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Vitamin D Receptor (VDR) TaqI Gene Polymorphisms as Profiling Markers for Cardiovascular Disease

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ABSTRACT

Cardiovascular diseases (CVDs) continue to be a major worldwide health problem, and they are increasingly being linked to genetic vulnerability in addition to traditional risk factors. Because it affects calcium-phosphorus balance, immunological regulation, and vascular function, the Vitamin D Receptor (VDR) gene—specifically, its TaqI polymorphism (rs731236)—has been identified as a significant modulator among the genes determining CVD risk. The biological relevance of vitamin D metabolism, the genetic makeup of the VDR gene, and the clinical consequences of its variants in relation to cardiovascular health are all examined in this study. Particular attention is paid to the people of the Dehradun area, where environmental variables like as dietary habits and varying amounts of sunshine exposure may influence the expression and consequences of VDR polymorphisms.

Keywords: *Vitamin D Receptor (VDR), TaqI Polymorphism, Cardiovascular Diseases (CVD), Genetic Susceptibility, Vitamin D Metabolism*

1. INTRODUCTION

Cardiovascular diseases (CVDs) account for a significant percentage of all deaths and disability-adjusted life years (DALYs), making them one of the biggest threats to global public health . Even though conventional risk factors including smoking, high blood pressure, a sedentary lifestyle, and dyslipidaemia are widely recognised, new research has shown how a person's genetic makeup might affect their chance of developing cardiovascular disease (Yusuf *et al.*, 2001) (Kennon and Connell, 2010). Genomics—the study of a person's whole genetic composition—has become a potent instrument in cardiovascular research (Squire, 2009). Finding genetic markers or polymorphisms—differences in the DNA sequence—that may predispose certain people to cardiovascular diseases over others is made easier by genomics (Shukla, Mason and Sabyah, 2019). Because of its regulatory function in immunological regulation, cell differentiation, and calcium metabolism, the Vitamin D Receptor (VDR) gene has been recognised as a major participant among these genes (Voltan *et al.*, 2023).

Vitamin D, sometimes referred to as the "sunshine vitamin," has long been recognised for preserving calcium-phosphorus equilibrium and bone health. Modern research, however, has made it far more relevant than only bone health (Nair and Maseeh, 2012). Additionally, vitamin D is essential for immune system modulation, chronic inflammation reduction, and vascular health maintenance—all of which are closely related to cardiovascular function. These functions are mostly carried out by the Vitamin D Receptor (VDR), a nuclear receptor that affects the expression of several genes crucial to cardiovascular physiology when it is activated by the bioactive form of vitamin D (1,25-dihydroxyvitamin D3) (Yin and Agrawal, 2014) (Pike *et al.*, 2017).

However, polymorphisms—naturally occurring genetic variations—can cause considerable individual differences in VDR function (Usategui-Martín *et al.*, 2022). TaqI (rs731236) is one of the most researched VDR polymorphisms. This single nucleotide polymorphism (SNP) may affect the efficiency of transcription and expression of the VDR gene, but it does not alter the amino acid sequence of the VDR protein (i.e., it is a silent mutation) (Górczyńska-Kosiorz *et al.*, 2024) (Abdollahzadeh, Hossein and Barazandehrokh, 2020). TaqI polymorphism variations have been linked to an increased risk of a number of chronic conditions, such as coronary artery disease (CAD), atherosclerosis, and hypertension

(Akhlaghi *et al.*, 2023). It is especially crucial to comprehend these polymorphisms at the regional level since environmental variables that might affect vitamin D status and gene expression include food, lifestyle, and sunshine exposure (Shraim *et al.*, 2022). For example, these environmental factors have a major impact on endogenous vitamin D production in Dehradun, an area with varying altitude and seasonal solar availability. Furthermore, vitamin D levels may be further influenced by regional food habits (Maia *et al.*, 2016)

