REVIEW ARTICLE

VDR GENE POLYMORPHISMS: THE INDEPENDENT LINK TO ASTHMA

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ABSTRACT

Vitamin D is synthesized in the body via the action of UV light on the skin or obtained from dietary sources and supplements. It helps the body regulate calcium and phosphate levels, plays a critical role in the development of immunity against infectious diseases and several studies have suggested a link between vitamin D supplementation and prevention of colon, prostate and breast cancers. Low levels of serum 25-hydroxyvitamin D have also been implicated in the development of pulmonary diseases including asthma, chronic obstructive pulmonary disease, pneumonia and viral/bacterial upper respiratory tract infections.

Asthma, a chronic inflammatory condition involving the lower airways, has become exceedingly prevalent in Pakistan. According to a study conducted in 2014, the prevalence of asthma is 14.7% among children between 3-7 years of age, with an overall prevalence of 23% for wheezing in the pediatric age group. Since the prevalence of asthma has grown, the factors that influence asthma development as well as the implications of those findings need to be explored in detail.

Vitamin D receptor gene polymorphisms have been studied to determine their association with asthma risk, development and severity. However, even though multiple studies have been carried out to determine an association, the results are inconclusive and unclear. The purpose of this review article is to go through the vast amount of literature published online, summarize it and discuss the reasons why the results found may be inconclusive.

KEYWORDS: Vitamin D, Vitamin D3 receptor, Calcitriol, Asthma

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INTRODUCTION

Defined by the Global Initiative for Asthma (GINA), asthma is a heterogeneous lower airway disorder characterized by chronic inflammation. Patients usually present with a history of wheezing, shortness of breath, cough and chest tightness. Additionally, there is a varying degree of airflow limitation, evidenced by a reduced FEV1/FVC ratio[1]. The overall prevalence of asthma, reported in a study conducted in Karachi in 2014, is 10.2%[2], while an estimated 5-10% of the population in developed countries suffers from asthma[3]. Approximately 20% of children, between the ages of 6-7 years, experience severe wheezing episodes in a year. With its growing prevalence, asthma is characterized as one of the most common chronic disorders affecting children and young-adults both and poses a growing global economic burden on healthcare systems today[4].

The vitamin D receptor (VDR) gene is located on chromosome 12, and consists of 9 exons. The VDR gene brings about all physiological responses to the active form of vitamin D known as 1,25 (OH)2D3. There are four single nucleotide polymorphisms of the VDR gene, identified through genetic analyses. These are namely, TaqI, ApaI, FokI and BsmI[5]. Vitamin D gene polymorphisms have been implicated in autoimmune diseases such as Crohn's disease, SLE, multiple sclerosis, Grave's disease amongst others, as well as certain renal patholo-

gies, nephrolithiasis, diabetes and cancers of the bone, breast, kidneys, colon and prostate[6].

Since asthma presentation is heterogeneous, its disease complexity impedes the identification of a single causal genetic pathway. The immune system plays a significant role in the pathogenesis of asthma with the presence of inflammation, mucus production and bronchoconstriction[7]. It has been hypothesized that low serum levels of vitamin D have a strong correlation with pulmonary disorders, resulting in an increased incidence of asthma, COPD, chronic bronchitis, pneumonia and viral infections [5]. As vitamin D plays a pivotal role in protection against infections and development of immune related disorders, it is pertinent to explore the link between VDR gene polymorphisms and asthma[7].

Currently, there is a wide variety of literature supporting the link between vitamin D levels and respiratory disorders[8]. This review article aims at outlining the correlation of each VDR gene polymorphism with the development of asthma and discuss its implications on asthma control and treatment. Selection of literature was done by surveying articles published between 1998 - 2017, mainly on PUBMED. The articles found included published review articles, original articles and other data sources on asthma incidence, VDR gene polymorphisms and their link with development of respiratory disorders, particularly asthma.

