

Genetic Vitamin D Receptor Polymorphisms and Risk of Disease

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I. Introduction

The secosteroid hormone vitamin D, its receptor (VDR), and the metabolizing enzymes involved in the formation of the biologically active form of the hormone, acting together, are major players in the vitamin D endocrine system. This system plays an important role in skeletal metabolism, including intestinal calcium absorption, but has also been shown to play an important role in other metabolic pathways, such as those involved in the immune response and cancer [1]. In the immune system, for example, vitamin D promotes monocyte differentiation and inhibits lymphocyte proliferation and secretion of cytokines, such as IL2, interferon- γ , and IL12. In several different types of cancer cells vitamin D has been shown to have anti-proliferative effects. These aspects of the vitamin D endocrine system are extensively discussed elsewhere in this volume.

At the same time it is also widely known that large interindividual differences exist. One approach to understand interindividual differences in the vitamin D endocrine system is to study the influence of variations in the DNA sequence of important proteins of this system. For example, deleterious mutations in the VDR gene cause 1,25-dihydroxyvitamin D resistant rickets, a rare monogenetic disease (Chapter 72). More subtle sequence variations (polymorphisms) in the VDR gene occur much more frequently in the population, but they have not been systematically analyzed and their effects on VDR function are poorly understood. Their influence on the vitamin D endocrine system is currently under scrutiny in relation to a number of so-called complex diseases and traits, such as osteoporosis. This so-called candidate gene approach in the genetic dissection of complex traits is currently gaining increased

importance over genome search approaches using linkage analysis [2,3].

The interpretation of polymorphic variations in the VDR gene is severely hindered by the fact that until now only a few polymorphisms in this large gene have been studied, and that most of these are anonymous restriction fragment length polymorphisms (RFLP). One expects them to be linked to truly functional polymorphisms elsewhere in the VDR gene (or in nearby gene(s)), which can then explain the associations observed. Thus, to understand the mechanisms underlying the associations one has to analyze the genomic organization of the VDR locus, to identify which genes are present in the chromosomal area, to categorize all relevant VDR polymorphisms, to determine the haplotypes across the gene, to determine their relationship with the RFLP markers used so far, and finally to perform association analyses with relevant phenotypic endpoints such as disease.

Below, we present a more detailed description of the genomic organization of the VDR gene, including discussion on polymorphisms, linkage disequilibrium, and haplotypes. We then describe association studies of VDR polymorphisms in relation to different diseases. Historically speaking, studies of VDR polymorphisms in relation to bone endpoints, including osteoporosis in particular, have received most attention while the analysis of VDR polymorphisms in relation to other diseases, including breast and prostate cancer and immune-related disorders, has reached the literature somewhat later on. This allows studies on associations with bone endpoints to be compared to a certain extent and to illustrate some of the difficulties in interpreting the results. This is much less possible for VDR polymorphism studies in relation to other disease endpoints, although similar interpretation problems exist. Essentially, these interpretation problems