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Association of vitamin D receptor gene polymorphisms with acute myeloid leukemia: a case-control study

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Objective: Vitamin D receptor (VDR) gene polymorphism has a role in susceptibility to risk of cancers. The aim of this study was to investigate the association of VDR gene polymorphisms with acute myeloid leukemia (AML).

Methods: In this case-control study, patients diagnosed with AML and healthy adult subjects were selected. Four single nucleotide gene polymorphisms of VDR gene (BsmI, TaqI, FokI, and ApaI) were determined using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) and the odds of having AML was determined by unadjusted and adjusted logistic regression analysis.

Results: One hundred and thirty-three AML patients and 300 healthy people were included in the study. There were significant associations between the polymorphisms of FokI, and ApaI on the one hand and increased risk of AML (P= .021, and P<.001) on the other. The odds of the disease in patients with FF genotype were 2.5 times higher than patients with ff genotype and the odds of the disease in individuals with AA genotype was 5.6 times higher than the reference category of aa. In contrast, BsmI polymorphism had a protective effect, such that for those with BB and Bb genotypes there were 91% and 86% lower odds for getting AML than bb genotype, respectively (P<.001).

Conclusion: This study shows that there is a significant association between VDR gene polymorphisms and odds of getting AML. Further studies on different ethnic groups in populations with due consideration of environmental factors interacting with genotypes are highly recommended.

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Introduction

Vitamin D controls various biological processes in the body such as skeletal

metabolism, immunity response and cell proliferation and duplication. Epidemiological and laboratory research has indicated that vitamin D deficiency is associated with many common diseases and disorders including rickets, skeletal disorders, diabetes, cardiovascular disorders, autoimmunity disorders and cancer [1].

The active form of vitamin D, 1, 25-dihydroxy vitamin D or cholecalciferol, acts by adjoining to its nuclear receptor in target cells (vitamin D receptor/VDR). The vitamin D receptor belongs to the transcriptional regulatory factors family. In order to have a suitable interaction with DNA, VDR undergoes heterodimerization with the retinoid-X- receptor/RXR and connects with the responsive elements of vitamin D in the promotor region of the target cells [2]. The responsive element of vitamin D is detected in most of the genes involved in cell proliferation and duplication, apoptosis, and invasion and metastasis of cancer cells. Thus, it seems that VDR and gene polymorphism have a major role in the risk of cancer.

Results of studies on the relationship between VDR gene polymorphisms and cancers are controversial. In fact, in studies on different regions and ethnic groups, inconsistent results have been reported. In the past years, the association between common VDR gene polymorphisms (FokI, BsmI, TaqI, ApaI and Cdx2) and the risk of different solid tumors in the skin, prostate, breast, colon, ovary, bladder, kidney and brain have been assessed [3]. However, according to research findings, this association has not been fully understood for adult acute Leukemia. The objective of this study was to determine and compare the frequency of VDR gene polymorphism in patients diagnosed with acute myeloid leukemia (AML) with healthy individuals in order to assess the association of polymorphisms with the risk of cancer for the first time.

Subjects and methods

Participants

In this cross-sectional study, patients were recruited from among individuals referring to the Blood and Cancer Section of Shahid Ghazi Hospital, Tabriz University of Medical Sciences, Tabriz and Shariaty Hospital, Tehran University of Medical Sciences, Tehran, Iran. The case group included patients with the following inclusion criteria: diagnosis with AML, older than 18 years, willing to participate in the study, and no other malignancies. The control group consisted of subjects older than 18 years, willing to participate in the study and not having a first degree relative diagnosed with cancer. Written informed consent was obtained from all the individuals participating in the study. The research project was approved by the Ethics Committee of Tabriz University of Medical Sciences (Ethical Code: 5/4/1720).

Sample size

Primary data for determining the sample size was obtained from Taieb et al. study (OR=1.94) [4]. Based on the G power software (3.2.1 version), with a 95% confidence interval and 80% power, the sample size was calculated to be 386 subjects in either group. Assuming the probability of a 10% missing of the subjects, the sample size was increased to 425 subjects. The subjects were recruited by convenience sampling with a 1 to 3 ratio rate (because of the infrequent prevalence of AML) for the case and control groups.

Extracting DNA from blood samples

A 2-ml blood sample was obtained from the left vein of each subject and stored in vials containing EDTA as an anticoagulant. For extracting DNA, the DNGTM-Plus kit was used (Sinaclon corporations, catalogue number: DN8118C). During the extraction period, the samples were stored at -20ºC.

Assessing VDR gene polymorphisms

The VDR gene sequence was duplicated for four single nucleotide polymorphisms including FokI, BsmI, TaqI and ApaI by polymerase chain reaction (PCR) and using a thermal cycler heating device (Eppendorf Mastercycler ep Gradient S, Germany). At the beginning of the procedure, in order to obtain maximum consistency with the suspected sequence, the detected primers were checked using the Basic Local Alignment Search Tool (BLAST) (Gen Fanavaran). After running PCR, the genotype of the subjects in the location of the corresponding genotype was determined by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method using enzymes FokI, BsmI, TaqI and ApaI, according to the protocol of the company (Fermentas Co.) and were electrophoresed on 1.5% agarose gel and then, after coloring with Ethidium bromide, were examined under UV light.

