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VDR Gene Expression Changes in Autism Spectrum Disorders: What is the Role of Maternal Effect?

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ABSTRACT

Objective: Autism spectrum disorders (ASD) are clinically heterogeneous conditions associated with cognitive impairments. Vitamin D (VD) deficiency has been proposed as a potential risk factor for neurodevelopmental disorders, including ASD. However, the roles of VD and vitamin D receptor (*VDR*) genes in ASD remain largely unexplored.

Materials and Methods: We evaluated *VDR* gene expression levels in peripheral blood samples from 23 children with ASD and their mothers, as well as 26 age- and sex-matched controls and their mothers.

Results: Reduced *VDR* gene expression was observed in both children with ASD and their mothers. Furthermore, *VDR* expression exhibited sex-specific differences, with male ASD patients showing significantly higher expression levels compared to female patients.

Conclusion: Few studies have investigated maternal *VDR* expression in the context of ASD. Future research involving larger family-based cohorts is warranted to further elucidate the role of *VDR* in ASD and its potential relevance to neuropsychiatric conditions.

Keywords: Autism spectrum disorders, gene expression, *VDR*, vitamin D.

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INTRODUCTION

Autism spectrum disorders (ASD) represent a clinically heterogeneous group of neurodevelopmental conditions characterized by stereotypical behaviors and deficits in social interaction and communication skills.[1–3] ASD typically emerges during early childhood.[4] Twin and familial studies indicate that its development is significantly influenced by genetic factors, with heritability estimated at about 50%.[5,6] Nevertheless, the precise etiology of ASD remains unclear, largely due to its substantial genetic heterogeneity.

Vitamin D (VD), a steroid prohormone, is synthesized in skin cells through the photoconversion of 7-dehydrocholesterol upon sun exposure.[7] Accumulating evidence suggests that VD regulates the biosynthesis of neurotransmitters and neurotrophic factors, implicating its deficiency as a

potential risk factor for neurodevelopmental disorders such as schizophrenia and ASD.[8–10] The biologically active form of VD, 1,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$], modulates diverse physiological processes and metabolic pathways.[11] Although VD crosses the blood-brain barrier, the direct neurofunctional effects of its supplementation remain unclear. The nuclear vitamin D receptor (*VDR*) is bound by VD, which then acts as a ligand-inducible transcription factor.[12] Insufficient food intake, insufficient exposure to sunlight, or decreased intestinal absorption are the main causes of vitamin D insufficiency (VDD).[13] *VDR*-mediated signaling underpins the biological activity of VD. Notably, *VDR* is expressed in key brain regions, including the hippocampus, hypothalamus, and prefrontal cortex.[14] Despite its widespread CNS distribution, the precise roles of *VDR* and its ligands (e.g., 1,25$(OH)_2D_3$) in neural circuits remain poorly characterized.[14] The *VDR* gene, located on chromosome 12q13,[15] has been linked to neurodevelopmental trajectories, with maternal VDD hypothesized to perturb fetal brain development.[9,16] Epidemiological studies associate perinatal VDD with an elevated risk of ASD, suggesting that genetic variants affecting VD transport or *VDR* binding may contribute to ASD etiology.

Emerging evidence indicates that low VD levels during gestation or early childhood may predispose individuals to neurodevelopmental disorders, including ASD.[11,12,17,18] Nonetheless, the mechanisms underlying this association remain largely unresolved. Most available studies focus on *VDR* gene polymorphisms across diverse populations.[19–24] Certain genetic variants, such as *Fok I* and *Taq I*, have been associated with a decreased risk of ASD. Additionally, changes in serum 25(OH)D levels have been observed in these individuals.[15,25] A more detailed investigation is required to establish a clearer relationship between *VDR* gene expression and ASD. In contrast to previous studies focusing primarily on polymorphisms, our study aimed to investigate how altered *VDR* gene expression might contribute to the ASD phenotype. Specifically, we assessed *VDR* mRNA expression in ASD patients and their mothers, making this the first study to adopt a mother-child paired design.

