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Report

Chromosome-Specific Quantification of TERRA in Peripheral Blood and Its Association with Depressive Symptoms

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Telomeric repeat-containing RNA (TERRA), a long non-coding RNA (lncRNA), is transcribed from both chromosomal ends and regulates gene expression at telomeres as well as within internal chromosomal regions. Although chromosomal dysfunction has been implicated in depression, the relationship between TERRA expression and depressive symptoms remains poorly understood. In this study, we developed a quantitative reverse transcription PCR (RT-qPCR) method to measure TERRA expression from 10 loci on chromosomes 3, 8, 11, 12, 16, and 22, which have been associated with depressive disorder. Using this method, we examined the association between TERRA expression in peripheral blood and depressive symptoms in 18 patients with major depressive disorder. TERRA expression levels at 8p and 11p exhibited limited correlation with those at other chromosomal loci. Moreover, when patients were stratified into two groups based on depressive symptom severity, TERRA expression at 8p was significantly lower in the group with severe depressive symptoms compared with those with mild symptoms ($P = 0.043$). This study established a method for quantifying chromosome-specific TERRA expression and provided insights into its potential association with depressive symptoms. The findings suggest that aberrant TERRA expression at 8p may contribute to the pathophysiology of depression. Further studies involving larger cohorts are warranted to validate these results.

Key words lncRNA, major depressive disorder, RT-qPCR, TERRA, method development

INTRODUCTION

Telomeres serve as protective caps at the ends of chromosomal DNA and are composed of the repeating base sequence "TTAGGG" in humans. At birth, telomeres are approximately 10,000 nucleotides in length but progressively shorten by ~50–100 nucleotides with each DNA replication cycle.[1,2] This shortening is further exacerbated by oxidative damage and other stressors. Telomeres act as markers of cellular aging and are influenced by oxidative stress and chronic inflammation, both of which accelerate telomere attrition.

Telomeric repeat-containing RNA (TERRA) is a long non-coding RNA (lncRNA) transcribed from subtelomeric and telomeric regions on both the short (p) and long (q) arms of each chromosome. TERRA, composed of hundreds to thousands of nucleotides and including the "TTAGGG" repeat, plays a critical role in telomere regulation. It inhibits telomerase activity by interacting with telomerase reverse transcriptase (TERT) and the telomerase RNA component (TERC), thereby contributing to telomere shortening.[3,4] However, when telomeres are severely shortened or damaged, TERRA can recruit telomerase to facilitate telomere repair and elongation.[5–7]

Beyond its role at telomere ends, TERRA contributes to genomic stability by regulating the expression of genes located within internal chromosomal regions through epigenetic mechanisms and interactions with chromatin remodelers such as ATRX.[8] TERRA has also been shown to interact with G-quadruplex structures and to recruit heterochromatic proteins, further highlighting its broad regulatory roles.[4] Dysregulation of TERRA has been implicated in various pathological conditions, including cancer, premature aging disorders, and neurodegenerative diseases.[9–11] The nature of TERRA dysregulation appears to vary depending on the disease context. For example, decreased expression of 16p TERRA and increased expression of 11q TERRA have been associated with cutaneous T-cell lymphoma,[12] reduced levels of 16p TERRA and 20q TERRA have been observed in postmenopausal endometrial cancer,[13] and elevated 11q TERRA expression has been implicated in cellular senescence.[14] These findings underscore the importance of investigating arm-specific TERRA expression to better understand its regulatory functions and involvement in disease progression.

