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RESEARCH ARTICLE

Vitamin D Receptor Gene (CDX-2) Polymorphism in Chronic Childhood Immune Thrombocytopenic Purpura

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Abstract: ***Background***: Immune thrombocytopenic purpura (ITP) is a hematological immune disorder characterized by bleeding and a low platelet count of less than <100x109/L. The deficiency of vitamin D (VD) is associated with autoimmune diseases as ITP. We aimed to highlight the association of the VDR gene (Cdx-2) polymorphism in childhood chronic ITP and compare gene and allele frequencies in both patients and controls to detect any relationship between this gene polymorphism and disease severity and treatment response. Results: VD deficiency was more frequent among children with chronic ITP compared to control group especially in non-responders. Additionally, the frequent distribution of Cdx-2 genotypes was the homozygous GG genotype in ITP patients and controls without a significant difference. Additionally, the G allele was more frequent in controls than in patients. Conclusion: VD deficiency was more prevalent among patients than controls, and children with adequate VD levels showed good response to treatment.

Keywords: Immune thrombocytopenic purpura, Vitamin D gene (Cdx2) polymorphisms, Genotype, Allele.

INTRODUCTION

Immune thrombocytopenic purpura (ITP) is a chronic autoimmune hematological disorder characterized by a persistently low platelet count, typically below 100 × 10^9/L, leading to an increased risk of bleeding. The condition arises due to immune-mediated destruction of platelets and impaired platelet production in the bone marrow. Patients with ITP may present with symptoms ranging from mild bruising and petechiae to severe bleeding complications, including mucosal hemorrhages and, in rare cases, life-threatening intracranial hemorrhages. The exact cause remains unclear, but it is thought to involve autoantibodies targeting platelet surface antigens, leading to their premature clearance by the spleen. [1]. ITP is a heterogeneous illness with varying clinical outcomes and therapeutic responses; children with ITP have better outcomes than adults. [2]**.** Generally, children with ITP recover within six to twelve months of diagnosis, with or without therapy. However, 20–25% of pediatric patients suffer from chronic ITP [3]**.** Immune thrombocytopenic purpura (ITP) can be classified into two main subtypes based on its underlying etiology: primary ITP and secondary ITP. Primary ITP, which accounts for approximately 80% of all cases, is most commonly observed in children and is often preceded by a nonspecific viral infection. It typically presents as an isolated thrombocytopenia without any other identifiable underlying disorder and is generally thought to be caused by an aberrant immune response leading to platelet destruction. In most pediatric cases, primary ITP tends to be self-limiting and resolves spontaneously within a few months. However, in some individuals, particularly adults, it can become chronic and require ongoing management.

Secondary ITP, on the other hand, is associated with a wide range of systemic conditions and can complicate the course of several autoimmune and lymphoproliferative disorders. Autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren's syndrome, and Evans syndrome are known to predispose patients to secondary ITP by triggering immune dysregulation and the production of autoantibodies that target platelets. Additionally, certain lymphoproliferative malignancies, particularly chronic lymphocytic leukemia (CLL), can contribute to secondary ITP by disrupting normal immune function and promoting platelet destruction. The management of secondary ITP often requires addressing the underlying condition in addition to therapies aimed at increasing platelet counts and reducing the risk of bleeding complications. [4]**.**

According to the evolution of the disease, Primary ITP can be subclassified according to the duration of the disease into: newly diagnosed ITP (< 3 months), persistent ITP (3 to 12 months) and chronic ITP (> 12 months) [5]. ITP is caused by an autoimmune response targeting circulating platelets in the peripheral blood and megakaryocytes in the bone marrow, resulting in increased platelet destruction and reduced generation of new platelets [6]**.**

Patients often present with symptoms related to bleeding as a result of thrombocytopenia, such as petechiae and purpura on the legs, orofacial bleeding, hematuria and menorrhagia [7].

In humans, vitamin D (VD) exerts numerous immune modulatory and anti-inflammatory effects, besides its major role in bone mineral homeostasis, and VD deficiency has been linked to an increase in susceptibility to autoimmune illnesses, including ITP, SLE, type 1 diabetes, Graves' disease, and multiple sclerosis (MS). The use of VD supplementations has been documented to decrease the risk for such disorders [8].