Vitamin D: Biological Role and Metabolism

A fat-soluble prohormone, vitamin D is essential for many bodily processes. Vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) are its two main forms (Holick, 2010). While vitamin D3 is produced in the skin of both humans and animals when exposed to ultraviolet B (UVB) radiation and may also be obtained from animal-based meals such fatty fish, liver, and egg yolks, vitamin D2 is mostly obtained from plants and fortified foods (Ouellette and Rawn, 2018). In the skin's epidermal layers, a precursor molecule called 7-dehydrocholesterol is photochemically converted by UVB radiation (wavelength 290–315 nm) to initiate the manufacture of vitamin D3 (Matthias Wacker and and Michaela F. Holick, 2013). Over the course of many hours, this reaction produces previtamin D3, which thermally isomerises into cholecalciferol (vitamin D3). After being produced or consumed, vitamin D3 travels to the liver via the circulation, where the enzyme 25-hydroxylase (CYP2R1) hydroxylates it for the first time, becoming 25-hydroxyvitamin D [25(OH)D], or calcidiol.

This is the main form of vitamin D that is in circulation and the most accurate biomarker for determining the body's vitamin D level (Ketha and Singh, 2017). After that, 25(OH)D is sent to the kidneys, where 1α-hydroxylase (CYP27B1) hydroxylates it a second time to produce 1,25-dihydroxyvitamin D [1,25(OH)2D3], also known as calcitriol, the active hormonal form. Serum calcium, phosphate levels, and parathyroid hormone (PTH) all tightly control calcitriol (Christakos *et al.*, 2010). The primary way that calcitriol performs its biological actions is by attaching itself to the vitamin D receptor (VDR), a nuclear receptor found in a variety of organs, including the heart, kidneys, intestines, bones, immune cells, and even brain tissue (Wu-Wong, 2009). The VDR and the retinoid X receptor (RXR) combine to create a heterodimer when calcitriol is bound. This complex then binds to vitamin D response elements (VDREs) on target genes to control gene transcription (Jimenez-Lara and Aranda, 1999).

Vitamin D is crucial for maintaining calcium and phosphate homeostasis, which is necessary for bone mineralisation, through VDR-mediated gene regulation (Verlinden and Carmeliet, 2021). It also has non-skeletal effects, including as immune response modulation, pro-inflammatory cytokine suppression, anti-inflammatory cytokine stimulation, and control of blood pressure, endothelial function, and vascular smooth muscle cell proliferation. Cardiovascular health is directly related to these tasks (Sprague and Khalil, 2009). Vitamin D deficiency has been linked to an increased risk of heart failure, myocardial infarction, atherosclerosis, and hypertension. Low blood levels of 25(OH)D have been linked to an increased incidence of cardiovascular events, according to several epidemiological studies. This is especially true for populations living in places with little sun exposure or with diets deficient in nutrients (Mozos and Marginean, 2015).

The Vitamin D Receptor (VDR) and Its Genetic Architecture

One of the most important mediators of vitamin D's actions in the human body is the Vitamin D Receptor (VDR) (Pike and Meyer, 2012). It is a transcription factor that is a member of the nuclear receptor superfamily that controls gene expression in response to ligand interaction. The gene that codes for VDR is situated at locus 12q13.11 on the long arm of chromosome 12 and spans around 75 kilobases (kb) (Takeyama *et al.*, 1999).

It consists of 11 exons with both coding and non-coding sequences that enable alternative splicing to produce different isoforms (Gimeno-Valiente *et al.*, 2024). The active hormonal form of vitamin D, 1,25-dihydroxyvitamin D3 (calcitriol), activates VDR, which then forms a VDR-RXR heterodimer with another nuclear receptor called Retinoid X Receptor (RXR) (Kim, Shevde and Pike, 2005). After that, this complex moves into the nucleus, where it attaches itself to certain DNA sequences called Vitamin D Response Elements (VDREs) found in target gene promoter regions. By starting or stopping transcription, this binding event controls genes related to immunological modulation, cell differentiation, calcium and phosphate metabolism, and cardiovascular function (Bikle, 2021) (Voltan *et al.*, 2023).

The VDR gene is widely expressed throughout the body. In organs like the kidneys, bones, and intestines that are essential for maintaining calcium homeostasis, it is strongly expressed (Lee *et al.*, 2015). Furthermore, it is expressed in non-classical tissues such as vascular endothelial cells, macrophages, cardiomyocytes, pancreatic β-cells, and T-lymphocytes, suggesting that vitamin D signalling has systemic effects in addition to bone health (Fenercioglu, 2024). Crucially, the VDR gene is polymorphic, which means that different people have different naturally occurring genetic variants.