Recent studies suggest that telomere dysfunction, particularly the shortening of telomeres may contribute to the patho-

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genesis of major depressive disorder.[15,16] Given TERRA's critical roles in telomere maintenance and genomic stability, its dysregulation may exacerbate telomere attrition and chromosomal instability, thereby influencing the development of stress-related disorders such as major depression. Nevertheless, the relationship between TERRA and depression remains largely unexplored. Notably, abnormalities in chromosomes 2, 8, and 17 have been associated with major depression.[17]

To measure chromosome-specific TERRA expression, primers designed to bind specific sequences within the subtelomeric regions are used, and reverse transcription quantitative PCR (RT-qPCR) is performed with GAPDH as an internal control, as described in a previous study.[18] Although Feretzaki *et al*. reported primers for 2q, 17p, and 17q, no primers were available for 2p, 8p, or 8q. In this study, we sought to develop a method to quantify chromosome-specific TERRA expression for chromosomes 3, 11, 12, 16, and 22, chromosomes previously implicated in depression and other psychiatric disorders,[19–24] in addition to 2p, 8p, and 8q. Using this newly developed method, we further examined the relationship between TERRA expression and depressive symptoms in patients with major depressive disorder.

MATERIALS AND METHODS

Patients Japanese patients diagnosed with depressive disorder according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) were recruited. Patients with severe hepatic or renal dysfunction (defined as aspartate aminotransferase or alanine aminotransferase levels >500 U/L and/or serum creatinine levels >3.0 mg/dL), those using Hypericum perforatum (St. John's wort), or those who were pregnant were excluded. Peripheral venous blood (5 mL) was collected from each patient using EDTA-2Na Venoject II tubes (Terumo, Tokyo, Japan). Blood samples were stored at −80°C within four hours of collection. At the time of blood collection, each patient also completed the Center for Epidemiological Studies Depression Scale (CES-D) to assess depressive symptom severity.[25]

Preparation of Total RNA and Analysis of TERRA Expression Total RNA (50 µL) was extracted from 200 µL of whole blood using the Monarch Total RNA Miniprep Kit (New England Biolabs, Tokyo, Japan). Complementary DNA (cDNA) synthesis was performed according to the manufacturer's protocol using the microScript microRNA cDNA Synthesis Kit (Norgen Biotek Corp., Thorold, Canada). cDNA synthesis was performed in a 20 µL total volume containing: 10 µL Reaction Mix (2×), 4 µL total RNA, 1 µL TruScript microRNA Enzyme Mix, and 5 µL nuclease-free water. The thermal cycling profile was as follows: 37°C for 30 min and 70°C for 15 min, followed by holding at 4°C. The synthesized cDNA was stored at −80°C until analysis.

TERRA Expression Analysis Subtelomeric sequence information for each chromosome was obtained from T2T-CHM13v2.0 or GRCh38.p14 assemblies for Homo sapiens from The National Center for Biotechnology Information (NCBI) Genome database. Specific primers targeting subtelomeric regions were designed using Primer3 Plus and subsequently verified using Nucleotide BLAST to ensure specificity and prevent off-target amplification. We developed a novel method to assess chromosome-specific TERRA expression from the p and q arms of chromosomes 2, 3, 8, 11, 12, 16, and 22. However, reliable assays could not be established for TERRA originating from the p arms of chromosomes 2, 12, and 16. Additionally, the 2q primer for chromosome 2, previously reported by Feretzaki *et al.*,[18] was found unsuitable in our system. For the p and q arms of chromosome 17, primers described by Feretzaki *et al*. were utilized.[18] TERRA expression levels were quantified using the QuantStudio 5 real-time PCR system (Thermo Fisher Scientific, Tokyo, Japan) with the ThunderBird SYBR qPCR Mix (TOYOBO, Tokyo, Japan), using GAPDH as the internal control for normalization. The qPCR reaction system was prepared in a 10 µL total volume containing 5 µL ThunderBird SYBR qPCR Mix (2×), 0.2 µL cDNA, 1.5 µL each of forward and reverse primers (2 µM stock), and 1.8 µL nuclease-free water. The thermal cycling profile consisted of an initial denaturation step at 95°C for 30 s, followed by 40 cycles of denaturation at 95°C for 3 s and annealing/extension at 60°C for 10 s. Single-product amplification was confirmed by agarose gel electrophoresis and melting curve analysis. For the melting curve analysis, a dissociation curve was generated immediately after amplification to verify the melting temperature of the amplicon, confirming single-product amplification under these conditions. Expression levels were calculated using the ΔCt method ($\Delta Ct = Ct_{GAPDH} - Ct_{TERRA}$), where a larger ΔCt value indicates higher TERRA expression. Primer sequences used in the analysis are provided in Table 1. Accurate amplification of the target sequences was further verified by DNA sequencing. Whole blood samples from healthy donors (BioIVT, Westbury, USA) were used for validation experiments.