The vitamin D receptor (VDR) is a crucial component of the steroid receptor superfamily and plays a pivotal role in mediating the diverse biological effects of vitamin D throughout the body. This receptor is widely expressed in various cell types, highlighting its broad physiological significance. It is particularly abundant in immune cells such as macrophages and lymphocytes, where it contributes to the modulation of immune responses. Additionally, VDR is found in several endocrine tissues, underscoring its involvement in hormonal regulation and metabolic processes.

The VDR gene is located on chromosome 12q12–q14 and exhibits a high degree of genetic variability. These genetic variations, known as polymorphisms, can significantly influence the receptor's functionality, altering the way vitamin D interacts with cellular pathways. Such variations may impact immune function, calcium homeostasis, and susceptibility to various autoimmune and inflammatory diseases.

Among the numerous polymorphisms identified within the VDR gene, five key single nucleotide polymorphisms (SNPs) have been extensively studied for their potential biological and clinical implications:

1. **FokI polymorphism**, which is located in **exon 2** of the gene, plays a role in modifying the length and function of the VDR protein, potentially affecting its ability to bind to vitamin D-responsive elements in target genes.
2. **BsmI polymorphism**, found in **intron 8**, is a non-coding SNP that influences VDR gene transcription and mRNA stability, thereby indirectly affecting receptor expression levels.
3. **ApaI polymorphism**, also present in **intron 8**, has been associated with variations in bone mineral density, immune system function, and susceptibility to chronic diseases.
4. **TaqI polymorphism**, located in **exon 9**, is known to influence VDR protein conformation and has been linked to multiple conditions, including osteoporosis, autoimmune disorders, and cancer risk.
5. **Cdx-2 polymorphism**, found within the exon 1 promoter region, regulates VDR gene expression by influencing transcriptional activity. Given its location, this polymorphism has been particularly studied in relation to immune system function, inflammatory diseases, and vitamin D metabolism.

These genetic polymorphisms collectively contribute to inter-individual variability in vitamin D metabolism, signaling pathways, and immune modulation. Understanding these variations is critical for assessing genetic predisposition to diseases, optimizing vitamin D-related therapeutic interventions, and exploring potential gene-environment interactions in health and disease[9,10].

The vitamin D-VDR receptor complex can bind to thousands of VDR response elements on the human genome. Certain SNPs of the VDR gene may result in reduction of the function of VD and had been linked to a range of autoimmune diseases such as SLE, MS, type 1 DM and Grave's disease [11,12].

MATERIAL AND METHODS

Study design and participants.

This study was a cross-sectional comparative study, included 50 children and adolescents with chronic ITP (3 to 18 years old),
(25 boys and 25 girls), and 50 age and sex matched healthy controls (19 males and 31 females). Patients and controls were recruited from the pediatric hematology outpatient clinics and the general outpatient clinics at Mansoura University Children's Hospital (MUCH), respectively.

The patients included were children and adolescents (3 to 18 years old) diagnosed with chronic ITP.

Patients were diagnosed based on the presence of bruising and/or petechiae or mucous membrane bleeding, platelet count < 100 × 109/L and increased or normal count of megakaryocytes in bone marrow aspirates[13]. Children with acute, persistent ITP, secondary ITP and or thrombocytopenia due to any other causes were excluded.

The patients were assessed for age, sex, residence**,** history of bleeding, treatment lines and response to treatment. They were subjected to general examination for dysmorphic features, hepatosplenomegaly and/or lymphadenopathy, examination for mucocutaneous, orofacial bleeding and bleeding score.

ITP patients were receiving a treatment protocol according to guidelines of the American Society of Hematology 2019 for ITP. Definition of response to treatement: complete responder (CR) with a platelet count >100 $^{x}10^{9}$/L, responder (R): with a platelet count >30$^{x}10^{9}$/L and non-responder (NR): with a platelet count <30 $^{x}10^{9}$/L. The platelet count was measured on 2 occasions >7 days apart in absence of bleeding [13].

Laboratory investigation:

A complete blood picture (CBC) and serum 25-hydroxyvitamin D [25(OH)D] concentration were measured in both patients and control groups to evaluate their hematological parameters and vitamin D status. These assessments were conducted using an enzyme-linked immunosorbent assay (ELISA) kit (K2110 Immunodiagnostic, Dutch Company, Holland), strictly following the manufacturer's recommended protocol to ensure accuracy and reliability. Measurement of serum 25(OH)D concentration allowed for the classification of participants based on their vitamin D status.

