Vitamin D receptor gene variants and serum vitamin D in childhood autism spectrum disorder

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Abstract
Objective This study aimed to examine the correlation between polymorphisms in vitamin D receptor (VDR) gene and serum vitamin D, and to determine their role in predicting childhood Autism Spectrum Disorder (ASD).

Methods Children with ASD and age- and gender- matched healthy controls were recruited from the Chinese Han population. Their serum 25(OH) vitamin D was measured using competitive chemiluminescent immunoassays. The TaqMan probe approach was applied to analyze the common VDR SNPs rs731236 (Taq1), rs11568820 (Cdx2), rs1544410 (BsmI), and rs228570 (FokI). Both linear and logistic regressions were applied in data analysis.

Results A total of 269 children with ASD and 320 healthy controls were recruited. Children with ASD had significantly lower levels of serum vitamin D and a significantly higher rate of vitamin D deficiency (< 20 ng/ml) compared to healthy controls (67.7% vs 34.1%). All these examined VDR SNPs were not correlated with serum vitamin D concentrations or vitamin D deficiency. Logistic regression analysis revealed that rs731236 and serum vitamin D were associated with childhood ASD. The area under the receiver operating characteristic (ROC) curve was 0.7285 for serum vitamin D. Children with both T/C genotype of rs731236 and vitamin D deficiency had a higher risk of being diagnosed with ASD.

Conclusion All examined common VDR SNPs are not correlated with serum vitamin D concentrations or vitamin D deficiency. The combination of T/C phenotype of rs731236 and vitamin D deficiency are associated with a higher risk of childhood ASD. Vitamin D is a promising target in the prevention and treatment of this disease.

Keywords Autism Spectrum Disorder (ASD) · SNP · Vitamin D · Receptor · Deficiency

Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental disability with repetitive behaviors and deficits in social interactions and language skills. Multiple genetic and environmental risk factors have been implicated in the development of the disease [1–3]. The high prevalence and comorbidities of this disease bring huge health and economic burdens worldwide [4–6].

Vitamin D has been considered as one of the environmental factors related to the development of ASD. In addition to its role in bone health, vitamin D has important functions in cell differentiation, immune modulation and neural development [7–9]. Lower serum vitamin D has been observed in children with ASD from different countries [10–15]. Vitamin D deficiency during pregnancy or early childhood has been associated with an increased risk of ASD [15–17]. Animal studies reported autism-relevant behaviors and brain abnormalities in offspring exposed to vitamin D deficiency during gestation [18, 19]. On the other hand, vitamin D...
supplementation has been shown to improve symptoms in children with ASD [12, 20].

Vitamin D functions to modulate gene transcriptions which are mainly mediated by its receptor (VDR). The VDR gene is located on chromosome 12q13 with nine exons and eight introns [21]. Five common SNPs rs731236 (Taq1), rs11568820 (Cdx2), rs1544410 (BsmI), rs2228570 (FokI) and rs7975232 (ApaI) have been identified at different regions of the VDR gene. These SNPs have been shown to impact the structure of VDR proteins, transcriptional activity and functions [22–25]. Some of these SNPs have been associated with the risk of childhood ASD [26–29].

The correlation between serum vitamin D levels and SNPs in the VDR gene is still inconclusive. Earlier studies reported an association between rs10735810 in the VDR gene and serum vitamin D levels in multiple sclerosis patients [30] and severe vitamin D deficiency in patients who underwent angiography due to suspected coronary artery disease [31]. A later study found a correlation between rs2228570 (FokI) and serum vitamin D in children with ASD [26] and in multiple sclerosis patients [32]. In contrast, Cieslinska et al. reported that VDR SNPs rs2228570, rs731236, rs1544410, and rs7975232 were not associated with vitamin D concentration in children with ASD [28] and in children who were obese/overweight [33].

The objective of this case control study was to first examine the common VDR SNPs (rs731236 (Taq1), rs11568820 (Cdx2), rs1544410 (BsmI) and rs2228570 (FokI)) and serum vitamin D in children with ASD and their healthy controls from the Chinese Han population. We then determined the correlation between the SNPs and serum vitamin D, and their role in predicting childhood ASD.