The expression, stability, or function of the receptor may be impacted by these single nucleotide polymorphisms (SNPs), which might arise in the promoter region, exons, or introns. TaqI (rs731236), a well-researched SNP in exon 9, is a silent polymorphism that may affect mRNA stability or splicing and impact the biological activity of the receptor without changing the transcribed amino acid (Othman, 2022). These polymorphisms are thought to have a role in inter-individual differences in vitamin D responsiveness and metabolism, which may affect a person's vulnerability to a number of illnesses, such as

metabolic syndromes, autoimmune diseases, cardiovascular diseases, and osteoporosis. Because of this, researching VDR polymorphisms is crucial to comprehending how genetics affect health and illness, particularly in situations when populations are affected (Charoenngam *et al.*, 2023).

Genetic Polymorphisms and Their Role in Disease

Natural differences in the DNA sequence seen in a population are known as genetic polymorphisms. Polymorphisms are prevalent in at least 1% of the population and reflect typical genetic variation, in contrast to uncommon mutations that happen seldom (Chiarella, Capone and Sisto, 2023). These differences may affect gene expression, protein function, or vulnerability to a number of illnesses, including as autoimmune, cardiovascular, and metabolic disorders. They may also be silent (Misiura, 1971).

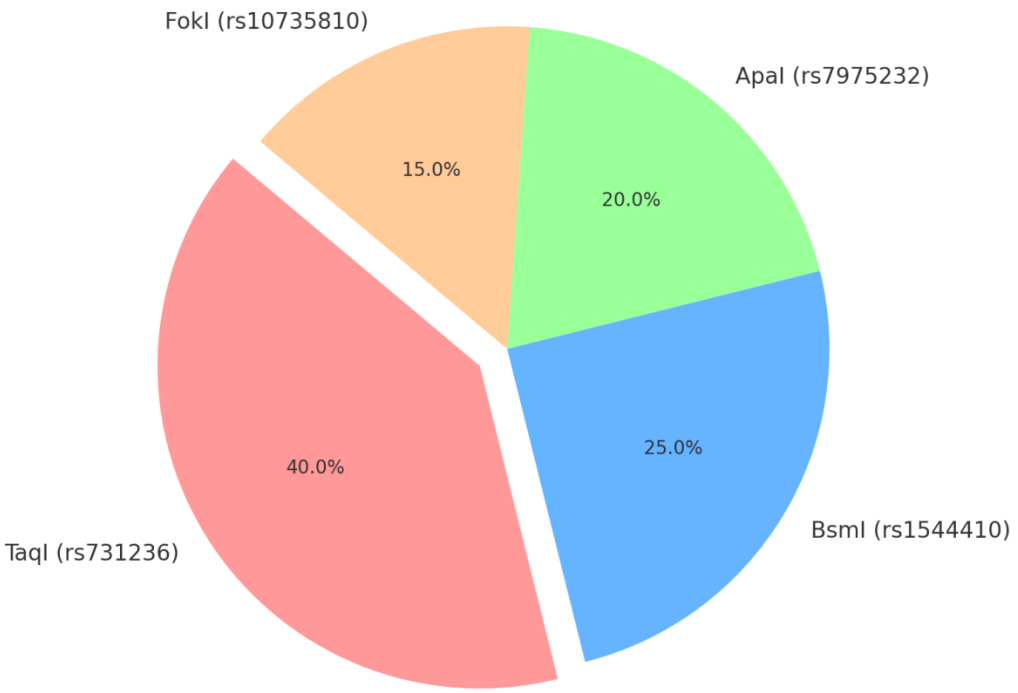
Single Nucleotide Polymorphism (SNP), the most prevalent kind of genetic polymorphism, occurs when a single nucleotide base in the DNA sequence changes (for example, A becomes G). SNPs may have functional implications and can arise in either the coding or non-coding regions of genes. For instance, SNPs in coding areas may impact protein production or stability, but those in regulatory regions may influence how genes are switched on or off (Chauhan *et al.*, 2022). The Vitamin D Receptor (VDR) gene is one of the most researched genes for SNPs because of its broad expression and function in a variety of physiological processes, including immunological control, cardiovascular health, and calcium homeostasis (Górczyńska-Kosiorz *et al.*, 2024).