BsmI (rs1544410) and FokI (rs10735810) Polymorphisms

The BsmI polymorphism sequence was duplicated using forward primer (5´-AGTGTGCAGGCGATTCGTAG-3´) and return primer (5´-ATAGGCAGAACCATCTCTCAG-3´), as described in the Avila et al.'s study [5]. The FokI polymorphism sequence was also duplicated using forward primer (5′-ATG GAA ACA CCT TGC TTC TCC CTC-3′) and return primer (5′-GAT GCC AGC TGG CCC TGG CAC TG-3′), as described in the Hutchinson et al's study [6].

The PCR condition of both BsmI and FokI polymorphisms consisted of 34 cycles ─ one cycle, primary denaturation at 94ºC for 5 minutes, denaturation at 94ºC for 30 seconds, annealing at 58ºC for 30 seconds, extension at 72ºC for 30 seconds, and a final extension at 72ºC for 5 minutes. Eventually, the duplicated products of enzymatic digestion created the genotypes BB (1 band containing 191 base pairs), bb (2 bands containing 117 and 74 base pairs), Bb (3 bands containing 191, 117 and 74 base pairs) for the Bsm1 polymorphism and the genotypes FF (1 band containing 272 base pairs), ff (2 bands containing 208 and 64 base pairs) and Ff (3 bands containing 272, 208 and 64 base pairs) for the Fok1 polymorphism.

Apa1 (rs7975232) and Taq1 (rs731236) Polymorphisms

The Apa1 polymorphism sequence was duplicated using forward primer (5′-CAGAGCATGGACAGGGAGC -3′) and backward primer (5′-AGGAGAGGCAGCGGTACTG -3´), as described in the Chang et al.'s study [7]. The Taq1 polymorphism sequence was duplicated using forward primer (5′-CAGAGCATGGACAGGGAGC-3′) and backward primer (5′-AGGAGAGGCAGCGGTACTG-3´), as described in the Hutchinson et al.'s study [6]. Both polymorphism sequences were duplicated at 34 cycles; primary denaturation at 94ºC for 5 minutes, denaturation at 94ºC for 30 seconds, annealing at 60ºC for 30 seconds, extension at 72ºC for 30 seconds and for 32 cycles and a final extension at 72ºC for 5 minutes. Eventually, the duplicated products of enzymatic digestion created the genotypes AA (1 band containing 454 base pairs), aa (2 bands containing 241 and 213 base pairs), Aa (3 bands containing 454, 241 and 213 base pairs) for the Apa1 polymorphism and the genotypes TT (a band containing 454 base pairs), tt (2 bands containing 159 and 295 base pairs) and Tt (3 bands containing 454, 159 and 295 base pairs) for the Taq1 polymorphism.

Statistical analysis

Statistical analysis was performed using the SPSS software (version 22). The qualitative data were expressed as frequencies and percentages and quantitative data as means and standard deviations. For assessing the relationship between VDR gene polymorphisms and risk of AML, logistic regression was performed. All the tests were two-sided with an 80% statistical power. A p-value < 0.05 was considered to show statistical significance.

Results

One hundred and thirty-three patients with AML and 300 healthy subjects as the control group completed the study. The mean age of the patients (57% males) and the control group (58%) was 42.27 ± 15.84 and 41.55 ± 6.70 years, respectively. There was no significant difference between the two groups as regards age (P = 0.71) or gender distribution (P = 0.916) (Table 1). On the whole, 18% of the patients were suffering from AML-M3 and the rest were afflicted with other types of AML. In general, FokI

Table 1. General characteristics of the patients

VDR gene polymorphism	Patients (n= 133)	Control (n= 300)	P value
Age (Mean ± SD)	42.27 ± 15.84	41.55 ± 6.70	0.721*
Gender (Male, N, %)	76 (57%)	174 (58%)	0.916**
FOKI (%)			
FF	63	50	
Ff	27	30	
Ff	5	17	0.021**
ApaI (%)			
AA	68	43	
Aa	27	36	
Aa	5	21	<0.001**
TaqI (%)			
TT	43	31	
TC	45	57	
CC	12	12	0.071**
BsmI (%)			
BB	16	37	
Bb	41	54	
Bb	43	9	< 0.001**

* P value was measured based on Independent T-Test
** P value was measured based on Fisher's Exact Test

polymorphism was significantly associated with AML (P = 0.021), such that the odds of the disease in patients with FF genotype were 2.5 times higher than those with ff genotype. In patients with ff genotype, the AML odds were 80% higher in comparison with the reference category of ff, but the difference was not statistically significant (Table 2).