Neuregulin 1 (NRG1) mRNA Expression Analysis NRG1 mRNA expression levels were quantified using the QuantStudio 5 Real-Time PCR System along with the ThunderBird SYBR qPCR Mix. GAPDH was employed as the internal control for normalization. The expression levels were calculated using the ΔCt method ($\Delta Ct = Ct_{GAPDH} - Ct_{NRG1}$). The primer sequences were as follows: forward, 5'-GCCAGCCTCAACTGAAGGAG-3'; and reverse, 5'-GCTTGTCCCAGTGGTGGATG-3'.

Statistical Analysis The Shapiro–Wilk test was used to assess the normality of data distribution. Two-tailed Student t-tests were applied to variables following a normal distribution, whereas two-tailed Welch t-tests were used for variables not following a normal distribution. Two-tailed Fisher's exact tests were performed to compare categorical variables (gender and number of anti-depressive drugs) between the two groups. Pearson's product-moment correlation coefficient was calculated for variables with a normal distribution, while Spearman's rank correlation coefficient was used for variables with a non-normal distribution. These analyses were performed to examine associations among TERRA expression levels and between 8p TERRA and NRG1 mRNA levels. Participants were divided into two groups based on CES-D scores: individuals scoring ≥16, representing a clinical threshold for depressive symptoms,[25] and those scoring <16. For normally distributed factors, a two-tailed t-test was applied. A P-value <0.05 was considered statistically significant.

RESULTS

Patient Background and Distribution of TERRA Expression Patient background information is summarized in Table 2. The distributions of age and CES-D scores dem-

Table 1. Primer Sequences Used for RT-qPCR

Primers		Sequence (5'-3')	Distance from TTAGGG repeats (bp)	Product (bp)
GAPDH	For	ATGGGGAAGGTGAAGGTCG		108
	Rev	GGGGTCATTGATGGCAACAATA		
3p	For	ACGACGTCTACTTTGTTCCTTGGT	777-800	71
	Rev	AAGAGCACACGGCCAGACA	829-847	
3q	For	GGAGTTGCGTTCTCTTCAGC	163-182	105
	Rev	AGAACTCTGCTCCGCCTTC	78-96	
8p	For	CATTTGTGTTCCGACACTGC	62-81	161
	Rev	CGGTTGCAGCCGTTAATAAT	203-222	
8q	For	GGTCCACTTGGTGTAGAGCTG	248-268	175
	Rev	ACAGGAGCACCCAGATTCAT	94-113	
11p	For	CTGTGCTCCGCCTTCAGAG	50-68	54
	Rev	GAGCTGCGTTGTCCTCTG	88-105	
11q	For	TCTCAGCACAGACCTTGGAG	94-113	50
	Rev	GCCCCGAATTGTCCCAAAC	64-83	
12q	For	CTGTTTGCAGCGCTGAATATTC	325-347	68
	Rev	ATTTCCCGTTTTCCACACTGA	279-299	
16q	For	CCGTTTGCTGCCCTGAATAATC	200-221	117
	Rev	CGCCTTGCCTTGGGAGAATC	105-124	
17p[*1]	For	CCCAAAGTACACAAAGCAATCC	283-305	80
	Rev	CTTATCCACTTCTGTCCCAAGG	341-362	
17q[*1]	For	GTCCATGCATTCTCCATTGATAAG	3670-3693	76
	Rev	AGCTACCTCTCTCAACACCAAGAAG	3618-3642	
22p	For	CGGTCAAGTTTCTGCCTACAG	15-35	80
	Rev	CCTGGCACCATAAGTACAGAGTAG	71-94	
22q	For	CGGAGCTGTGTTCTGTTCAG	374-393	103
	Rev	GTTGTCCCAAAGCCATGCAG	291-310	

*1 Primers described by Feretzaki *et al*. were utilized (Feretzaki *et al*. 2017).