DISCUSSION

Vitamin D is a fat soluble vitamin, that is synthesized by the body and obtained through different dietary sources and supplement[9]. The synthesis of vitamin D is initiated when 7-dehydrocholesterol, a cholesterol precursor found in the skin, is exposed to ultraviolet radiation. 7-dehydrocholesterol is initially converted to pre-vitamin D3 through a light-induced photolytic reaction[10].Pre-vitamin D3 is an intermediate, which is subsequently thermally isomerized to vitamin D3 (cholecalciferol). In the plasma, bound to the vitamin D binding protein, vitamin D3 is transported to the liver as well as other endocrine organs, where its 25-hydroxylation occurs. 25-hydroxycholecalciferol, the product of this reaction, then undergoes further bio-activation in the kidney to finally produce the active form of vitamin D, known as calcitriol (1,25 dihydroxycholecalciferol)[11].

Once synthesized, the pleiotropic functions of 1,25 (OH)2 D3are mediated by genomic and non-genomic actions[35].Vitamin D first binds to VDR and its simultaneous heterodimerization with the retinoic X receptor (RXR) results in the formation of the VDR-RXR complex[6]. This VDR-RXR complex interacts with multiple co-regulatory nuclear proteins which may up- or down-regulate the transcription of target genes. Therefore, polymorphisms of the VDR gene can result in defects in the activation of genes, causing alterations in calcium metabolism, cellular proliferation and immunity. Since multiple enzymatic processes are involved in the synthesis of vitamin D, the co-factors required for these reactions may also increase vitamin D sensitivity[12].

The role of vitamin D on the immune system has been studied in detail in recent years. The RXR has been found to directly influence the development of Th2 cells, while suppressing Th1 cells[13]. Additionally, vitamin D regulated genes, such as renal 1-alphahydroxylase, 24-hydroxylase and RXR, have been found to be located in allergy linkage regions, further suggesting a link between the risk of developing atopic diseases and vitamin D levels. While a vitamin D binding protein gene has been linked toincreased risk of developing COPD and osteopontingene is associated with highIgE levels in asthmatic patients[31], the presence of single nucleotide polymorphisms in the VDR gene and its implications have not been fully established[12].

Derived from the Greek words "poly" meaning multiple and "morph" meaning form, polymorphism refers to variations in the DNA sequence that may be seen in an individual or among a group of people belonging to a population[14]. These genetic variants are seen in at least 1% of the worlds' population, and can occur in both the non-coding (introns) and coding (exons) parts of a gene. When occurring in a non-coding part of a gene, the changes they cause are not seen in the protein product. However, when changes occur in exons, the expression of genes and therefore the levels of protein produced is affected[6].

The VDR gene is situated on the 12th chromosome, and several restriction fragment length polymorphisms (RFLPs) in this gene have been described. The ApaI and BsmI polymorphisms are located in intron 8, while TaqI is located in exon 9. However, even though these polymorphisms are silent codon changes rendering them ineffective in altering protein structure, they result in alterations in VDR mRNA stability and transcription.The fourth polymorphism, located in exon 2, is FokI and this alteration in the gene leads to variations in size of the protein product and transcriptional activity. The shorter form of the protein, 424 aa is more active than the longer(427 aa) form[15].

The presence of VDR gene polymorphisms and their association with development and/or severity of asthma has been studied on populations in Egypt, Tunisia, Cyprus, Turkey, Greece and China, amongst others. However, the results have differed significantly.

ApaI polymorphism
Studies done to determine the association between the ApaI gene and asthma show conflicting results. While an increased risk of asthma development in patients who had over-transmission of the ApaI C allele is seen in 2 cohorts, the same study showed that a third cohort demonstrated an under transmission of the allele in affected children, signifying a negative correlation[16].

A review and meta-analysis showed that the AA homozygote genotype of the ApaI gene has a protective effect against the development of asthma in comparison to the Aa and aa genotypes[15], while a Greek study published in 2014 highlighted that carriers for the aa genotype had a significantly higher C-ACT score, indicating better asthma control.In children with well-controlled asthma, i.e. resulting in no limitation of daily activities, the frequency of the aa genotype was higher, further confirming the possibility of a protective role of the ApaI aa gene[17].

While the AA and aa genes have shown to confer some level of protection against asthma, heterozygous mutations (Aa) in the ApaI gene have been shown to increase the risk of atopy, compared to the wild genotype in the Turkish population[18].In addition, despite the fact that most studies have shown an association, a case control conducted in Tunisia in 2013 observed no significant difference in gene polymorphisms and allele frequencies between asthmatic and non-asthmatic participants[19].