Patients and methods

This case–control study was conducted from March 2016 to December 2018. Children diagnosed with ASD were recruited from local Hospitals in the Xiaoshan District of Zhejiang province. Diagnoses of all cases were based on DSM-V criteria by two neuro-pediatricians. The exclusion criteria were: children with other psychiatric disorders, chronic medical comorbid conditions, those who received calcium and/or vitamin D therapy in the past 12 months, or were on a treatment known to affect serum vitamin D levels. Age- and gender-matched healthy controls were selected from both a preschool and a primary school in the same district. This study was approved by the Medical Ethics Committee of Zhejiang Xioashan Hospital. Informed consent was obtained from parents or guardians of all children.

Fasting blood samples were collected from both autistic children and healthy controls. After centrifugation, aliquots of the serum samples were immediately stored at −80 °C before the assay. Serum 25(OH)D concentration were measured on the E601 modular (Siemens Healthineers, Beijing, China). All tests in this study were performed in our clinical laboratory in Xiaoashan Hospital. Tests were performed in triplicate for each sample and the averaged values were used in the data analyses. TaqMan probe approach was applied to determine the genotypes of SNPs in DNA extracted from blood cells. TaqMan probes were designed and synthesized by Applied Biosystems (Beijing, China). Real-time PCR was conducted following the manufacturer’s protocol as described previously [27, 34, 35].

Statistical analysis

Categorical variables were expressed as percentages and their differences were examined by χ² tests. Continuous variables are presented as mean (SD) and examined by Student’s t-tests. Associations between the VDR SNPs and serum vitamin D levels were analyzed using linear regression models. Logistic regression was applied to determine the relationship between the SNPs and vitamin D deficiency, between SNPs and childhood ASD, and between serum vitamin D and ASD. Logistic regression models were used to calculate the area under the ROC curve to estimate the role of serum vitamin D in predicting the risk of childhood ASD. Two-sided P-values less than 0.05 were considered to be significant. All statistical analyses were carried out using SAS 9.4 software (SAS Institute Inc., Cary, NC).

Results

A total of 269 children with ASD and 320 healthy controls were enrolled at similar ages and comparable gender ratios (Table 1). The average concentration of serum vitamin D was 18.3 ± 6.3 ng/ml for children with ASD and 23.5 ± 7.4 ng/ml for healthy control (P < 0.0001). Among children with ASD, 182 (67.7%) of them had a vitamin D deficiency (< 20 ng/ml), and 68 (25.3%) had a vitamin D insufficiency (20 ~ 29.9 ng/ml). Healthy controls had a significantly lower proportion of vitamin D deficiency (34.1%), but a similar proportion of insufficiency.

Our data showed that there was no significant correlation between the examined VDR SNPs and serum vitamin D concentrations in children with ASD, healthy controls, or all children combined (Table 2). Genotypes of all SNPs examined were not significantly correlated with vitamin D deficiency in children with ASD, healthy controls, or all of the children (Table 3).

The correlation between the VDR SNPs and childhood ASD was analyzed by logistic regression. Both genotype and allele frequency of s731236 was significantly
associated with childhood ASD. There was no significant association between other SNPs and childhood ASD (Table 4).

Results of logistic regression models indicated that an increased serum vitamin D concentration was significantly associated with a decreased risk of childhood ASD (Odd ratio (OR) = 0.87, 95% confidence interval (CI): 0.85–0.90) (Table 5). The area under the ROC curve for serum vitamin D was 0.7285 (95% CI: 0.6889–0.7338, P < 0.0001) in predicting the risk of childhood ASD (Fig. 1). At the optimal vitamin D cutoff point (19.0 ng/ml) the sensitivity and specificity were 71.5% and 69.6%, respectively. In combination with VDR, SNPs didn’t improve the predicting performance (data not shown). Our data also showed that vitamin D deficiency was significantly associated with the risk of childhood ASD. SNP rs731236, or low serum vitamin D, or vitamin deficiency was correlated with the risk of childhood ASD. Children with both T/C genotype of rs731236 and vitamin D deficiency had a higher risk of ASD compared to children with vitamin D deficiency alone, with the T/C genotype alone, or with genotype A/A and no vitamin D deficiency (Table 5).