Table 2. Patient Characteristics

	Number of patients (% of total), mean ± S.D., or median (range)		*P* value
	Severe, CES-D score ≥ 16(n=12)	Mild, CES-D score <16 (n=6)	
Age (years)	45.8±19.9	65.0±17.5	0.070[*1]
Gender (Male/Female)	8(66.7)/4(33.3)	2(33.3)/4(66.7)	0.180[*2]
Number of anti-depressive drugs (number)	1(0-3)	1(0-2)	0.426[*2]
0	1(8.3)	2(33.3)	
1	8(66.7)	2(33.3)	
2, 3	3(25.0)	2(33.3)	
Antidepressants			
Mirtazapine	6(33.3)		
Venlafaxine	4(22.2)		
Escitalopram	3(16.7)		
Duloxetine	3(16.7)		
Paroxetine, Paroxetine CR	2(11.1)		
Sertraline	1(5.6)		
Trazodone	1(5.6)		
Vortioxetin	1(5.6)		

CR; controlled release. *1 Two-tailed Student t−test, *2 Two-tailed Fisher's exact test.

onstrated normality according to statistical tests. All analyzed TERRA expression levels also exhibited normal distributions. Correlation analyses between the expression levels of each TERRA, as shown in Table 3, revealed significant positive correlations among most TERRA pairs. However, notable exceptions were observed for TERRA expression at 8p and 11p, which did not show significant correlations with many other TERRA loci (Table 4). No significant correlation was detected between age and TERRA expression levels at either 8p or 11p.

Association Between CES-D Score and TERRA Expression No direct correlation was observed between CES-D scores and TERRA expression levels at 8p or 11p. However, when the 18 patients were stratified into two groups based on CES-D scores (≥16 indicating severe depressive symptoms, n = 12; <16 indicating mild symptoms, n = 6), a statistically significant difference in TERRA expression at 8p was identified. Patients with severe depressive symptoms exhibited significantly lower TERRA expression levels at 8p compared with those with mild symptoms (P = 0.043; Fig. 1). In contrast, no significant differences in TERRA expression at 11p

Table 3. Chromosomal Loci Combinations with Significant Correlation in TERRA Expression Levels

