

# Folic Acid, Vitamin D and Prehistoric Polymorphisms in the Modern Environment

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## Abstract

*A variety of genetic polymorphisms reduce the biological activity of folic acid and vitamin D and increase the risk of specific diseases in humans. For example, polymorphisms in the gene encoding methylenetetrahydrofolate reductase interfere with folic acid-dependent biochemical activities and increase the risk of neural-tube defects and coronary artery disease. Similarly, polymorphisms in the gene encoding the vitamin D receptor increase the risk of osteoporosis, breast and prostate cancers, and other diseases. If these polymorphisms had been disadvantageous during human evolution, they would have been eliminated from the gene pool. Rather, large numbers of people still carry these prehistoric polymorphisms. During human evolution, high dietary levels of folic acid and regular exposure to sunlight (catalyzing the production of vitamin D) likely saturated genetic and biochemical pathways and compensated for any deleterious effect of these polymorphisms. Today, lower intake of folic acid and less exposure to sunlight increase the risk of diseases arising from these surviving prehistoric polymorphisms. Supplemental micronutrients and regular exposure to sunlight can likely offset any negative health consequences of these polymorphisms.*

## Introduction

Polymorphisms are genetic variations that occur with a relatively high prevalence, that is, in more than 1 percent of the population. Because polymorphisms alter the genetic coding of proteins and enzymes, as well as the subsequent utilization of micronutrients, their presence can increase the risk of specific diseases. For example, polymorphisms affecting the gene that

encodes methylenetetrahydrofolate reductase, an enzyme crucial for folic acid utilization, reduce the efficiency of folic acid metabolism. The consequences impair methylation and DNA synthesis, resulting in an increased risk of neural-tube defects<sup>1</sup> and coronary artery disease.<sup>2</sup>

From an evolutionary perspective, such polymorphisms do not appear to be inherently disadvantageous. If they had been disadvantageous over the span of human evolution, they would have been eliminated from the gene pool and not be common today. In fact, polymorphisms in the gene encoding for methylene tetrahydrofolate reductase affect upwards of half of some populations.<sup>3</sup> Such polymorphisms have likely survived because traditional diets rich in folic acid offset their potentially deleterious consequences. In effect, abundant folic acid maintains the activity of methylene tetrahydrofolate reductase and has ensured relatively normal function of essentially a sluggish gene and associated biochemical pathways. During paleolithic times, from about 40,000 B.C. to 10,000 B.C., humans consumed substantial amounts of folic acid, estimated to be approximately 360 mcg daily (about twice the current U.S. dietary consumption).<sup>4</sup> In recent years, folic acid supplements have been used to normalize this particular polymorphism and to reduce the risk of neural-tube defects and heart disease.<sup>5-8</sup>

A somewhat similar situation may very well exist with polymorphisms in the gene encoding for the vitamin D receptor (VDR), which regulates vitamin D utilization. Vitamin D (vitamin D3, 1,25-dihydroxyvitamin D3, calciferol) is universally considered an essential nutrient, perhaps best known for its role in regulating calcium homeostasis and enhancing the assimilation of calcium into the bone matrix. How-

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ever, from evolutionary and biological perspectives, the “nutritional” role of vitamin D appears relatively recent. Except for fish and relatively recent food-fortification practices, vitamin D is not widely present in human diets. In truth, the term vitamin D is actually a misnomer for an endogenously synthesized hormone that, like other hormones, has diverse roles in cell regulation and health.

