Role of *TP53* P72R polymorphism in human papillomavirus associated premalignant laryngeal neoplasm

Leena-Maija Aaltonen, Ren Wei Chen, Stina Roth, Antti A Mäkitie, Heikki Rihkanen, Antti Vaheri, Lauri A Aaltonen

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Department of Virology, Haartman Institute, FIN-00014 University of Helsinki, Helsinki, Finland
L-M Aaltonen
R W Chen
A Vaheri

Department of Otorhinolaryngology, Helsinki University Central Hospital, Helsinki, Finland
L-M Aaltonen
A A Mäkitie
H Rihkanen

Department of Medical Genetics, Haartman Institute, PO Box 21, FIN-00014 University of Helsinki, Helsinki, Finland
S Roth
L A Aaltonen

Correspondence to:
Dr Aaltonen,
lauri.aaltonen@helsinki.fi

Table 1 *TP53* polymorphism in adult onset laryngeal papilloma patients and controls

Amino acid at position 72	Patients (n=42)	%	Controls (n=186)	%	p value
Arg	24	57	88	47	0.31
Pro/arg	18	43	75	40	0.58
Pro	0	0	23	12	0.01

No significant differences were detected between Arg and Pro/Arg amino acid sequences at position 72 in patients and controls. The Pro allele was more common in controls than in patients (Fisher's exact test, two tailed).

Laryngeal papillomatosis, a disease in which malignant transformation takes place in 3-7% of patients,^{1,2} is caused by low risk human papillomavirus (HPV) types 6 and 11. The mechanism by which HPV affects *TP53* involves the HPV E6 oncoprotein, which has been shown to bind *TP53* protein and cause its degradation through the ubiquitin pathway.³ It has been proposed that subjects with homozygous arginine (Arg) at position 72 in the *TP53* amino acid sequence are more susceptible to HPV associated uterine cervical and cutaneous tumorigenesis than are heterozygotes, and that the *TP53* Arg allele is susceptible to *TP53* E6 mediated degradation regardless of whether the infection is by a low risk or high risk HPV type.⁴ However, although these findings could not be confirmed in studies of large populations of women with premalignant and malignant cervical neoplasia,⁵ recently Zehbe *et al*⁶ reported an association between *TP53* codon 72 Arg homozygotes and development of cervical cancer.

Our study is based on Finnish adult onset (age at diagnosis ≥ 17 years) laryngeal papilloma patients treated at Helsinki University Central Hospital, Department of Otorhinolaryngology, during the years 1975-1994.⁷ Diagnosis of laryngeal papillomatosis was confirmed by detection of HPV DNA by polymerase chain reaction (PCR) from patients' laryngeal biopsies. Because only paraffin embedded biopsies (n=59) were available, and only 29 of them were HPV positive, results on fresh frozen HPV positive biopsies of an additional 13 randomly selected adult onset patients treated during the years 1997-1999 were included.

The *TP53* proline 72 arginine (P72R) polymorphism was analysed from lymphocyte DNA by sequencing the genomic PCR product

of exon 4 of these 42 adult onset patients. The results were confirmed by digestion of the PCR products. All data derived from the patient samples by sequencing and by digestion analysis were identical. Our reference population was 186 cancer free anonymous blood donors and their samples were analysed by digestion only. No differences existed in Arg and Pro/Arg allele frequencies between patients and controls (table 1).

Of the HPV 6 positive patients, 15/27 (56%) were Arg homozygotes, and of the HPV 11 positive, 7/10 (70%). In addition, three patients' biopsies were both HPV 6 and 11 positive, and two patients had some other HPV type in their laryngeal biopsy. Based on experimental studies with HPV 11 and analysis of skin cancers representing mixed HPV types, Storey *et al*⁴ proposed that in addition to high risk HPV types, Arg homozygosity predisposed to tumours promoted to low risk HPV types as well. This conclusion is not in accordance with our data. Although HPV 11 E6 may induce degradation of *TP53* Arg in vivo, this mechanism is not necessarily involved when laryngeal tumours are caused by HPV 6 or 11 virus types. These findings argue against a role for the P72R polymorphism in this HPV associated premalignant neoplasm and against the hypothesis that *TP53* Arg affects the susceptibility of *TP53* to E6 mediated degradation also in infections caused by low risk HPV types.

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