Correlation of TERRA expression levels		Correlation coefficient (r)	P value
3p TERRA	8q TERRA	0.694	0.001
3p TERRA	11p TERRA	0.484	0.042
3p TERRA	11q TERRA	0.535	0.022
3p TERRA	12q TERRA	0.951	<0.001
3p TERRA	16q TERRA	0.589	0.010
3p TERRA	17p TERRA	0.639	0.004
3p TERRA	17q TERRA	0.741	<0.001
3p TERRA	22p TERRA	0.597	0.009
3p TERRA	22qTERRA	0.739	<0.001
3q TERRA	8p TERRA	0.480	0.044
3q TERRA	8q TERRA	0.754	<0.001
3q TERRA	11q TERRA	0.659	0.003
3q TERRA	12q TERRA	0.624	0.006
3q TERRA	16q TERRA	0.659	0.003
3q TERRA	17p TERRA	0.808	<0.001
3q TERRA	17q TERRA	0.711	0.001
3q TERRA	22p TERRA	0.684	0.002
3q TERRA	22q TERRA	0.613	0.007
8p TERRA	8q TERRA	0.624	0.006
8p TERRA	11p TERRA	0.648	0.004
8q TERRA	11p TERRA	0.587	0.010
8q TERRA	11q TERRA	0.524	0.026
8q TERRA	12q TERRA	0.760	<0.001
8q TERRA	16q TERRA	0.694	0.001
8q TERRA	17p TERRA	0.860	<0.001
8q TERRA	17q TERRA	0.836	<0.001
8q TERRA	22p TERRA	0.732	0.001
8q TERRA	22q TERRA	0.757	<0.001
11p TERRA	12q TERRA	0.489	0.039
11p TERRA	17p TERRA	0.489	0.039
11p TERRA	22p TERRA	0.515	0.029
11q TERRA	12q TERRA	0.638	0.004
11q TERRA	16q TERRA	0.662	0.002
11q TERRA	17p TERRA	0.558	0.016
11q TERRA	17q TERRA	0.564	0.015
11q TERRA	22p TERRA	0.708	0.001
11q TERRA	22q TERRA	0.589	0.010
12q TERRA	16q TERRA	0.734	0.001
12q TERRA	17p TERRA	0.765	<0.001
12q TERRA	17q TERRA	0.829	<0.001
12q TERRA	22p TERRA	0.722	0.001
12q TERRA	22q TERRA	0.823	<0.001
16q TERRA	17p TERRA	0.870	<0.001
16q TERRA	17q TERRA	0.903	<0.001
16q TERRA	22p TERRA	0.966	<0.001
16q TERRA	22q TERRA	0.894	<0.001
17p TERRA	17q TERRA	0.939	<0.001
17p TERRA	22p TERRA	0.865	<0.001
17p TERRA	22q TERRA	0.866	<0.001
17q TERRA	22p TERRA	0.917	<0.001
17q TERRA	22q TERRA	0.905	<0.001
22p TERRA	22q TERRA	0.883	<0.001

were observed between the two groups (P = 0.222). Similarly, no significant difference in age was found between the groups stratified by CES-D scores (P = 0.070; Table 2).

Table 4. Chromosomal Loci Combinations without Significant Correlation in TERRA Expression Levels

Correlation of TERRA expression levels		Correlation coefficient (r)	P value
3p TERRA	3q TERRA	0.453	0.059
8p TERRA	3p TERRA	0.330	0.181
8p TERRA	11q TERRA	0.316	0.201
8p TERRA	12q TERRA	0.334	0.176
8p TERRA	16q TERRA	0.305	0.218
8p TERRA	17p TERRA	0.331	0.179
8p TERRA	17q TERRA	0.371	0.129
8p TERRA	22p TERRA	0.387	0.112
8p TERRA	22q TERRA	0.344	0.162
11p TERRA	3q TERRA	0.355	0.148
11p TERRA	11q TERRA	0.467	0.051
11p TERRA	16q TERRA	0.398	0.102
11p TERRA	17q TERRA	0.463	0.053
11p TERRA	22q TERRA	0.373	0.127