### VDR Gene Polymorphisms in the Modern Environment

Of all vitamin supplements, vitamin D may be the one most frequently noted for potential risks resulting from its overdose. Although chronic overdose of vitamin D can result in hypercalcemia (which may be fatal), this risk has been greatly overstated.<sup>9</sup> Studies have found that low blood levels of vitamin D are common, even among people with apparently adequate vitamin D dietary intake, suggesting that the real-world risk of vitamin D deficiency is far greater than that of vitamin D overdose.<sup>10,11</sup>

During most of human evolution, people spent considerable time outdoors and exposed to sunlight. Ultraviolet (UV) radiation in sunlight initiates the conversion of steroid precursors in the skin to vitamin D. People who live and work in sunny climates synthesize approximately 10,000 IU of vitamin D daily, which is approximately 50 times more than the current U.S. governmental recommendation of 200 IU (5 mcg) daily for children and for adults up to age 50 years. (Recommended levels increase modestly to 400 IU daily for people ages 51-70 years and 600 IU daily for people age 70 and older.) The body’s ability to safely produce 10,000 IU of vitamin D daily, considered in conjunction with our evolutionary heritage, suggests that this level may be biologically optimal for health. Such a high level of vitamin D likely saturates the VDR receptor, and VDR polymorphisms are probably of little consequence as long as high (historically normal) vitamin D lev-

els are maintained. Polymorphisms in the VDR gene are likely deleterious only when vitamin D levels are low. This view is consistent with the concept of “orthomolecular” health proposed in 1968.<sup>12</sup>

Over the past 50,000 years, endogenous synthesis of vitamin D has become less reliable than in earlier times, a trend that has continued and even accelerated over the past century. Around 50,000 years ago, humans migrated away from the equator and became subject to significant seasonal variations in UV ray exposure and vitamin D synthesis. In addition, wearing more clothes and spending more time indoors at home, in offices, and in autos has also greatly limited exposure to UV rays and reduced vitamin D synthesis. There is also evidence that a major component of the modern diet—consumption of refined and whole grains—reduces vitamin D metabolism. (This and other evidence suggests that humans may be maladapted to grains, which entered the human diet approximately 10,000 years ago, too short of a time for genetic adaptation.)<sup>13</sup> Since the 1920s, vitamin D has often been treated as a nutrient rather than an endogenous hormone.

As vitamin D synthesis has declined, the health risks related to VDR polymorphisms appear to have become more problematic. Recent research has identified numerous polymorphisms in the VDR associated with low vitamin D blood levels and an increased risk of disease. A high prevalence of VDR gene polymorphisms have been identified in people with osteoporosis,<sup>14,15</sup> periodontal disease,<sup>16</sup> type 2 diabetes,<sup>17</sup> Addison’s disease,<sup>18</sup> inflammation,<sup>19</sup> psoriasis,<sup>20</sup> and breast,<sup>21,22</sup> prostate,<sup>23</sup> and colon cancers.<sup>24</sup> Indeed, the relationship between low vitamin D and cancer is so well established that there is widespread research on vitamin D analogs as chemotherapeutic drugs.<sup>25,26</sup> Low levels of vitamin D also have been found in people with type 1 diabetes, multiple sclerosis,<sup>27</sup> and congestive heart failure,<sup>28</sup> suggesting that VDR

gene polymorphisms may be involved in these diseases as well. It is possible that modern increases in longevity, with subsequent increases in random age-related genetic mutations, amplifies the deleterious effects of VDR gene polymorphisms.

### Conclusion

The modern diet, even with some fortified food products, provides relatively little vitamin D, compared with endogenous synthesis of approximately 10,000 IU daily in individuals who spend substantial time outdoors. Furthermore, modern indoor lifestyles and limited exposure to sunlight severely limit our native ability to synthesize vitamin D. As a consequence, many people are now vitamin D deficient or marginally deficient, even when consuming officially adequate (200-600 IU) daily amounts of the vitamin. Low vitamin D levels cannot overcome the metabolic inefficiencies created by polymorphisms, thus increasing the risk of a variety of diseases.

The deleterious effect of these polymorphisms in the modern world may be offset by greater exposure to sunlight and vitamin D supplementation. The evidence suggests that daily vitamin D synthesis of ~10,000 IU of vitamin D may be biologically optimal – and that current official recommendations are suboptimal at best. Because vitamin D is, from evolutionary and biological perspectives, an endogenous hormone (rather than a nutrient), it is conceivable that ultraviolet light-initiated endogenous synthesis of vitamin D is safer than oral intake.

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