

Mutation and Polymorphism Analysis Androgen Receptor Gene and Genotype-Phenotype Correlations in Prostat Cancer Patients

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Introduction: Prostate cancer (PCa) is non-cutaneous malignancy diagnosed in men, especially in the elderly. The development, growth and function of the prostate gland depend on Androgen signalling. Defect on androgen signalling caused by mutations or polymorphisms in the androgen receptor gene (AR) has been known to play a role in the carcinogenesis of the prostate tissue. The aim of this study was to performed AR mutations/polymorphism analysis and genotype-phenotype correlations in PCa patients in Indonesian population.

Methods: Thirty eight PCa patients from Jav anese ethnic group enrolled in this study. The diagnosis of PCa was based on histopathology of prostate tissue using Gleason Score criteria. All exons and exon-intron boundaries of AR gene was amplified by Polymerase Chain Reaction and sequenced by Sanger sequencer ABI XL3100. In silico analysis was performed by using polyphen2, SIFT, and Mutation Taster@ software. Correlation test was conducted to analyze the correlation of the genotype with the phenotype.

Results: The age range majority of PCa patients who were enrolled in this study was 69-73 years (31,58%). Two types of polymorphism was identified in exon 1, first is a missense polymorphism p.P214E and second one is the CAG repeat sequences (CAGn) with the length of the repeat between 13 to 34. There was no correlation between the length of CAGn either with the Gleason Score (R = 0.0035, p = 1.00) or with the levels of PSA (R = -0.0092, p = 1.00). Two types of mutations (rare variant) were identified in the exon, first is a missense mutation (c.47C>A / p. P146Q) which is a novel mutations and second one is a deletions of GCA sequence (c.255_257delGCA / p.G91del).

Conclusions: The frequency of AR gene mutations was 2.6% (2/76 alleles) and there is no correlation between genotype with phenotype in PCa patients Jav anese.

Keyword: AR, Gleason Score, prostate cancer (PCa), PSA.

Mutation Detection of WDR1 Gene as A Novel Candidate Gene in Non-Syndromic Cleft Palate with History of Environmental Tobacco Smoking (ETS)

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Background : Non syndromic cleft palate (NSCP) is a common congenital anomaly in the oral which has complex etiology involving genetic and environmental risk factor. Identification of genetic factors including FOXE1, ALX3, MKX, PDGFC, and SUMO1 gene in either family study or population study remain inconclusive. Environmental tobacco smoke (ETS) was reported having interaction with certain single nucleotide polymorphism in NSCP cases. Genome Wide Association Study (GWAS) by Wu et al in 2014 identified markers in SLC2A9 (P= 2.2x10⁻⁷) and WDR1 (P= 1.79x10⁻⁷ dan P=1.98x10⁻⁷) in chromosome 4p16.1 have strong evidence in interaction of gene-environment if ETS during periconception were included (genome wide significance, 10⁻⁶<P<10⁻⁴). WDR1 gene (WD Repeat domain 1, also called actin-interacting protein 1) promoted cofilin-mediated actin filament disassembly and played important role in unidirectional cell migration.

Method : Sanger sequencing of all coding exons and surrounding splice sites of WDR1 gene were performed in 13 NSCP patients with history of ETS in their mother during periconception until first trimester of pregnancy. Sequence result was compared to published reference sequence using Mutation Surveyor software version 5.0 (Applied Biosystems Genetic Analyzers, MegaBACE, and Beckman CEQ electrophoresis systems). The identified variants were checked in the dbSNP 137, 1000 Genome Project, and Exome Sequencing Project.

Result : Unlikely pathogenic variants were identified in exon 1 [rs11557743 (5'UTR), cDNA: 108G>C, MAF=0.34] and exon 5 [rs13441, cDNA: 747A>G, p.185.I>V, MAF=0.46].

Conclusion : WDR1 as a novel candidate gene cause non-syndromic CL cases with a history of maternal ETS exposure during peri-conception period is still inconclusive. Future study should be done in SLC2A9 gene in order to identify variants that might be causative for the disorder.

Keyword: non-syndromic cleft palate, environmental tobacco smoking, WDR1, mutation