DISCUSSION

This study introduces a method for measuring chromosome-specific TERRA expression at loci including 3p, 3q, 8p, 8q, 11p, 11q, 12q, 16q, 22p, and 22q. Previously, Feretzaki *et al*. developed a method to quantify TERRA expression at 1q, 2q, 7p, 9p, 10q, 13q, 15q, 17p, 17q, XqYq, and XpYp.[18] By integrating their technique with our approach, we have expanded the capacity for detailed analyses, providing new opportunities for investigating TERRA function. Accurate quantification of individual TERRA molecules is essential for elucidating the transcriptional networks that regulate TERRA expression across distinct chromosome ends, and our method offers a valuable tool for this purpose. Given the established association between depression and chromosomal dysfunction, particularly involving chromosomes 2, 8, and 15, we applied our method to assess TERRA expression at loci implicated in depression and other psychiatric disorders. We quantified TERRA expression at 12 loci, 3p, 3q, 8p, 8q, 11p, 11q, 12q, 16q, 17p, 17q, 22p, and 22q, in 18 patients with major depressive disorder. Notably, expression patterns at 8p and 11p were distinct from those observed at other loci. Based on these findings, we hypothesized that TERRA expression at 8p and 11p may be associated with depressive symptoms. Subsequent analyses revealed a significant difference in TERRA expression at 8p relative to depressive symptom severity, as measured by CES-D scores. These observations are consistent with previous research highlighting the involvement of telomere dysfunction in major depressive disorder.[15,16] Immunodeficiency, centromeric instability, and facial anomalies (ICF) syndrome, caused by mutations in DNA methyltransferase DNMT3B, is characterized by elevated TERRA expression due to impaired DNA methylation at subtelomeric regions.[26,27] Furthermore, altered expression of TERRA from at least seven q arm subtelomeres has been reported in mice.[28] These findings suggest that aberrant TERRA expression from specific telomeric regions can destabilize telomeres and contribute to the pathogenesis of both ICF syndrome and depression. In our study, no significant association was observed between depressive symptom severity and TERRA expression at 11p. However, further investigations with larger sample sizes are warranted to clar-

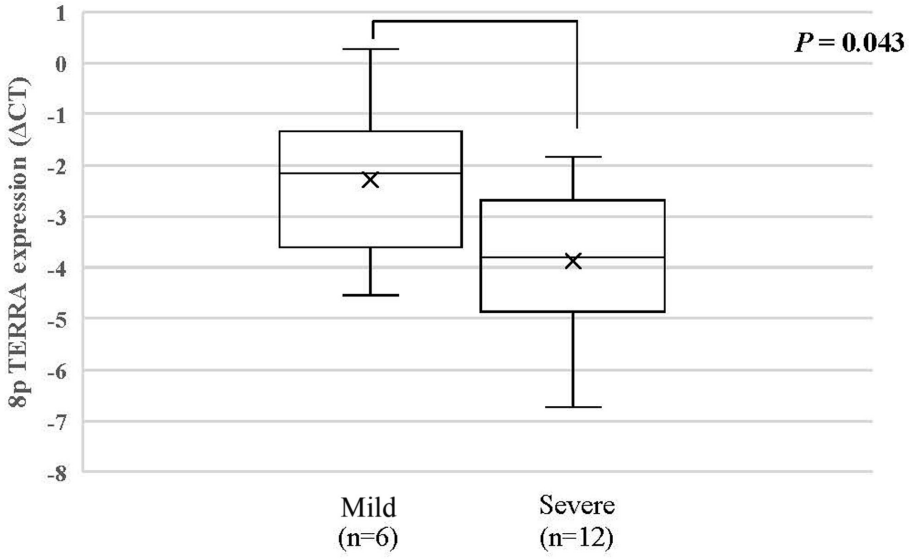

Fig. 1. Association Between 8p TERRA Expression and Depressive Symptoms

Subjects were divided into two groups based on a CES-D score threshold of 16. 8p TERRA expression levels were significantly lower in the severe group compared with the mild group ($P = 0.043$).