MATERIALS AND METHODS

Study Group and Controls

This study included 23 Turkish children (20 boys and 3 girls; mean age=6.3±2.48 years) who were newly diagnosed with ASD based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria.[26] All children underwent comprehensive psychiatric, clinical, neurological, and neuropsychological evaluations, including mental status examinations. These assessments were conducted independently by two experienced clinicians.

KEY MESSAGES

- Vitamin D (VD) deficiency may be a risk factor for autism spectrum disorders (ASD).
- *VDR* gene expression was reduced in both patients and their mothers.
- Vitamin D is associated with the risk of childhood ASD and the severity of the disease.

Cognitive functioning was evaluated using the Wechsler Intelligence Scale for Children (WISC). Inclusion criteria for the ASD group were as follows: (a) age between 3 and 12 years; (b) a confirmed diagnosis of ASD; and (c) evaluation with the Childhood Autism Rating Scale (CARS).[27] Patients with genetic syndromes or severe epileptic seizures were excluded from the study. The control group comprised 26 healthy children (19 boys and 7 girls) with a mean age of 7.81±3.06 years. In addition, detailed dysmorphological examinations and comprehensive patient histories were obtained. Mothers of participants were included if they were between 20 and 50 years of age. All healthy siblings underwent clinical assessments, and none exhibited ASD-related symptoms; all CARS scores were within the normal range (<30). Ethical approval for this study was granted by the Erciyes University Ethical Committee (approval no: 2022/791; date: 07/12/2022). Written informed consent was obtained from the parents of all participants. Demographic data for all groups are summarized in Table 1. This study was conducted in accordance with the ethical standards of the Declaration of Helsinki.

RNA Isolation, cDNA Synthesis, and Quantitative Real-Time Polymerase Chain Reaction (qRT → PCR)

Peripheral venous blood samples (2 mL) were collected between 9:00 AM and 12:00 PM into tubes containing ethylenediaminetetraacetic acid (EDTA). Total RNA was extracted from whole blood using the QIAmp RNA Blood Mini Kit (Qiagen, Düsseldorf, Germany) and stored at -80°C until further processing. RNA concentration (measured by absorbance at 260 nm) and purity (assessed by the A260/A280 ratio) were determined using a BioSpec-Nano spectrophotometer (Germany). All RNA samples exhibited an A260/A280 ratio between 1.8 and 2.0 and a total RNA concentration greater than 40 ng/µL.

Reverse transcription was carried out using 1 µg of total RNA per sample and a commercial cDNA synthesis kit (SABiosciences, Frederick, MD, USA). Quantitative real-time PCR (qRT-PCR) was performed to quantify *VDR* gene expression levels. The amplification protocol included an initial denaturation step at

Table 1. Demographic characteristics of the study groups (statistical details included in the table)

Variables	Control (n=26)	Patient (n=23)	p
Gender (male/female)	19 (73.1%) / 7 (26.9%)	20 (87%) / 3 (13%)	0.199
Age (years)[a]	7.81±3.06 (range: 3–12)	6.3±2.48 (range: 3–11)	0.067 (95% CI: -3.117–0.1100)
Mother's age (years)[a]	35.05±6.1 (range: 24–49)	38.04±5.79 (range: 24–49)	0.111 (95% CI: -0.7238–6.705)

a: Unpaired t-Test; CI: Confidence interval.

Table 2. Primers used for PCR analysis

Gene	Primer sequence (5' to 3')	
VDR	F: CAAGGACAACCGACGCCACTG	R: CCTCCTCCTCCTTCCGCTTCAG
GAPDH	F: CATTGCCCTCAACGACCACTTT	R: GGTGGTCCAGGGGTCTTACTCC

PCR: Polymerase chain reaction; F: Forward; R: Reverse.

Table 3. Gene expression levels in control and patient groups, overall and stratified by gender

Variables	Control (n=26)	Patient (n=23)	p
Total *VDR* gene expression[a]	1.927±2.745	2.176±2.042	0.135
Mothers *VDR* gene expression[a]	1.281±2.455	0.2003±0.3628	**0.0001****
Male *VDR* gene expression[a]	1.678±3.099	2.746±2.511	**0.009***
Female *VDR* gene expression[b]	3.201±2.681	0.6545±0.5659	**0.005*** (95% CI: -4.205 to -0.8884)

Data are presented as mean±standard deviation. a: Mann-Whitney test; b: Unpaired t-Test; *: P<0.001; **: P<0.0001; CI: Confidence interval.

