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Prevalence of the MspI and Ile^{462}Val SNPs of Cytochrome P-450 1A1 in Hidradenitis Suppurativa

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Abstract: Hidradenitis Suppurativa (HS) is a chronic inflammatory skin disease that affects the hair follicles in the axillary, perianal and inguinal area. Its cause and pathogenesis are unknown, but cigarette smoking increases the risk of developing HS conceivably by accumulating toxic metabolites in sweat. The xenobiotic compounds from tobacco are metabolized by the cytochromes P-450. The cytochrome P-450 1A1 (CYP1A1), one of the most active isoenzymes, harbours several polymorphisms. Two of them, MspI and Ile^{462}Val single nucleotide polymorphism (SNP), are associated with enhanced activity and inducibility. Performing direct DNA sequencing, we investigated the frequencies of these SNP in 51 patients with HS, 45 of these were smokers. We found similar overall SNP rates in our patients in comparison with previous data for Caucasian or German controls. Obviously, there is no relation between the occurrence of these SNPs and the risk of developing HS.

Key words: cytochrome P-450 1A1 – Hidradenitis Suppurativa – SNP

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Background

Hidradenitis Suppurativa (HS), a chronic inflammatory skin disease with a prevalence of about 0.3–4.1%, affects the hair follicles in the axillary, perianal and inguinal area. Patients suffer from cutaneous and subcutaneous nodular inflammation, fistulae and production of a malodorous secretion, and healing occurs with substantial scarring.

At present, the cause and pathogenesis of HS are unknown (1). Epidemiological studies suggested that obesity, pharmacological factors, a positive family history as well as cigarette smoking add to the risk of developing HS. According to some studies, 70–89% of patients with HS are smokers. It was proposed that smoking may accumulate toxic metabolites in sweat, thus contributing to the progress of this disease (1–3).

The cytochromes P-450 are a family of isoenzymes that metabolize a large number of foreign and endogenous substrates as well as xenobiotic compounds including those from tobacco such as polyaromatic hydrocarbons and aromatic amines. The cytochrome P-450 1A1 (CYP1A1) on chromosome 15 is one of the most active isoenzyme members. By catalyzing the first reaction step, it has a key function in the metabolism of polycyclic aromatic hydrocarbons, such as benzo(a)pyrene of tobacco. The CYP1A1 gene harbours several polymorphisms, two of them are associated with enhanced activity and inducibility as has been revealed by functional studies. The first polymorphism designated as MspI single nucleotide polymorphism (SNP), represents a T to C exchange at position 3801 in the 3‘ non-coding region of the gene downstream of polyadenylation site. The second, occurring less frequently than the MspI and denoted as Ile^{462}Val or BsrD1 SNP stands for a 2455 A to G change in exon 7 of the heme-binding region. The rates of both SNPs vary considerably between different populations and appear most commonly in Asians. Both SNPs are closely linked in Asians and, less closely, also in Europeans (4). The non-variant CYP1A1 genotype showing lower enzymatic activity is associated with the development of psoriasis in smokers. Thus, the authors assumed that non-metabolized xenobiotics of tobacco, such as nicotine, could play a role as etiological agents in psoriasis (5,6).

In contrast, Paraskevaidis et al. (7) demonstrated a higher frequency of the more active MspI SNP variant in conventional acne. They suggested that the enhanced CYP1A1 activity may impair the biological efficacy of natural retinoids because of their rapid metabolism to inactive compounds, leading to the abnormal sebocyte differentiation and hyperkeratinization in acne.

Questions addressed

The aim of this study was to estimate the frequencies of the activating CYP1A1 SNPs MspI and Ile^{462}Val in patients

with HS and to compare the results with corresponding data of the general population.

Experimental design

The patients with HS ($n = 51$) were treated and monitored in the Charité University Hospital, Department of Dermatology and Allergy, 45 (88.2%) of these patients were smokers. A written informed consent was received from all patients in this study. All patients were of German origin (Caucasians).

Both SNPs were identified by direct DNA sequencing. Genomic DNA of peripheral blood mononuclear cells was obtained from the patients with HS as described. Then, the MspI SNP was amplified according to Ng et al. (8), and the Ile^{462}Val polymorphism was amplified with the primers ACTGCAGCCAGATCAGTGTCTATG (forward) and TTTGTAAACCAGTGGCAGATCAAC (reverse), which we deduced from the exon 7 gene sequence. A direct bidirectional sequencing of all PCR products was carried out using the BigDye® Terminator v1.1. Cycle Sequencing kit according to the manufacturer's protocol (Applied Biosystems, Weiterstadt, Germany) followed by automated DNA sequencing on the ABI PRISM® 310 Genetic Analyser (Applied Biosystems). To identify the polymorphisms in question, the sequence data were evaluated and aligned by the SeqScape® vs 2.5 software (Applied Biosystems).

Results

The results are shown in Table 1. The table presents the frequencies of MspI and Ile^{462}Val SNP as well as the frequencies of two additional SNPs (Thr^{461}Asp and Arg^{464}Ser) that can be detected in the amplified part of exon 7 in 51 patients with AI. All MspI and Ile^{462}Val SNP (i.e. activating SNP) were found in the group of the smokers. Of the six non-smokers, four remained without mutations, one patient showed the Thr^{461}Asp exchange; another the Arg^{464}Ser SNP. In comparison, corresponding SNP rates published for a non-affected US white population (4) and a German population (5) were quoted.

The outcome shows similar overall SNP rates in our patients in comparison with the data for Caucasian or German controls.

Table 1. Frequencies of CYP1A1 single nucleotide polymorphisms (SNPs) in Hidradenitis Suppurativa (HS) and controls

SNP	Alleles	HS		Controls %[1,2]
		n[3]	%	
Msp1	T/C	7	13.7	15.7[1],17[2]
	C/C	0	0	0[1],1[2]
Ile^{462}Val	Ile/Val	3	6	7[1], 8[2]
	Val/ Val	0	0	0.4[1], 0.7[2]
Msp1+Ile^{462}Val	T/C+Ile/Val	3	6	0[1]
Thr^{461}Asp	Thr/Asp	6	12	8[2]
	Asp/Asp	0	0	0.2[2]
Arg^{464}Ser	Arg/Ser	1	2	No data
	Arg/Arg	0	0	No data

[1]Richter-Hinz et al. (5).
[2]Masson et al. (4).
[3]n Total 51/50: in one sample the PCR for the Ile^{462}Val SNP failed.

Conclusions

We could not find elevated or decreased frequencies of the CYP1A1 activating SNP MspI or Ile^{462}Val in AI. Thus, there is obviously no relation between the occurrence of these SNPs and the risk of developing HS in the patient group investigated here. No other HS-associated SNP were described in the literature hitherto. Recently, two investigations of the Card15/NOD2 gene, which is altered frequently in Crohn's disease, were undertaken in patients with HS, one of it in our department. However, both studies failed to detect an increased mutation frequency compared to non-affected controls (9,10).

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