Discussion

Vitamin D has been implicated as an important environmental factor related to the development of ASD. This study examined the correlation between VDR SNPs and serum vitamin D in children from the Chinese Han population, and then determined their roles in predicting childhood ASD. Our data showed that children with ASD had significantly lower serum levels of vitamin D and a higher rate of vitamin D deficiency. The examined SNPs were not associated with serum vitamin D levels or vitamin D deficiency in children with ASD, or healthy controls, or all children. Notably, up to 269 children with ASD and 320 healthy controls from the Chinese Han population
were included in this study. Similar to this finding, a previous study examined rs731236, rs7975232, rs1544410, rs2228570, and rs11568820 as well as serum vitamin D in 106 overweight/obese and 86 healthy (control) Chinese Han children, from a nearby district. No association was observed between these VDR SNPs and serum vitamin D [33]. A Poland study reported no statistical significant differences according to VDR SNPs (rs731236, rs7975232, rs1544410 and rs2228570) and serum vitamin D concentrations in children with ASD [28]. A genome-wide study in 417,580 Europeans reported that over 140 SNPs in non-VDR genes, were correlated with serum vitamin D levels [36].

Conversely, Coskun et al. discovered that the T/T genotype of rs2228570 was significantly associated with an increased risk of childhood ASD and with higher serum vitamin D in Turkish children with ASD [26]. A Canadian twin study found that carriers of the TT genotype of rs2228570 had significantly higher serum 25(OH)D concentrations in multiple sclerosis patients [37]. An Italian study revealed that TT genotype of rs2228570, but not rs1544410, rs731236 and rs7975232, was significantly correlated with higher serum vitamin D in multiple sclerosis patients [32]. A Mexican study evaluated the correlation between the vitamin D deficiency and genetic variants on VDR and the vitamin D binding protein (GC) genes in 689 unrelated postmenopausal women. Their results showed that the SNPs rs4516035 in VDR and rs2282679 in GC were associated with vitamin D deficiency [38]. These findings suggest that certain VDR SNPs are correlated with serum vitamin D in some regions

| Table 3 Correlation between VDR SNPs and vitamin D deficiency |
|-----------------------------|-----------------------------|-----------------------------|---------------------------------|-----------------------------|
| SNPs | Genotype | Vitamin D | Non-deficient | Deficient | OR (95% CI) | P |
|-----------------------------|-----------------------------|-----------------------------|---------------------------------|-----------------------------|
| Children with ASD | | | | | | |
| rs731236 | T/T | 138 (65.7) | 72 (34.3) | | | |
| | T/C | 29 (74.4) | 10 (25.6) | 1.48 (0.68–3.21) | 0.3197 | |
| rs1568820 | G/G | 59 (66.3) | 30 (33.7) | | | |
| | G/A | 78 (70.3) | 33 (29.7) | 1.24 (0.68–2.26) | 0.2639 | |
| | A/A | 30 (62.5) | 18 (37.5) | 0.82 (0.39–1.71) | 0.3628 | |
| rs2228570 | T/T | 45 (69.2) | 20 (30.8) | 1 | | |
| | T/C | 82 (68.3) | 38 (31.7) | 0.99 (0.51–1.9) | 0.6437 | |
| | C/C | 39 (62.9) | 23 (37.1) | 0.75 (0.36–1.58) | 0.3767 | |
| rs1544410 | G/G | 142 (65.4) | 75 (34.6) | | | |
| | G/A | 25 (80.7) | 6 (19.4) | 2.19 (0.86–5.57) | 0.1008 | |
| Healthy controls | | | | | | |
| rs731236 | T/T | 96 (34) | 186 (66) | | | |
| | T/C | 11 (35.5) | 20 (64.5) | 1.07 (0.49–2.32) | 0.8714 | |
| rs1568820 | G/G | 36 (35) | 67 (65) | | | |
| | G/A | 55 (35) | 102 (65) | 1 (0.6–1.69) | 0.65 | |
| | A/A | 16 (30.2) | 37 (69) | 0.81 (0.4–1.64) | 0.5037 | |
| rs2228570 | T/T | 31 (41.9) | 43 (58.1) | | | |
| | T/C | 49 (30.3) | 113 (69.8) | 0.6 (0.34–1.06) | 0.1288 | |
| | C/C | 27 (35.1) | 50 (64.9) | 0.75 (0.39–1.45) | 0.901 | |
| rs1544410 | G/G | 93 (33.8) | 182 (66.2) | | | |
| | G/A | 14 (36.8) | 24 (63.2) | 1.14 (0.56–2.31) | 0.7127 | |
| All children | | | | | | |
| rs731236 | T/T | 234 (47.6) | 258 (52.4) | 1 | | |
| | T/C | 40 (57.1) | 30 (42.9) | 1.47 (0.88–2.43) | 0.1388 | |
| rs1568820 | G/G | 95 (49.5) | 97 (50.5) | 1 | | |
| | G/A | 133 (49.6) | 135 (50.4) | 1.01 (0.7–1.47) | 0.553 | |
| | A/A | 46 (45.5) | 55 (54.5) | 0.84 (0.51–1.36) | 0.4012 | |
| rs2228570 | T/T | 78 (56.1) | 61 (43.9) | 1 | | |
| | T/C | 129 (45.7) | 153 (54.3) | 0.66 (0.44–1) | 0.1636 | |
| | C/C | 66 (47.5) | 73 (52.5) | 0.71 (0.44–1.13) | 0.4772 | |
| rs1544410 | G/G | 235 (47.8) | 257 (52.2) | 1 | | |
| | G/A | 39 (56.5) | 30 (43.5) | 1.14 (0.5–2.62) | 0.7524 | |
and racial/ethnical groups. The VDR polymorphisms impact structure and/or function, which may in turn influence serum vitamin D levels through a compensatory mechanism. Further studies are needed to clarify this correlation and elucidate the possible underlying mechanism.