95°C for 10 minutes, followed by 40 cycles of a two-step PCR: denaturation at 95°C for 10 seconds and annealing at 60°C for 60 seconds. Gene expression was normalized to GAPDH, which served as the internal reference gene. Primer sequences used in this study are listed in Table 2. Relative expression levels were calculated using the $2^{-\Delta\Delta CT}$ method.

Statistical Analysis

Descriptive statistics, including means and standard deviations, were used to summarize the data. Data distribution was assessed through histogram inspection, Q–Q plots, and the Shapiro-Wilk test for normality. For normally distributed data, group comparisons were conducted using unpaired t-tests. When normality assumptions were not met, the Mann-Whitney U test was applied. Multiple group comparisons were performed using the Kruskal-Wallis test. All statistical analyses were carried out using GraphPad Prism version 9.0. A p-value <0.05 was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic potential of *VDR* gene expression in distinguishing ASD cases from controls.

RESULTS

Expression Results of *VDR* Transcript Between Groups

No significant difference in *VDR* gene expression was observed between the overall patient and control groups (p=0.6551) (Fig. 1a). In contrast, the mothers of children with ASD exhibited significantly reduced *VDR* expression levels compared to mothers in the control group (p=0.0006) (Fig. 1a). When comparing *VDR* gene expression between children and their respective mothers, both the ASD and control pairs showed statistically significant differences (ASD: p<0.0001; control: p=0.015), with children displaying higher mRNA expression than their mothers (Fig. 1a). Expression levels are summarized

