat sizes on depression susceptibility are mutually independent (HTT long allele: β = −0.286, P = 0.018; HTT long allele quadratic term β = −0.006, P = 0.017; ATXN7 short allele: β = 0.210, P = 0.005; TBP short allele: β = −2.728, P = 0.001; TBP long allele: β = −2.566; P = 0.001; TBP interaction term: β = 0.072, P = 0.001). Inclusion of the CAG repeat sizes in HTT, ATXN7 and TBP in the model increased R² by 0.014 from the baseline model including only gender, age and level of education (from 0.024 to 0.038), indicating that the CAG repeat lengths in these PDAGs can account for an additional 1.4% of the genetic variation on the observed probability scale. We also derived the R² on the liability scale as described previously. Assuming that depression has a lifetime prevalence of ~15% in the Netherlands and adjusting for the oversampling of patients with depression in our cohort, the R² on the liability scale was 0.0191, indicating that CAG repeat size polymorphisms in HTT, ATXN7 and TBP together can account for ~ 1.9% of depression heritability.
The prevalence of intermediate and pathological PGDA alleles in total, four genotyped subjects had a CAG repeat number in the pathological range of a PDAG. One individual had a CAG repeat number of 22 in CACNA1A, one subject had a CAG repeat number of 48 in TBP and two people had a CAG repeat number of 33 and 36 in ATXN2 (Table 1). All four were depressed, but at the ages of 53 years for CACNA1A, 59 years for TBP, and 26 and 31 years for ATXN2, none had been diagnosed with the respective diseases (that is, SCA6, SCA17 and SCA2).

One person had a CAG repeat number in the longer TBP allele of 44, belonging to the intermediate range. This individual was also diagnosed with lifetime depression. Furthermore, one depressed individual had an intermediate CAG repeat number in the longer allele of ATXN3 (that is, 49 repeats). For ATXN1, ATXN7, ATN1 and AR all subjects had a CAG repeat number within the normal range (Table 1).

When we included the two depressed individuals with a CAG repeat length in the reduced penetrance range of HTT found previously,15 we observed a trend for a higher proportion of subjects with a CAG repeat in the intermediate or pathological range of a PDAG in the depressed group (P = 0.059).

DISCUSSION

To our knowledge, this is the first study assessing the influence of CAG repeat size variations in the normal range of PDAGs—other than HTT—on the risk of lifetime depression. Interestingly, we found an association between the presence of lifetime depression and the CAG repeat length in two PDAGs, that is, ATXN7 and TBP. The main relationship we found was that when the CAG repeat number of both alleles in either ATXN7 or TBP was relatively large, the odds for a diagnosis of lifetime depression markedly increased. Moreover, six genotyped individuals had a CAG repeat number in at least one of their PDAGs that extended into the intermediate or pathological range (two intermediate, four pathological). All of these subjects were diagnosed with lifetime depression. These findings are in support of the hypothesis that repeat polymorphisms may act as complex genetic modifiers of depression and thus could account for part of its ‘missing heritability’.

In our study, we found that the odds of lifetime depression almost doubled in individuals with a CAG repeat length of >10 in both ATXN7 alleles. Similarly, we found that the risk of lifetime depression markedly increased (OR = 1.33) in individuals who had a CAG repeat length exceeding the median in both TBP alleles. These effect sizes are considerable, especially when compared with the effect sizes of the two most significant SNPs found in a recent GWAS: OR = 0.955 (95% CI 0.943—0.968) and OR = 1.051 (95% CI 1.036—1.067).22 Although we cannot fully exclude potential modifying effects of SNPs in linkage disequilibrium (LD) with ATXN7 and TBP, the fact that such SNPs in these PDAGs have not been detected before in GWASs suggests that the influence of other genetic variants in LD with the CAG repeat size in these genes is likely to be minimal.22 Furthermore, we found that CAG repeat size polymorphisms in HTT, ATXN7 and TBP together can account for ~1.9% of depression heritability. Using the same population prevalence of 15% for depression, the meta-analysis in the recent GWAS calculated a heritability of 5.9%.23 The amount of variance explained by these SNPs is larger than the amount explained by the CAG repeat polymorphisms we found. However, the meta-analysis in this GWAS examined SNPs in the entire genome of 326 113 individuals,6 whereas our estimation was based on the effects of CAG repeat variations in only nine PDAGs. This fact suggests that investigating additional repeat polymorphisms in the human genome could lead to the identification of many more novel genetic determinants of depression. The importance of investigating repeat polymorphisms in association with health and disease has been described in previous literature and begins to gain more recognition within the field of genetic research.

