What Are the Frequency, Distribution, and Functional Effects of Vitamin D Receptor Polymorphisms as Related To Cancer Risk?

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It is clear that, apart from its essential role in preventing rickets, vitamin D has a key role in varied biochemical, immunological, and carcinogenic pathways. 1,25 dihydroxy vitamin D binds to the vitamin D receptor (VDR) gene and initiates transcription of about 200 genes. The VDR gene is located on chromosome 12q13 and is large (>100 Kb). The VDR gene contains six un-translated exons and eight protein-coding exons. To date, over 490 single nucleotide polymorphisms (SNPs) have been identified and these can be grouped into three distinct linkage disequilibrium (LD) blocks, termed block A, B, and C. The most extensively studied SNPs have been in LD block B (*Bsm1*, *Apa1* and *Taq1*) and the *Fok1* SNP situated in exon 2. More recently SNPs have been identified in the promoter region of the gene and these have been associated with carcinogenesis.

Bsm1, *Apa1*, and *Taq1* have been shown to have no effect on expression levels or activity of translated VDR protein though other VDR SNPs appear to have functional consequences. For example, the Fok1 polymorphism is associated with a shorting of the VDR protein resulting in increased biological activity. The Poly (*A*) repeat polymorphism in the 3' untranslated region, the Cdx-2 polymorphism and two further promoter region SNPs, namely the GATA and an SNP situated near exon 1a have also been shown to have functional effects. Despite demonstrating functional effects at the cellular level, we are unclear what effects such polymorphisms have in individuals, especially in relation to carcinogenesis. A systematic assessment of functional VDR polymorphisms on a population basis would help to demonstrate associations with diseases and thereby identify SNPs that have functional relevance.

Prostate cancer is a good disease to study in relation to the functionality of the VDR SNPs due to its reported association in ecological and case control studies with UVR exposure. Despite this, molecular epidemiological studies have shown conflicting results regarding the association of VDR polymorphisms and cancer risk. Our recent data have demonstrated the importance of the promoter region of the gene in relation to prostate cancer susceptibility. When we stratify promoter region VDR genotypes and haplotypes by levels of UVR exposure (as a gene-environment interaction), these associations are further strengthened.

In our view, future work into the VDR gene needs to move away from solely the traditionally studied SNPs and focus more on gene environmental interactions. SNPs in the promoter region of the gene require further study as preliminary results look encouraging in relation to carcinogenesis. Diet, UVR exposure, and genetic factors are known to be important in carcinogenesis and any future work into VDR SNPs should encompass these parameters.