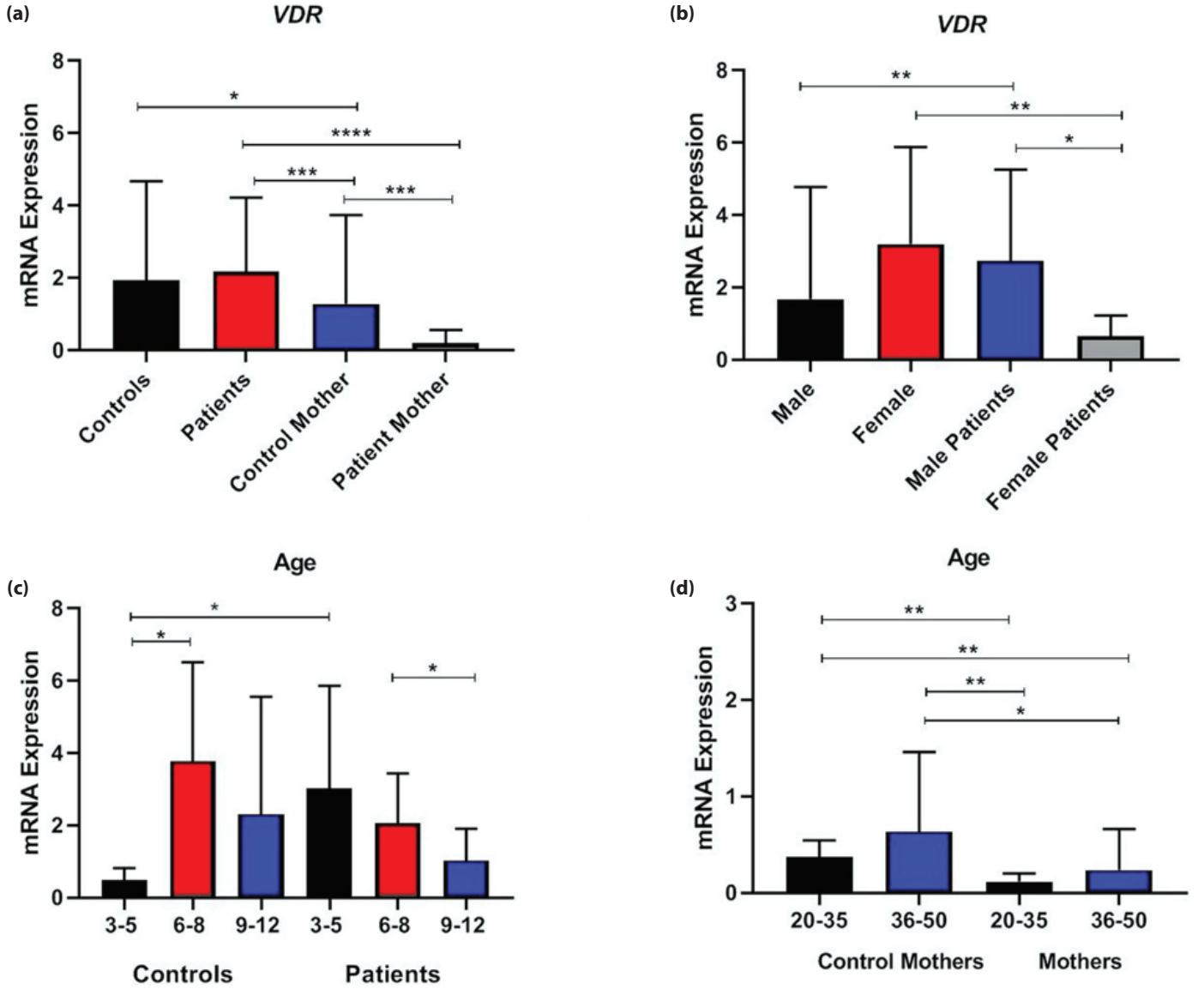

Figure 1. (a) Comparison of *VDR* gene expression by age group in patients. **(b)** Comparison of *VDR* gene expression by sex. **(c)** Comparison of *VDR* gene expression and age groups, including controls. **(d)** Comparison of *VDR* gene expression and age groups in mothers. *: p<0.05, **: p<0.001; ***: p<0.0001; ****p<0.00001.

in Table 3. We next analyzed *VDR* expression by sex within the ASD group and observed a significant sex-specific difference: female patients exhibited significantly lower *VDR* expression compared to male patients (p=0.0047) (Fig. 1b).

To further explore age-related trends, we stratified participants into three age groups: 3–5, 6–8, and 9–12 years. Among ASD patients, *VDR* expression declined with age, with the lowest levels observed in the 9–12 age group. This decrease was statistically significant when compared to the 6–8 group (p=0.0408) (Fig. 1c). In the control group, *VDR* expression was significantly lower in the 3–5 age group compared to the 6–8 group (p=0.0195) (Fig. 1c). Moreover, a marked difference in *VDR* expression was found between ASD and control children within the 3–5 age range (p=0.0108) (Fig. 1c).

VDR expression in mothers of ASD patients was also significantly reduced compared to control mothers, both in the 20–35 age group (p=0.001) and the 36–50 age group (p=0.0108) (Fig. 1d).