Numerous variations in the VDR gene have been found and linked to an increased risk of developing the disease: TaqI (rs731236), this silent mutation, which is found in exon 9, does not change the VDR protein's amino acid sequence. Nevertheless, it could change gene expression and mRNA stability, which might have an impact on VDR function and subsequent biological consequences (Cafiero *et al.*, 2022). BsmI (rs1544410): Located close to the 3' untranslated region, BsmI may change the stability or processing of mRNA, which might impact the quantity of protein generated (Gholami *et al.*, 2024). ApaI (rs7975232): This SNP, which is found in intron 8, is also believed to affect the stability or effectiveness of splicing of mRNA (Ferrer-Suay *et al.*, 2021).

The non-synonymous polymorphism FokI (rs10735810) is located at the start codon (exon 2). It may result in a shorter and less active form of the VDR protein, which might reduce its effectiveness in transcriptional control (Ruiz-Ballesteros *et al.*, 2020). To affect the risk of illness, these polymorphisms may interact with environmental variables such as lifestyle choices, exposure to sunshine, and dietary vitamin D consumption. In particular, TaqI polymorphism has been thoroughly investigated in relation to cardiovascular diseases (CVD), where it has been connected to elevated risks of atherosclerosis, coronary artery disease, and hypertension due to its effects on inflammatory regulation and vitamin D signalling (González Rojo *et al.*, 2022).

Table 1: Common VDR Gene Polymorphisms, Their Genomic Features, and Clinical Associations in Cardiovascular Diseases

Polymorphism	SNP ID	Location	Type	Functional Effect	CVD-Related Associations	References
TaqI	rs731236	Exon 9	Silent (Synonymous)	Does not change amino acid; may affect mRNA stability or splicing	Associated with atherosclerosis, hypertension, CAD	Górczyńska-Kosiorz et al., 2024; Akhlaghi et al., 2023; De Souza Freitas et al., 2020
BsmI	rs1544410	Intron near 3′ UTR	Non-coding (Intronic)	May influence mRNA processing and expression levels	Linked with hypertension, obesity, and chronic kidney disease	Gholami et al., 2024; Santoro et al., 2015; Akhlaghi et al., 2023
ApaI	rs7975232	Intron 8	Non-coding (Intronic)	Impacts mRNA splicing efficiency	Indirect role in CVD through effects on inflammation and oxidative stress	Ferrer-Suay et al., 2021
FokI	rs10735810	Exon 2 (Start Codon)	Missense (Non-synonymous)	Alters protein structure, leads to a shorter VDR protein	Decreased transcriptional efficiency; possible link to vascular dysfunction	Ruiz-Ballesteros et al., 2020; Charoenngam et al., 2023



Graph 1: VDR Gene Polymorphism Distribution

The four main polymorphisms of the Vitamin D Receptor (VDR) gene in this review—TaqI (rs731236), BsmI (rs1544410), ApaI (rs7975232), and FokI (rs10735810)—are graphically represented by the pie chart. Because of its significant and reliable correlation with the phenotypes of cardiovascular disease, including atherosclerosis, coronary artery disease, and hypertension, TaqI polymorphism is the one that garners the most attention. A brief discussion of the other SNPs' connections to vitamin D metabolism, gene regulation, and possible indirect associations with cardiovascular outcomes is provided.