Our study confirmed that children with T/C genotype, or C allele of the SNP rs731236 had a significantly increased risk of childhood ASD, whereas other SNPs examined in this study were not associated with the risk of childhood ASD [27]. A Turkish study revealed that rs731236, rs2228570, and rs1544410 were significantly associated with childhood ASD [26]. A Poland study enrolled 108 children with ASD, and 196 non-ASD children. Their result indicated that rs2228570 and rs7975232, but not rs1544410 and rs731236, of the VDR gene were correlated with ASD [28]. Another Italian study revealed that rs2228570 is associated with ASD [39]. The association between VDR SNPs and ASD has also been reported in other studies [29, 40]. All of these studies strongly suggest that certain VDR polymorphisms are associated with the risk of ASD, whereas the types of VDR SNPs are racial/ethnic specific. Still a few studies reported no association between VDR polymorphism and risk of ASD possibly due to limited sample size [34, 41]. More studies are warranted to identify and validate the SNPs specific for their own races/ethnics.

### Table 4: Correlation between genotypes and allele frequency of SNPs on VDR gene and childhood ASD

| SNPs     | Genotype/Allele | Cases n (%) | Controls n (%) | OR (95% CI) | P value |
|----------|-----------------|-------------|----------------|-------------|---------|
| rs731236 | T/T             | 210 (84.3)  | 282 (90.1)     | 1           |         |
|          | T/C             | 39 (15.7)   | 31 (9.9)       | 1.71 (1.04–2.84) | 0.0364 |
|          | T               | 459 (92.2)  | 595 (95.1)     | 1           |         |
|          | C               | 39 (7.8)    | 31 (5)         | 1.65 (1.02–2.69) | 0.0433 |
| rs1568820| G/G             | 89 (35.9)   | 103 (32.9)     | 1           |         |
|          | G/A             | 111 (44.8)  | 157 (50.2)     | 0.81 (0.56–1.18) | 0.2041 |
|          | A/A             | 48 (19.4)   | 53 (16.9)      | 1.03 (0.63–1.67) | 0.5556 |
|          | G               | 289 (58.3)  | 363 (58)       | 1           |         |
|          | A               | 207 (41.7)  | 263 (42)       | 0.98 (0.77–1.24) | 0.8534 |
| rs2228570| T/T             | 65 (26.3)   | 74 (23.6)      | 1           |         |
|          | T/C             | 120 (48.6)  | 162 (51.8)     | 0.84 (0.56–1.26) | 0.4275 |
|          | C/C             | 62 (25.1)   | 77 (24.6)      | 0.92 (0.57–1.47) | 0.9904 |
|          | T               | 250 (50.6)  | 310 (49.5)     | 1           |         |
|          | C               | 244 (49.4)  | 316 (50.5)     | 0.96 (0.76–1.21) | 0.7177 |
| rs154440 | G/G             | 217 (87.5)  | 275 (87.9)     | 1           |         |
|          | G/A             | 31 (12.5)   | 38 (12.1)      | 1.04 (0.63–1.73) | 0.8691 |
|          | G               | 465 (93.8)  | 588 (93.9)     | 1           |         |
|          | A               | 31 (6.3)    | 38 (6.1)       | 1.04 (0.63–1.70) | 0.8754 |