Vitamin D levels were categorized into four distinct groups based on serum 25(OH)D concentrations. Severe vitamin D deficiency (VDSD) was defined as a serum 25(OH)D level of less than 10 ng/mL, indicating a critically low concentration associated with a high risk of bone demineralization, immune dysfunction, and increased susceptibility to various chronic diseases. Moderate vitamin D deficiency (VDMD) was characterized by serum 25(OH)D levels ranging between 10 and 20 ng/mL, reflecting a suboptimal status that may contribute to mild skeletal and immune system impairments. Individuals with vitamin D insufficiency (VDI) had serum 25(OH)D concentrations between 21 and 29 ng/mL, suggesting that while their levels were not critically low, but still inadequate for optimal physiological function. Finally, vitamin D sufficiency (VDS) was defined as a serum 25(OH)D level of 30 ng/mL or higher, indicating an adequate supply necessary for maintaining bone health, immune modulation, and overall well-being.

Analysis of the VDR polymorphisms (SNPs) of the Cdx-2 gene (rs11568820) with the following primers: G-For: 5'-AGGATAGAGAAAATAATAGAAAACATT-3', G-Rev: 5'-AACCCATAATAAGAAATAAGTTTTTAC-3 , A-For: 5'-TCCTGAGTAAACTAGGTCACAA-3', A-Rev: 5'-ACGTTAAGTTCAGAAAGATTAATTC-3' was performed using molecular biology methods including: DNA extraction, gene polymorphism detection using tetra-primer amplification-refractory mutation system-polymerase chain reaction (T-ARMS-PCR) technique and agarose gel electrophoresis **(Figure 1)**.

Statistical analysis:

The Statistical Package for Social Sciences (SPSS) version 21 for Windows (SPSS, Inc., Chicago, IL, U.S.A.) was utilized for comprehensive data analysis, ensuring accuracy and reliability in statistical evaluations. The normality of the data distribution was assessed using the one-sample Kolmogorov–Smirnov test. This step was essential in differentiating between parametric and non-parametric data.

For genetic analysis, the distribution of VDR Cdx2 polymorphism genotypes and allelic frequencies was calculated for both patients and control groups. Using the Pearson chi-square (χ^2) test to evaluate whether the observed genotype frequencies were deviated from expected values. Additionally, odds ratios (ORs) with 95% confidence intervals (CIs) were computed to determine the strength of associations between the presence of specific genotypes and the risk of developing the disease.

To compare the two groups statistically, different tests were applied based on data normality. The Student's t-test was employed for parametric data to compare mean values between the patient and control groups, while the Mann–Whitney U test was used for non-parametric data. A p-value of ≤ 0.05 was considered significant.

RESULTS

The study comprised two well-defined groups: the patients group, which included 50 children with chronic ITP, and a control group consisting of 50 healthy children matched by age and sex. Among the ITP cohort, there was an equal distribution of males and females, with 25 boys and 25 girls. The control group, while also balanced, included 19 males and 31 females. This careful matching ensured that any observed differences in the study outcomes could be attributed to disease status rather than demographic discrepancies.

Analysis of vitamin D levels categorized participants into four distinct groups: 9 individuals (18%) exhibited vitamin D insufficiency (VDI) with 25(OH)D levels below 20 ng/ml. A further 14 children (28%) fell within the moderate deficiency (VDMD) range, with level between 20 - 30 ng/ml. Meanwhile, 12 children (24%) were found to have severe vitamin D deficiency (VDSD) with levels falling below 10 ng/ml. The remaining 15 children (30%) demonstrated vitamin D sufficiency (VDS), with 25(OH)D levels exceeding 30 ng/ml. These findings highlight the substantial variability in vitamin D status among the study population, emphasizing the potential implications of deficiency in children with chronic ITP.

Genotypic analysis of the VDR Cdx2 polymorphism revealed no statistically significant differences between the patient and control groups in terms of genotype distribution or allelic frequency. Within the ITP group, the GG genotype was the most prevalent, accounting for 56% of cases, while the AA genotype was the least frequent, appearing in only 6% of patients. The AG genotype was observed in 38% of the patient cohort. Similarly, in the control group, genotype

frequencies were distributed as follows: GG at 54%, AA at 8%, and AG at 38%. These closely mirrored distributions further reinforce the absence of a meaningful association between Cdx2 polymorphism and chronic ITP in this population.

