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Gene Section
Short Communication

SRD5A2 (steroid-5-alpha-reductase, alpha polypeptide 2 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 2))

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Identity

HGNC (Hugo): SRD5A2

Location: 2p23.1

DNA/RNA

Description

Genomic DNA of SRD5A2 gene spans about 58.6 kbp on chromosome 2p23.

Transcription

Five exons with a long 3' UTR.

Protein

Description

SRD5A2 is a microsomal protein of 254 amino acids in length.

Expression

Androgen sensitive tissues, such as prostate.

Localisation

Microsome.

Function

SRD5A2 protein is an enzyme that converts testosterone to 5-alpha dihydrotestosterone (DHT) and progesterone or corticosterone into 5-alpha-3-oxosteroids.
It is active at acidic pH, and is inhibited by finasteride.

Homology

50% homology with human SRD5A1 isoenzyme and 46% homology with rat 5-alpha-reductase.

Mutations

Note

There were over 29 mutations of SRD5A2 gene documented in literature, including 12 single amino acid missense substitutions (Makridakis et al., 2000; Vilchis et al., 2008; Nie et al., 2011).
It has been suggested that exon 4 may be a mutation hotspot region on the SRD5A2 gene (Vilchis et al., 2008).
Some of the more studied polymorphisms of SRD5A2 included V89L, A49T, and the (TA)n dinucleotide repeat.

Implicated in

Prostate cancer

Note

Various genetic studies from multiple ethnic populations have shown genetic variations in the SRD5A2 gene are associated with prostate cancer. Polymorphisms V89L, A29T, and the (TA)n repeat are some of well-known SRD5A2 variation that have been liked to prostate cancer risk.
However, these associations are not always consistent. For example, the V89L (rs523349) variant is a missense single nucleotide polymorphism resulting in a valine to leucine substitution at condon 89 that reduced SRD5A2 enzyme activity.
More than couple dozen of studies performed genetic association studies between V89L polymorphism and prostate cancer risk since 1997.
Although the association has been found significant repeatedly, the results were inconsistent and conflicting

(Nam et al., 2001; Salam et al., 2005, Hsing et al., 2001).

Recently, a meta-analysis review (Wang et al., 2010) was conducted on 25 genetic studies of SRD5A2 V89L polymorphism and prostate cancer, which included additional subgroup analysis in Asian, African, European and age ≤ 65 group. In overall analysis, no significant association was found between V89L and prostate cancer risk. Subgroup analysis revealed a slight but significant increased risk in European men with at least one L-allele (LL+LV vs VV, OR=1.11; 95%CI=1.03-1.19; P<0.01), and in men younger than 65 with LL genotype when compared to those with VV genotype (OR=1.70; 95%CI=1.14-2.68; P=0.02). The interethnic discrepancy of the effect of V89L may have arisen from a variable influence of the risk allele due to the significantly varied allelic distribution of V89L between the ethnic groups (Zeigler-Johnson et al., 2002).

It was concluded that the V89L polymorphism plays a low-penetrant role in the risk of prostate cancer among European and men younger than 65 years of age.

Oncogenesis

Androgen levels have been suggested to play an important role in the etiology of prostate cancer. The same SRD5A2 genetic variations linked to prostate cancer has also been repeatedly shown to be associated with various circulating androgen level in the blood, including testosterone, dihydrotestosterone and various forms of their metabolites (Makridakis et al., 2000; Allen et al., 2001; Hsing et al., 2001).

Therefore, it is possible that these risk-predisposing polymorphisms may cause changes in the SRD5A2 enzyme functional activity that results in the variation of circulating androgens, and ultimately leads to the development of prostate cancer.

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