TaqI polymorphism
The association of TaqI polymorphism has been demonstrated in some studies, while others exhibited no correlation. The heterozygous Tt genotype of the TaqI gene is shown to be associated with an increased risk of asthma. Concurrently, individuals with the TT and tt genotypes have a decreased risk of asthma development, implying a protective effect. [15]. On the contrary, a Tunisian study showed that the presence of one or two copies of the 'T' allele results in a 2.33 times increased risk of development of asthma. This would imply that the TT and Tt genotypes are seen in patients with the condition[19].

It can therefore be established that the Tt allele is associated with asthma development, while based on current study results, the correlation between the TT and tt gene and asthma cannot been confirmed.

FokI polymorphism
The FokI polymorphism, found in exon 2 of the VDR gene, occurs due to a T to C change. However, even though this polymorphism is the only one that occurs in a coding region of the gene, no significant association was found between its presence and asthma development in the Chinese Han population[20]. The role of VDR in altering gene activation is dependent upon more than just genetics. Ethnicity, environmental influences as well as linkage disequilibrium play a vital role in disease pathogenesis and presentation[21]. Supporting the role of these factors is the statistically significant association between FokI and asthma identified in Tunisian as well as Siberian populations [33]. The frequency of the homozygous FF genotype was significantly higher in individuals with asthma. This suggests that the odds of developing asthma in children carrying the 'F' allele was higher than healthy individuals[19].

While Einisman et al identified no significant association between FokI polymorphism and asthma, when healthy, controlled, and uncontrolled children with asthma were compared, there was one noteworthy finding. All patients who were currently on step 4 of the GINA treatment guidelines were heterozygous for allele C of the FokI gene[22].

BsmI polymorphism
As seen with the other SNP's mentioned above, the results for BsmI gene association with asthma are also contradictory.

In individuals who had inherited the BB allele, the odds of developing asthma were higher when compared to the homozygous minor bb allele as well as the tt genotype for Taq polymerase in a 2014 study[15]. These findings were replicated in Tunisian asthmatic children, therefore indicatingthat for BsmI polymorphism, the 'B' allele confers an increased risk of developing the disease.

An association analysis conducted in China identified that the frequency of the 'b' allele of BsmI gene was significantly higher in the Asian population, compared to Caucasians. These findings suggest that the distribution of gene frequencies may differ between ethnicities. However, the same study was unable to identify a significant difference in inheritance of BsmI polymorphisms between cases and controls [23].

Causes for conflicting results
Asthma is a complex disease with multifactorial inheritance, affected by both environmental as well as genetic influences[24].Due to this, the distributive frequencies for the same gene polymorphisms differ between populations[25]. While the results reviewed in this article suggest that there is a protective effect of ApaI alleles and certain alleles for TaqI, BsmI and FokI confer an increased risk of asthma development in some populations, the results could not be replicated in all studies. The SNP's seen in the VDR gene are distinct in individuals belonging to a particular ethnicity, geographic location and environment. They may be influenced by diet, race and latitude. This results in an inconsistent set of findings between multiple groups of people. It

should also be noted that when a gene polymorphism appears to be associated with a phenotype, in this case asthma, this does not necessarily indicate that the phenotype occurs due to the polymorphism. Linkage disequilibrium may be a cause of certain alleles appearing with each other in a population[6]. The small sample size and ineffective power in some studies may have also contributed to inaccurate results that are not fully representative.

CONCLUSION

As the prevalence of vitamin D deficiency is rapidly increasing in Pakistan, there is growing awareness about its multisystem effects. The need for widespread screening, food fortification and supplementation has been identified[26].However, while the VDR gene polymorphisms associated with type I diabetes[27] and prostate cancer[28] have been identified in the Pakistani population, their occurrence along with its effect on asthma risk and severity needs to be researched. As stated above, because gene polymorphisms may differ according to geographic location and external factors, it is imperative to identify the alleles found in Pakistani children and young-adultsand subsequently elucidate the implications of these findings.

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