Regarding allelic frequency, the G allele was more commonly represented in both groups, accounting for 66% in ITP patients compared to 27% in controls. Conversely, the A allele was observed in 34% of patients, while its prevalence was higher in controls at 73%. Although minor differences were observed, statistical analyses confirmed that these variations did not reach significance, suggesting that Cdx2 polymorphism is unlikely to serve as a major genetic determinant in the pathogenesis of chronic ITP **(Table 1)**.

Table 1: Comparison of single nucleotide polymorphism Cdx-2 genotypes and alleles frequency between patients and controls.

Genotypes	Patients group (n=50)	Control group (n=50)	Test of significance	P value
Genotypes				
GG (mutant homozygous)	28 (56.0%)	27 (54.0%)	MC	0.216
AA (wild homozygous)	3 (6.0%)	4 (8.0%)		
AG (mutant heterozygous)	19 (38.0%)	19 (38.0%)		
Alleles				
G	66 (66.0%)	27 (27.0%)	χ^2 =1.16	0.282
A	34 (34.0%)	73 (73.0%)		

MC: Monte Carlo test, χ^2: Chi square test

The Cdx-2 genotypes and the serum Vit D level did not have a significant relationship (p value >0.05). The percentages of severe deficiency were 21.1% and 28.6% in the GG and AG genotypes, respectively. The percentages of moderate deficiency were 15.8%, 66.7%, and 32.1% in the GG, AA, AG genotypes respectively (**Table 2).**

Table 2: Relation between single nucleotide polymorphism Cdx-2 genotypes and vitamin D level:

Vitamin D	Genotypes			Test of significance	P value
	GG (n=19)	**AA (n=3)**	**AG (n=28)**		
Sufficient (VDS)	9 (47.4%)	0 (0%)	6 (21.4%)	MC	0.258
Insufficient (VDI)	3 (15.8%)	1 (33.3%)	5 (17.9%)		
Moderate deficiency (VDMD)	3 (15.8%)	2 (66.7%)	9 (32.1%)		
Severe deficiency (VDSD)	4 (21.1%)	0 (0%)	8 (28.6%)		

MC: Monte Carlo test.

No significant associations were detected between the VDR Cdx2 genotypes and the response to treatment (p value >0.05). Among the GG group 52.6% were CR, 26.3% were partial responders, and 21.1% were non-responders. While in the AA group 33.3% were CR, 66.7% were partial responders, and 0% were non-responder. In addition, 39.3% of the AG group were CR, and 42.9% were partial responders and 17.9% non-responder**s (Table 3) and (Figure 1).**

Table 3: Relation between single nucleotide polymorphism Cdx-2 genotypes and response to treatment

Response to treatment	Genotypes			Test of significance	P value
	GG (n=19)	**AA (n=3)**	**AG (n=28)**		
Non responder	4 (21.1%)	0 (0%)	5 (17.9%)	MC	0.633
Responder	5 (26.3%)	2 (66.7%)	12 (42.9%)		
Complete responder	10 (52.6%)	1 (33.3%)	11 (39.3%)		

MC: Monte Carlo test

There was no statistically significant association observed between the VDR alleles and the response to treatment. Among the G allele group 47% were CR, 33.3% were partial responders, and 19.7% were non-responders, while in the A allele group 38.2% were CR, 47.1% were partial responders and 14.7% were non-responders.

Figure Legends:

Fig 1: Agarose gel electrophoresis (2%) of polymerase chain reaction (PCR) product of tetra-primer ARMS-PCR for CDX2 genotypes.