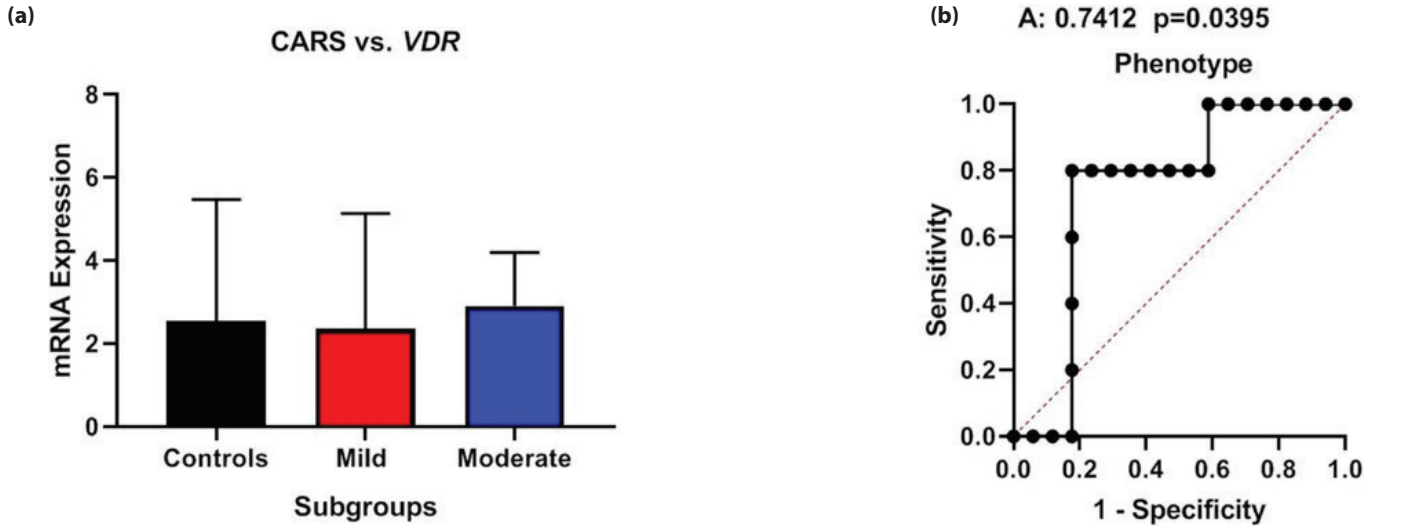

Figure 2. (a) Comparison of Childhood Autism Rating Scale (CARS) scores and *VDR* gene expression. **(b)** Receiver operating characteristic curve analysis of phenotype prediction. A: Area under the curve.

Effect of Phenotype on *VDR* Transcript

Comparison of *VDR* expression across different clinical phenotypes based on CARS scores revealed no statistically significant differences. Specifically, no significant differences were observed between control and mild cases (p=0.8541), control and moderate cases (p=0.7206), or between mild and moderate ASD groups (p=0.5631) (Fig. 2a). The diagnostic potential of *VDR* gene expression indicated a statistically significant diagnostic capacity for distinguishing ASD cases from controls (A: 0.7412, p=0.0395) (Fig. 2b).

DISCUSSION

A wide range of genes have been implicated in the pathogenesis of ASD.[1,28] Neurodevelopmental abnormalities may arise in individuals with impaired vitamin D metabolism, including deficiencies in VD-metabolizing enzymes, maternal VD deficiency during pregnancy, or insufficient VD levels during early childhood.[12] Numerous studies have examined the roles of VD and the *VDR* in brain development,[12,16,29] particularly given that VD exerts its effects via binding to the *VDR*.[29] Increasing evidence from genotyping studies supports the involvement of *VDR* signaling in the etiology of ASD.[15,24] Our findings confirm that *VDR* gene expression differs between children with ASD and their mothers. Moreover, we observed sex-related differences in expression levels among patients, with males exhibiting higher *VDR* expression than females.

Several studies have reported that polymorphisms in the *VDR* gene—including *Apa I*, *Taq I*, *Bsm I*, and *Fok I*—may alter the protein's activation threshold. In a case-control study involving 81 individuals diagnosed with ASD and 138 healthy controls, Mobasheri et al.[19] found no association between VD levels and the *Fok I* (rs2228570) or *Taq I* (rs731236) polymorphisms in a South Korean population. In contrast, significant associations were identified between the *Fok I* and *Taq I* variants and ASD risk in Turkish individuals.[15] Similarly, Zhang et al.[24] reported that the *Taq I* polymorphism (CT genotype and C allele) was associated with increased ASD risk in the Chinese population. Additional studies have demonstrated that the T allele of *Taq I* and the A allele of *Apa I* may be associated with a reduced risk of ASD.[20] However, in a Turkish sample, no significant differences were observed in the frequencies of related polymorphisms between ASD and non-ASD individuals.[21]

In a cohort of 100 Italian families with children diagnosed with ASD, *VDR* gene variants were investigated in both mothers and their unaffected siblings. The study found that the C allele of the *Fok I* polymorphism was protective. Additionally, the rs2228570 TT genotype in children with ASD was associated with hyperactive behaviors, and its presence in mothers correlated with a higher likelihood of having children diagnosed with ASD.[22] In the Han Chinese population, rs17219315 and rs4646536 were associated with increased ASD risk.[24] Children with ASD also exhibited significantly reduced serum 25(OH)D levels, which were inversely correlated with scores on the Autism Behavior Checklist (ABC). Following vitamin D supplementation, both ABC and CARS scores improved significantly.[30]