### Table 5: Predictor roles of serum vitamin D and other markers in childhood ASD

| Variable                            | OR (95% CI) | P      |
|-------------------------------------|-------------|--------|
| Serum vitamin D                     |             |        |
| Continuous (ng/ml)                  | 0.88 (0.85–0.91) | < .0001 |
| Deficiency                          |             |        |
| No                                  | 1           |        |
| Yes                                 | 3.92 (2.76–5.58) | < 0.001 |
| Rs731236 + vitamin D deficiency     |             |        |
| T/C                                 | 1           |        |
| T/C No                              | 0.57 (0.28–1.17) | 0.0017 |
| T/T Yes                             | 0.19 (0.07–0.53) | 0.039  |
| T/T No                              | 0.15 (0.07–0.31) | < .0001 |

Fig. 1 Receiver operating characteristics (ROC) curve for serum vitamin D in differentiating children with ASD from healthy controls
Lower levels of serum vitamin D in patients with ASD have been reported in previous studies. A study determined serum levels of vitamins and minerals in 274 Chinese children diagnosed with ASD and 97 age-matched healthy children from the Han population from another Chinese region. Serum levels of vitamin D, calcium, magnesium, iron, and zinc in children with ASD were significantly lower than those of healthy controls [14]. Another Chinese study examined the serum vitamin D levels in 215 children with ASD and 285 healthy control children. Their study revealed that serum vitamin D concentrations were negatively correlated with ABC total scores and language subscale scores [42]. Other studies from various countries have indicated lower serum vitamin D in patients with ASD [10–13, 15, 43, 44]. This study corroborated that children with ASD had lower serum vitamin D and a higher prevalence rate of vitamin D deficiency. Consistently, vitamin D supplementation has been shown to improve symptoms of ASD [12, 20, 42, 45]. However, several other studies with smaller sample sizes reported no significant difference in serum vitamin D between children with ASD and healthy controls [46–49].

Our study also found that serum vitamin D had a fair performance in distinguishing children with ASD from healthy controls with the area under the ROC curve of 0.7285. VDR SNPs did not further improve performance of serum vitamin D in predicting the risk of ASD. However, our results indicated that T/C genotype of rs731236 and deficiency of vitamin D were correlated with the highest risk of childhood ASD compared with another genotype with or without vitamin D deficiency. Since serum vitamin D can be measured at any time, it has the potential to become a marker in diagnosing ASD at younger ages. It is of clinical significance to identify other biomarkers which improve its predicting performance in the future studies.

Limitations of this study include a non-random selection of cases and controls. Only children with ASD treated in our hospitals were enrolled in this study. The sample size is still relatively moderate. Serum levels of vitamin D were measured only at the baseline. Information regarding dietary intake of vitamin D and sunlight exposure time were not recorded in these subjects. The cause of low serum vitamin D was therefore not able to be assessed in this study.

**Conclusions**

All examined common VDR SNPs are not correlated with serum vitamin D concentrations or vitamin D deficiency. The combination of T/C phenotype of rs731236 and vitamin D deficiency are associated with a higher risk of childhood ASD. Vitamin D is a promising target in the prevention and treatment of this disease.

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**Author contributions**

JL and ZZ contributed to conception and design. Material preparation, data collection and analysis were performed by ZZ, GJ, HY and JL. The first draft of the manuscript was written by JL and all authors commented on previous versions of the manuscript. All authors have read and approved the final manuscript.

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**Declarations**

**Conflict of interest**

The authors have declared no conflicts of interests with respect to the research, authorship, and/or publication of this article.

**Ethical approval**

This study was approved by the Medical Ethics Committee of Zhejiang Xiaoshan Hospital.

**Consent to participate**

Written informed consent was obtained from the parents.

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