1 Kb
DNA ladder

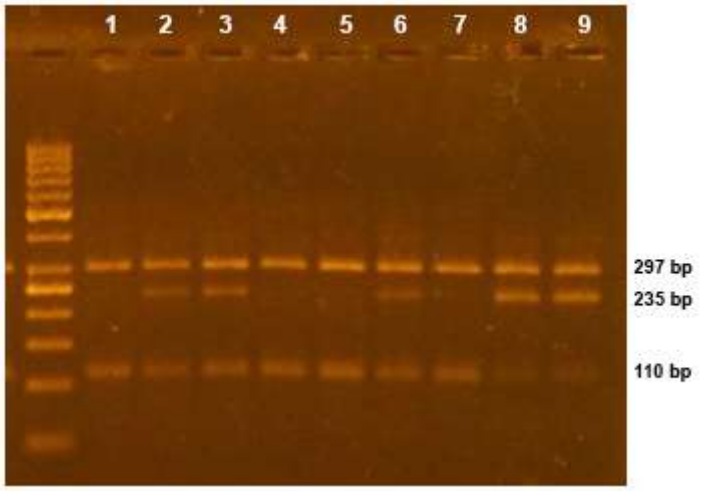

Fig. 1: Agarose gel electrophoresis (2%) of polymerase chain reaction (PCR) product of tetra-primer ARMS-PCR for CDX2 genotypes. Lane 1, 4, 5,7 wild homozygous **(AA),** Lane 2,3,6**:** mutant heterozygous **(AG)**. Lane 8,9: mutant homozygous (**GG).**

DISCUSSION

This study evaluated the platelets count, initial 25OH-VD levels, single nucleotide polymorphism (SNPs) Cdx-2 genotypes and alleles in patients and controls, and the response to treatment in 50 children with chronic ITP.

Initial 25OH-VD levels:

Our study revealed that the children in the patient group had a statistically significant lower serum VD level compared to the control group (P value 0.002). Our study's findings agreed with those of Čulić et al. [15], who found VD deficiency (values < 75 nmol/L) in 11 patients with newly diagnosed ITP, and 7 patients with chronic ITP in their study on 21 children with both chronic and newly diagnosed ITP. Three patients with newly diagnosed ITP and none with chronic ITP had normal VD levels.

A higher percentage of hypovitaminosis D was in patients diagnosed with autoimmune disorders such as MS, type 1 DM, SLE, RA, thyroiditis, and autoimmune gastritis. Moreover, VD deficiency in ITP can be contributed to the excess use of corticosteroid which results in increased VD catabolism through the activation of expression of steroids and xenobiotic nuclear receptors, which in turn enhances VD degradation [16].

Frequency of single nucleotide polymorphism (SNP) Cdx-2 genotypes and alleles in patients and controls:

According to our findings, the patient group had a higher presentation of the GG genotype, and a higher presentation of the G allele than the A allele without a statistically significant difference, while the control group had a higher presentation of the AA genotype, these results were in concordance with those of Hesham et al. [17] and Yesil et al. [18]. These outcomes suggest that a higher risk of chronic ITP in children is associated with the presence of both the G allele and the GG genotype.

Hesham et al. [19] study on 42 chronic ITP patients reported that the most presented genotype was the GG, which was present in 29 patients (69 %) and the AG genotypes which were present in 11 patients (26.2%), and the AA genotype was present in 2 patients (4.8%).

Relation between SNP Cdx-2 genotypes and alleles and vitamin D level in patients and controls:

Regarding the relation between genotypes and VD level, our findings indicated that there was no significant relationship between the serum VD levels and the three VDR genotypes. Moreover, there was no significant difference between the two alleles A and G regarding serum VD levels (p-value 0.258). Consistent with these results, Yesil et al. [19] who discovered that the mean serum 25(OH) D did not significantly differ between ITP patients who had the Cdx2 A allele (20.8 ± 8.72 ng/mL; range, 11.5–37 ng/mL) and those who did not (18.68 ± 9.18 ng/mL; range, 4.4–46.2 ng/mL; P = 0.576).

SNP Cdx-2 genotypes and alleles and response to treatment in patients:

Genotypic Distribution and Treatment Response:

With respect to the relationship between genotypic variations, allelic frequency, and response to treatment in children with chronic immune thrombocytopenic purpura (ITP), our findings indicated that the distribution of treatment outcomes differed among the various genotypes (GG, AA, and AG). Patients were categorized based on their response into complete responders, partial responders, and non-responders. While variations were observed in the proportion of responders within each genotype group, these differences did not reach statistical significance. This suggests that, within the sample studied, the VDR Cdx2 polymorphism did not have a major influence on

treatment efficacy. Nonetheless, the observed trends warrant further exploration in larger, multicenter studies to determine whether certain genetic variants may predispose individuals to better or worse therapeutic outcomes.