To address inconsistencies in the literature regarding associations between *VDR* single-nucleotide polymorphisms

(SNPs) and ASD risk, Yang et al.[8] conducted a meta-analysis. Qiu et al.[1] subsequently reanalyzed the data and identified a suggestive association between rs731236 and increased ASD risk under allelic and homozygous models. In a recent study, the expression levels of *LINC00511* and *SNHG6*, as well as *VDR* and *CYP27B1*, were evaluated for their potential involvement in ASD pathogenesis. While *VDR* and *LINC00511* levels did not differ between ASD patients and controls, *SNHG6* emerged as a non-core diagnostic marker based on ROC curve analysis.[31] Our findings align with this, as we observed reduced *VDR* expression in the ASD group and demonstrated, via ROC analysis, that *VDR* levels could distinguish ASD cases from controls when stratified by CARS scores.

In a small-scale study of Turkish ASD patients, Balta et al.[29] examined *VDR* gene expression and promoter polymorphisms. Although no significant genotypic or allelic differences were found, elevated *VDR* expression was detected in patients' whole blood samples. Contrary to that study, we found significantly lower *VDR* mRNA expression in mothers of ASD patients compared to the patients themselves. Notably, reduced *VDR* expression was more pronounced in female ASD patients compared to males. Although no correlation was observed between *VDR* expression and clinical severity, this may be attributed to the relatively small sample size. Additionally, the absence of severely affected individuals in our clinical classification may have limited our ability to detect phenotype-related associations. We therefore recommend that future studies include patients across the full clinical spectrum, including those with severe ASD.

A recent meta-analysis identified only a borderline positive correlation between 25(OH)D levels and cognitive development, but a stronger inverse association between 25(OH)D levels and risk for ADHD and ASD.[32] These findings support the hypothesis that higher prenatal circulating 25(OH)D concentrations may offer a protective effect. This notion is further reinforced by maternal-fetal studies such as the one by Murthi et al.[33] In our study, *VDR* expression was significantly reduced in mothers from both patient and control groups. This finding adds to the growing evidence that adequate VD levels during early pregnancy may reduce the risk of developing ASD.[34] Well-designed studies are urgently needed to evaluate the therapeutic potential of VD in neurodevelopmental disorders and to determine whether prenatal VD supplementation supports normal cognitive development.

Structural brain abnormalities are well documented in ASD and are believed to contribute to its neurobiological underpinnings.[35] Increased head circumference (HC) during early life is considered a potential early biomarker of autism.[36] Specifically, male children with ASD are hypothesized to exhibit greater HC than male controls between 6 and 36 months of age.[37] In our study, male ASD patients showed higher *VDR* mRNA expression levels than females. This sex-based difference may underlie the observed expression patterns. Additionally, we observed differential expression between children and their mothers. Considering maternal age as a possible risk factor, variations in maternal *VDR* expression may contribute to the clinical features of ASD.

This study has several limitations. The sample size was relatively small, and serum VD levels were not measured in either group. Furthermore, gene expression is influenced by multiple regulatory mechanisms, including promoter polymorphisms and epigenetic modifications such as DNA methylation. Our study did not assess these factors, which should be considered in future research to fully elucidate the regulatory dynamics of *VDR* expression.

CONCLUSION

In contrast to previous studies, our investigation is the first to evaluate *VDR* mRNA expression levels in both mothers and their children within ASD-affected families. While our findings highlight significant differences in *VDR* expression, further research with larger, multi-ethnic cohorts is needed to validate the clinical relevance of *VDR* dysregulation in ASD etiology. Expanding future studies to include additional family members (e.g., fathers, siblings) could provide deeper insights into familial patterns of VD metabolism. Importantly, our results suggest that vitamin D supplementation may serve as a practical intervention to mitigate functional *VDR* deficiencies, though randomized controlled trials are essential to confirm its therapeutic potential.

Ethics Committee Approval: The Erciyes University Clinical Research Ethics Committee granted approval for this study (date: 07.12.2022, number: 2022/791).

Informed Consent: Written informed consent was obtained from the parents of all participants.

Conflict of Interest: The authors have no conflict of interest to declare.

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