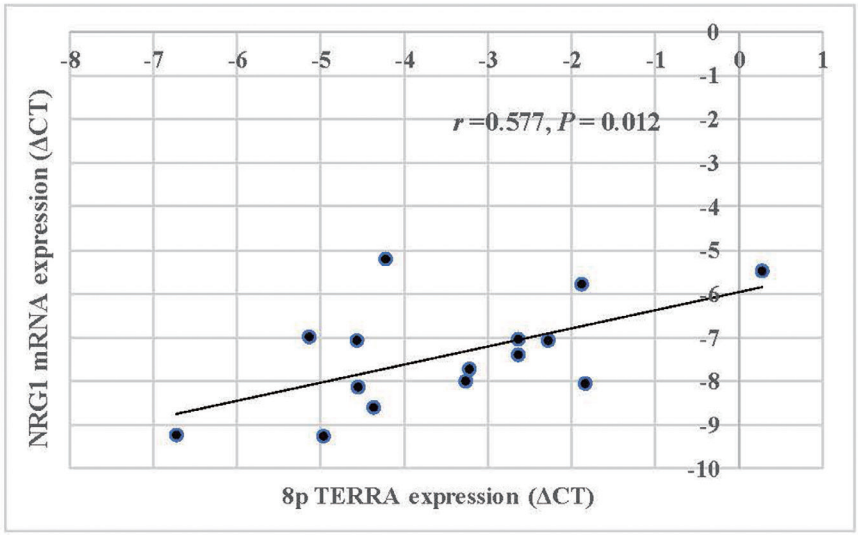

Fig. 2. Correlation Between 8p TERRA Expression and NRG1 mRNA Expression

A positive correlation between 8p TERRA and NRG1 mRNA expression levels was identified in 15 patients with depression ($r = 0.577$, $P = 0.012$).

ify this relationship. Genes associated with depression, such as *neuregulin 1* (NRG1), are located on the p arm of chromosome 8. Notably, NRG1 mRNA expression in peripheral blood cells differs significantly between patients with depression and healthy individuals.[29,30] TERRA, as a long non-coding RNA, is known to regulate gene expression both at telomeric and internal chromosomal sites,[31] underscoring the importance of investigating the potential regulatory interactions between TERRA and depression-associated genes, including *NRG1*, on chromosome 8. We examined the correlation between 8p TERRA expression levels and *NRG1* mRNA expression levels. Although *NRG1* mRNA expression was analyzed in only 15 of the 18 patients, a significant positive correlation was observed ($r = 0.577$, $P = 0.012$; Fig. 2). However, this study found no significant difference in NRG1 expression between the two groups divided by the CES-D score cutoff of 16. The correlation between 8p TERRA and *NRG1* mRNA expression suggests that 8p may play a role in regulating NRG1 expression. However, it does not appear to influence depression symptoms. In addition to *NRG1*, 20 other genes—*ADRA1A, ARHGEF10, CHRNA2, CHRNA6, CHRNB3, DKK4, DPYSL2, EGR3, FGF17, FGF20, FGFR1, FZD3, LDL, NAT2, NEF3,*

PCM1, PLAT, PPP3CC, SFRP1, and *VMAT1/SLC18A1*—are located within the 8p region.[32] Further investigations are warranted to evaluate the effects of 8p on these genes. Although primer specificity was confirmed by melting curve analysis, agarose gel electrophoresis, and sequencing, amplification efficiency was not assessed in the real-time PCR system used in this study. The observed differences in the correlations between TERRA expression at 8p and 11p and at other loci may reflect variations in amplification efficiency. Therefore, future studies should evaluate amplification efficiency (e.g., using standard curves) to ensure the quantitative reliability of the results.

This study did not evaluate the effects of age or antidepressant treatment on TERRA expression among the 18 patients. Previous research suggests that TERRA expression may vary with age.[33,34] Although we observed a trend toward age-related differences ($P = 0.070$) between groups stratified by CES-D scores, the difference was not statistically significant. Given the limited sample size and wide age range (20–82 years), this trend requires further investigation. While no studies have directly examined the effects of antidepressant administration on TERRA expression, recent findings have linked telomerase activity, regulated in part by TERRA, to depressive symptoms.[35] These studies suggest that while the direct impact of antidepressants on telomerase activity is minimal, depressive symptoms exert a more pronounced effect. Future studies should explore the impact of antidepressant administration on TERRA expression, ideally using large, well-characterized cohorts that include healthy controls.

Conclusion This study highlights a significant association between TERRA expression and depressive symptoms. Further research involving larger sample sizes and advanced molecular approaches is needed to validate these findings. Additionally, longitudinal studies are critical to elucidating the molecular mechanisms underlying this association and to advancing the potential use of TERRA as both a biomarker and a modulator of depression.

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Conflict of interest The authors declare no conflict of interest.

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