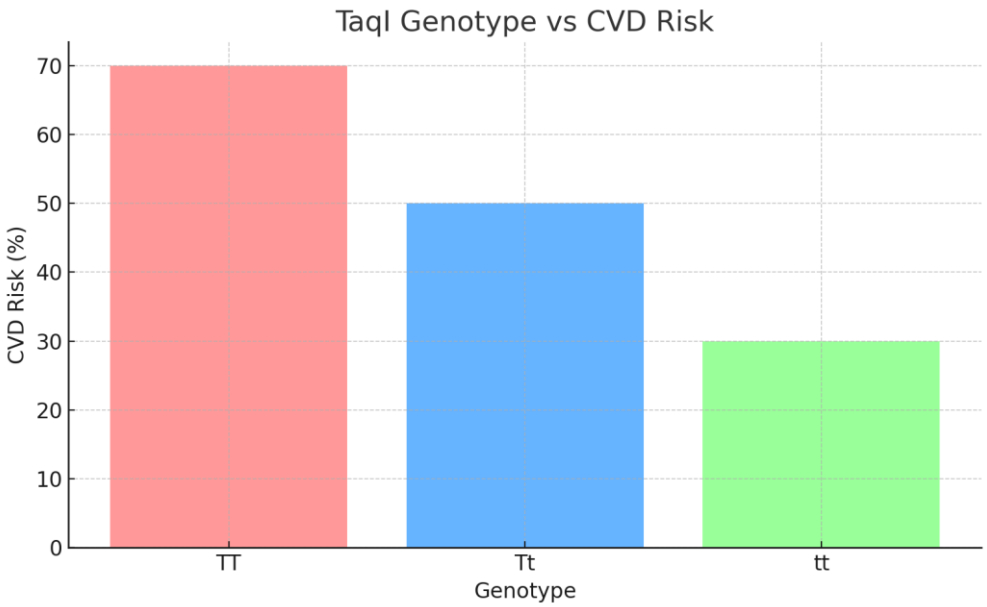
TaqI VDR Polymorphism and Cardiovascular Diseases

According to a study investigating the function of the VDR TaqI polymorphism on cardiovascular health, those with the TT genotype were far more likely to develop atherosclerosis (De Souza Freitas *et al.*, 2020). The findings suggest a possible connection between endothelial dysfunction, a precursor to cardiovascular disease, and VDR polymorphism (Abouzid *et al.*, 2021). Examined TaqI and other VDR gene variants in individuals with cardiovascular comorbidities and chronic kidney disease (CKD) (Santoro *et al.*, 2015).

According to their findings, the TaqI polymorphism was linked to increased rates of obesity and hypertension, two conditions that are known to be risk factors for CVD (Artham *et al.*, 2009). By changing the VDR's regulatory effects on the renin-angiotensin-aldosterone system (RAAS) and adipocyte function, the study hypothesised that TaqI mutations may affect blood pressure control and obesity (Thethi, Kamiyama and Kobori, 2012). Concentrated on individuals with hypertension and showed a robust association between high blood pressure and the TT genotype (Chiu *et al.*, 2023). This result lends credence to the theory that some VDR genotypes, particularly the homozygous TT form, may make people more susceptible to vascular stiffness or decreased vascular compliance, which would raise their chance of developing hypertension.

The findings strengthens the mounting evidence that a TaqI polymorphism is associated with cardiovascular stress and haemodynamic instability (Patel *et al.*, 2023). TaqI genotypes' effects on vitamin D blood levels and, consequently, cardiovascular risk was investigated. According to their findings, people with certain TaqI polymorphisms typically had lower levels of vitamin D in their blood, which may be because of changes in feedback regulation or receptor efficiency. Since a lack of vitamin D is a risk factor for cardiovascular disease, this polymorphism may increase the risk of the illness through both direct and indirect processes (Bhola *et al.*, 2017).

The impact of TaqI polymorphism on biochemical markers like serum calcium and phosphorus among patients with coronary artery disease (CAD). They observed that the polymorphism may interfere with mineral metabolism, further aggravating arterial stiffness and calcification—key factors in CAD progression. This reinforces the concept that VDR polymorphisms have pleiotropic effects, influencing both systemic mineral balance and cardiovascular structure (Akhlaghi *et al.*, 2023).



Graph 2: TaqI Genotype vs CVD Risk

TaqI VDR genotypes and the risk of cardiovascular disease are related.The possible relationship between the risk of cardiovascular disease and the various TaqI genotypes (TT, Tt, and tt) is depicted in the graph. People with the TT genotype are at the highest risk, which is in line with research that links this variation to endothelial dysfunction, hypertension, and atherosclerosis.

Regional Relevance: The Dehradun Perspective

Research on genetics and public health should pay particular attention to the Dehradun district, which is situated in the foothills of the Indian Himalayas and represents a distinct environmental and demographic situation (Munir and Khan, 2003). The area has varying patterns of sunshine exposure throughout the year because to its geographic height, forested terrain, and climatic fluctuations. These differences can have a major effect on the production of vitamin D through the skin, which is mostly dependent on receiving enough UVB rays. As a result, many people in Dehradun may be at risk for vitamin D insufficiency or deficiency, especially those who have indoor lives or live in high-altitude areas with lower UV indices (Res *et al.*, 2018).