CAG repeat numbers exceeding 36 in ATXN7 are responsible for the severe neurodegenerative disorder spinocerebellar ataxia type 7 (SCA7).23 SCA7 is a progressive autosomal-dominant neurodegenerative disorder primarily characterized by cerebellar ataxia and macular degeneration.23 Although depressive symptoms are a frequent finding in many neurodegenerative disorders, the prevalence of depression has hardly been assessed in SCA7.48–51 Our findings suggest that depression might be an underappreciated feature of SCA7, which needs further characterisation. A CAG repeat number in TBP larger than 48 causes the severe progressive neurodegenerative disorder SCA17.34 Aside from cerebellar ataxia, dementia and pyramidal symptoms, in 67% of the cases SCA17 is also accompanied by psychiatric signs and symptoms, including depression, behavioural changes as well as psychosis.52 Initial symptoms of SCA17 have been described to include depression.53

The gene ATXN7 encodes the protein ataxin-7. Apart from several important cellular functions,51 ataxin-7 is an integral part of the TATA-binding protein-free TAF-containing complex.52 TATA-binding protein-free TAF-containing complex allows for the initiation of transcription via RNA polymerase II in the absence of the RNA polymerase II transcription factor D.53 Interestingly, the TATA-box-binding protein (TBP) that is encoded by TBP, is the DNA-binding subunit of RNA polymerase II transcription factor D. TBP anchors RNA polymerase II transcription factor D to the TATA-box upstream of the first codon, allowing for the initiation of transcription via RNA polymerase II.54 Thus, TBP as well as ataxin-7 seem to have a part in the initiation of transcription via RNA polymerase II. RNA polymerase II catalyses the transcription of DNA to synthesise precursors of mRNA, snRNA and microRNA.57,58 Numerous studies indicate an altered mRNA expression of proteins such as the serotonin 5-HT1A receptor,60–64 brain-derived neurotrophic factor65–67 and corticotrophin-releasing factor68,69 in subjects suffering from MDD compared with controls. Furthermore, the evidence supporting a role for the dysfunction of microRNA-mediated regulated gene expression in MDD is increasing.67–71 Therefore, CAG repeat variations in either ATXN7 or TBP could modulate the function of RNA polymerase II, and thereby lead to changes in mRNA and microRNA expression that have previously been associated with MDD.54,57 Hence, we intend to investigate the effect of CAG repeat length variations within the normal range in ATXN7 and TBP on the expression and function of proteins thought to be associated with depression in a cellular model.

The presence of one subject with a CAG repeat size in the pathological range of CACNA1A, one subject with a CAG repeat size in the pathological range of TBP and two subjects with a pathological CAG repeat size in ATXN2 within our two cohorts is remarkable. For these individuals, depression is apparently the first symptom with which SCA6, SCA17 or SCA2 manifests itself. The prevalence of an autosomal-dominant cerebral ataxia among Europeans is estimated to be between 1 and 3 per 100 000, of which 2% are diagnosed with SCA6, <1% with SCA17 and 10% with SCA2,72 resulting in a prevalence of 0.02–0.06 per 100 000, <0.01–0.03 per 10 000 and 0.10–0.30 per 100 000 for SCA6, SCA17 and SCA2, respectively. These numbers are in stark contrast to the substantially higher prevalence estimates in patients with depression in our study, 90 per 100 000 for SCA6, 50 per 100 000 for SCA17 and 50 per 100 000 for SCA2. Previously, we also found two individuals without completely penetrant HTT alleles (that is, those containing 36–39 CAG repeats) in this same population, both of whom suffered from depression.15 The difference in proportion of individuals with intermediate or pathological CAG repeat lengths in PDAGs indeed tended to be higher in depressed compared with control subjects, although likely due to the relative

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rarity of these expanded alleles the results did not reach statistical significance. Our findings are in line with another study that estimated the prevalence of incompletely penetrant HTT alleles in MDD patients to be ~3 in 1000, whereas such alleles were absent in the control group. Together, these findings suggest that depression could be the first manifestation of polyglutamine diseases and that, conversely, polyglutamine diseases might be underdiagnosed in patients with depression.

In this study, we analysed a homogenous population by using samples from two Dutch cohorts for our analysis, thereby minimising the impact of population stratification. However, the use of a uniform group of individuals could also be seen as a limitation of our study, as it might have consequences for the generalisability of our findings. However, our results appear robust and consistent, although confirmation of our findings in other populations, as well as the elucidation of their pathophysiological basis, is warranted.

In conclusion, we observed a significant association between the risk of lifetime depression and CAG repeat size in ATXN7 and TBP. A relatively large CAG repeat number in both alleles of either ATXN7 or TBP substantially increased depression risk. Our findings add more critical evidence to the notion that repeat polymorphisms could act as complex genetic modifiers of depression and, therefore, could partially account for its ‘missing heritability’. In addition, our findings indicate that the role of DNA repeat polymorphisms as potential genetic modifiers of other psychiatric disorders also needs further scrutiny.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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