Given the complex interplay of genetic, environmental, and immunological factors in ITP, it is possible that additional gene polymorphisms or epigenetic modifications could play a role in determining responsiveness to standard treatment regimens. Further research into genetic markers and their impact on disease progression and treatment resistance may help refine individualized treatment strategies, leading to better patient outcomes.

- VD acts as a balancing regulator of the cell-mediated Th1 and humoral Th2 immune response.
- Vitamin D enacts these changes in its calcitriol form by interacting with nuclear vitamin D receptors (nVDR) expressed on B and T lymphocytes, neutrophils, monocytes, and dendritic cells.
- Hypovitaminosis D may result in immune abnormalities and the development of autoimmune diseaes as ITP and supplementation of VD might reduce chronic disease risk by modulating the immune system.

Study Limitations and Future Directions

While this study provides valuable insights into the relationship between vitamin D polymorphisms, genetic factors, and chronic ITP, several limitations should be acknowledged. One major limitation was the relatively small sample size, which may have reduced the statistical power needed to detect subtle but potentially meaningful associations. A larger cohort could provide more robust conclusions and clarify whether genetic polymorphisms influence disease susceptibility or treatment response in a clinically significant manner.

Additionally, the study was conducted at a single center, which may limit the generalizability of the findings to broader populations. Differences in patient demographics, regional environmental factors, and healthcare practices may impact both vitamin D status and genetic predisposition, necessitating multicenter or multinational studies to validate these results.

Furthermore, disease heterogeneity remains a significant challenge. Variations in ITP pathogenesis and progression across different age groups could contribute to discrepancies in findings. Children and adults with ITP may exhibit distinct immune profiles, response patterns, and genetic predispositions, which should be taken into account in future studies.

Future Research Recommendations

Expanding the scope of research beyond the VDR Cdx2 polymorphism could provide additional insights into the genetic landscape of chronic ITP. Investigating other common vitamin D receptor gene polymorphisms, including FokI, BsmI, and ApaI, may yield more comprehensive findings regarding the genetic factors that influence disease susceptibility, severity, and treatment response. These polymorphisms have been implicated in immune regulation and may play a role in autoimmune diseases, including ITP.

CONCLUSION

A higher prevalence of VDD among patients than controls was found. We could not find a significant relationship between VD receptor polymorphisms, either genotypes or allelic frequency and disease severity, the VD level, or the response to treatment.

Further research incorporating functional studies on vitamin D metabolism and its interaction with immune cells in ITP patients may help clarify whether vitamin D supplementation could serve as an adjunct therapy. Additionally, evaluating the interplay between genetic polymorphisms and cytokine profiles could shed light on the underlying immunopathology of the disease.

Abbreviations

CR; Complete responder
ITP; Immune thrombocytopenic purpura
PCR; Polymerase chain reaction
SNP; Single nucleotide polymorphism
SPSS; Statistical package for social science
VDI; Vitamin D insufficiency.
VDMD; Vitamin D Moderate deficiency.
VDS; Vitamin D sufficiency.
VDSD; Vitamin D severe deficiency.

Ethics approval and participant consent:

The study received ethical approval from the Institutional Review Board (IRB) of Mansoura University's Faculty of Medicine in Egypt (Code No.: MD.19.04.164). Before enrollment in the study, written informed consent was obtained from the parents of the participants. The study was conducted from June 2022 to January 2024. All research work steps were conducted in accordance with the Declaration of Helsinki. The subjects included were children and adolescents (3-18 years) diagnosed with chronic ITP.

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Tables titles:

Table 1: Comparison of single nucleotide polymorphism Cdx-2 genotypes and alleles frequency between patients and controls.

Table 2: Relation between single nucleotide polymorphism Cdx-2 genotypes and vitamin D level.

Table 3: Relation between single nucleotide polymorphism Cdx-2 genotypes and response to treatment

Figure Legends:

Figure 1: Agarose gel electrophoresis (2%) of polymerase chain reaction (PCR) product of tetra-primer ARMS-PCR for CDX2 genotypes. Lane 1, 4, 5,7 wild homozygous (AA), Lane 2,3,6: mutant heterozygous (AG). Lane 8,9: mutant homozygous (GG).

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Conflict of Interest

The authors declare no conflicts of interest related to this study. All findings and conclusions presented are based solely on the data collected and analyzed, with no external influences affecting the integrity of the research.

Authors Contribution

All authors contributed equally in this paper.