Furthermore, vitamin D level is also influenced by regional socioeconomic circumstances, food patterns, and cultural behaviours. In certain regions of Uttarakhand, for example, traditional diets could not include enough vitamin D-rich foods like fatty fish, fortified dairy products, or supplements. Individual genetic predispositions, such as polymorphisms in the Vitamin D Receptor (VDR), may interact with these environmental and lifestyle variables to change a person's susceptibility to a number of illnesses, including cardiovascular diseases (CVDs) (Kshatri *et al.*, 2022).

It is also important to concentrate on the TaqI polymorphism (rs731236) of the VDR gene in the Dehradun population since this genetic variation may intensify or lessen the physiological consequences of low vitamin D levels. Region-specific insights into cardiovascular risk can be obtained by determining the prevalence of these genotypes (TT, Tt, and tt) in the local population and if they are associated with higher rates of heart failure, coronary artery disease, or hypertension (Albu-Mohammed, Anvari and Fateh, 2022). Such localised genetic epidemiology can also serve as a foundation for precision treatment strategies. For instance, doctors might suggest targeted dietary therapies, lifestyle changes, or early screening programs for high-risk patients if certain VDR genotypes are demonstrated to confer increased cardiovascular risk in the context of low vitamin D (Banjabi *et al.*, 2020).

Crucially, knowing the Dehradun population's genetic makeup in connection to vitamin D metabolism might assist policymakers in creating regionally specific public health initiatives. These might include population-based screening for VDR variants, information campaigns regarding sun exposure, or vitamin D fortification regulations. Dehradun is a crucial location for researching the function of VDR polymorphisms in CVD because of its unique environmental circumstances and genetic heterogeneity. In this particular geographic area, such studies have the potential to enhance both the outcomes for individual patients and more general public health initiatives.

Table 2: Vitamin D Deficiency and CVD Prevalence by Region

Region	Vitamin D Deficiency (%)	CVD Prevalence (%)	Supporting References
Urban Low UV	70%	45%	Nair & Maseeh, 2012; Mozos & Marginean, 2015 – Urban dwellers often have low sun exposure
Rural High UV	40%	25%	Holick, 2010 – Higher UV exposure reduces deficiency; rural lifestyle lowers CVD risk
Dehradun	60%	38%	Res et al., 2018; Kshatri et al., 2022 – Variable sunlight, altitude, and limited diet
Coastal Region	30%	20%	Holick, 2010; Wu-Wong, 2009 – High fish diet, good sun access linked to better vitamin D

2. CONCLUSION

This review emphasises how genetic polymorphisms, namely the TaqI variation of the Vitamin D Receptor (VDR) gene, are increasingly becoming recognised as significant risk factors for cardiovascular disease (CVD). Although the clinical landscape is still dominated by conventional risk factors including obesity, hypertension, and lifestyle choices, there is now substantial evidence that gene-environment interactions have a role in regulating the start and course of illness. The VDR gene is a crucial genetic candidate for cardiovascular health because of its regulatory function in immune response, calcium homeostasis, and vitamin D metabolism.

Despite being silent at the protein level, the TaqI polymorphism (rs731236) may have an impact on VDR expression and mRNA stability, which in turn may impair the effectiveness of vitamin D signalling. This SNP has been connected in several studies to increased risks of coronary artery disease, hypertension, atherosclerosis, and changed biochemical indicators such blood calcium and vitamin D levels. These correlations demonstrate its possible use as a biomarker for tiered preventive plans and early risk assessment.

Crucially, Dehradun's population offers a singular case study because lifestyle and environmental variables, like varying UVB exposure, customary eating habits, and socioeconomic inequality, may combine with genetic backgrounds to modify an individual's vulnerability to cardiovascular disease. In order to provide individualised healthcare solutions, it is essential to acknowledge the geographical and genetic uniqueness of such connections.

In conclusion, cardiovascular risk prediction and treatment may be revolutionised by combining VDR gene polymorphism screening, particularly TaqI, with clinical and environmental evaluations. Future studies should examine the therapeutic implications of modifying VDR activity in genetically vulnerable people and verify these findings through extensive, multiethnic cohort studies.

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