ApaI polymorphism also had a significant association with AML (P <0.001), such that the odds of the disease in individuals with the AA genotype was 5.6 times higher than the reference category of aa. Patients with Aa genotype were also found to be 3 times more likely to be suffering from AML than the reference category of aa (Table 2).

There was no statistically significant association between TaqI polymorphism and AML (P = 0.071), but the association between BsmI polymorphism and AML was significant, such that for those with BB and Bb genotypes, there were 91% and 86% lower odds for getting AML than bb genotype, respectively (Table 2). Based on the logistic regression analysis, considering VDR gene polymorphisms (FokI, ApaI, and BsmI) simultaneously, their associations with AML were found to be statistically significant as well (P = 0.032, P <0.001, and P <0.001, respectively).

Discussion

Our findings show that there is a significant association between VDR gene polymorphisms and odds of getting AML. The results of meta-analyses and reviews on the relationship between VDR gene polymorphism and different cancers are controversial. Both harmful and protective roles have been reported for polymorphisms in malignancies. Even in one type of malignancy, similar polymorphisms were found to exhibit different effects. For example, based on the results of several review studies, Fok1 [8-14] and Taq1 polymorphism [15-17] increased the risk of breast cancer. However, in other studies, there was no association between Fok1 and Taq1 polymorphism and the risk of breast cancer [18, 19]. In addition, Li [8] and Kostner [9] indicated that Bsm1 polymorphism increased the risk of breast cancer.

Contradictory results have also been reported regarding prostate cancer. Although in some studies a positive association between Fok1 and Taq1 polymorphism and the risk of prostate cancer was reported, in other studies Fok1, Bsm1 and Taq1 polymorphisms were seen to have a protective effect in prostate cancer [9, 17, 21]. On the other hand, Berndt et al [24] and Guo et al [25] did not observe any significant association between VDR gene polymorphisms and the risk of prostate cancer. Controversial results have also been reported as regards ovary, skin, colorectal, lung, kidney and esophagus cancers [42-46]. These controversial results may be due to genetic differences, ethics, geographical location and environmental factors.

Different findings have also reported in studies on hematologic malignancies. Although Fok1, Bsm1 and Taq1 polymorphisms and

Table 2. Association between VDR gene polymorphism and risk of AML[#]

Univariate analysis				Multivariate analysis		
VGP*	OR#	95% CI	P value	OR#	95% CI	P value
FOKI						
FF	2.57	1.27 to 5.20	.009	3.26	1.34 to 7.91	.009
Ff	1.81	.86 to 3.84	.120	2.62	1.03 to 6.64	.042
Ff	Reference category			Reference category		
ApaI						
AA	6.67	2.76 to 16.12	<.001	12.29	3.53 to 42.74	<.001
Aa	3.21	1.27 to 8.08	.013	7.80	2.17 to 28.02	.002
Aa	Reference category			Reference category		
TaqI						
TT	1.38	.68 to 2.79	.373	.96	.42 to 2.20	.928
TC	.80	.40 to 1.59	.521	.59	.27 to 1.31	.196
CC	Reference category			Reference category		
BsmI						
BB	.09	.05 to .18	<.001	.08	.04 to .17	<.001
Bb	.16	.09 to .29	<.001	.19	.10 to .35	<.001
Bb	Reference category			Reference category		

increasing risk of youngster's leukemia [43], multiple myeloma [44] and aplastic anemia [45] were evident in some studies, no associations were observed between polymorphisms and Hodgkin's lymphoma [46] and non-Hodgkin's lymphoma [47] in other studies. In the Prudue et al. study [48] a positive association between Bsm1 and Taq1 polymorphism and non-Hodgkin's lymphoma was reported. In most solid tumors, Bsm1 polymorphism has a protective or insignificant role. In the present study Bsm1 had a protective role against AML.

This study was the first study to assess the association between common VDR gene polymorphisms and AML. A positive association was found between Fok1 and Apa1 polymorphism and the risk of AML. Also, it was noted that the Bsm1 polymorphism had a positive effect on AML. This association was not significant in the case of Taq1. Our findings have indicated that in patients diagnosed with AML, similar to solid tumors, VDR gene polymorphisms could have either positive or negative associations with the risk of AML. Some limitations of our study were as follows: not considering environmental factors, such as exposure to sunlight, smoking and other factors, and their possible effects on acquired genotypes. However, as mentioned above, the aim of this study was to investigate the association of VDR gene polymorphisms with acute myeloid leukemia (AML) and also to assess the risk of getting AML.

Conclusion

The findings of this study indicate that VDR gene polymorphism may have a significant role in increasing the risk of one of the most common adult hematologic malignancies known as AML. Since medical science is now putting particular emphasis on "individualized medicine", these findings would have an important role in tracing genetic profile and detecting at-risk individuals. It is recommended to conduct further studies in different groups of patients in the country, in order to be able to generalize findings and assess effects of environmental.

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Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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