Polymorphism of the catechol-O-methyltransferase gene in Han Chinese patients with psoriasis vulgaris

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Abstract
Psoriasis vulgaris is defined by a series of linked cellular changes in the skin: hyperplasia of epidermal keratinocytes, vascular hyperplasia and ectasia, and infiltration of T lymphocytes, neutrophils and other types of leukocytes in the affected skin. Catechol-O-methyltransferase (COMT) 158 polymorphism can reduce the activity of the COMT enzyme that may trigger defective differentiation of keratinocytes in psoriasis. Immunocytes can degrade and inactivate catecholamines via monamine oxidase (MAO) and COMT in the cells. We hypothesized that the COMT-158 G > A polymorphism was associated with the risk of psoriasis vulgaris in Han Chinese people. In a hospital-based case-control study, 524 patients with psoriasis vulgaris and 549 psoriasis-free controls were studied. COMT-158 G > A polymorphism was genotyped using the PCR sequence-specific primer (PCR-SSP) technique. We found no statistically significant association between the COMT-158 allele A and the risk of psoriasis vulgaris (p = 0.739 adjusted OR = 1.03; 95% CI = 0.81-1.31). This suggests that the COMT-158 G > A polymorphism may not contribute to the etiology of psoriasis vulgaris in the Han Chinese population.

Key words: COMT, gene polymorphism, genetic susceptibility, psoriasis.
Catechol-O-methyltransferase (COMT) is an enzyme that catalyses the O-methylation of biologically active toxic catechols and plays an important role in the metabolism of drugs and neurotransmitters (Tursen et al., 2002). In humans, the COMT protein exists as two length variants, soluble (S-COMT) and membrane-bound (MB-COMT), which are encoded by a single gene localized at chromosome 22q11.1-q11.2 (Grossman et al., 1992; Lundstrom et al., 1995; Karayiorgou et al., 1997). The MB-COMT variant has an additional 50 amino acids at the N-terminal, but is otherwise identical to S-COMT (Lundstrom et al., 1991). A single base-pair change (G > A) in exon 4 of the COMT gene, resulting in an amino acid change (Val > Met) at codon 158 of MB-COMT and codon 108 of S-COMT, reduces the thermostability and the activity of the enzyme (Lotta et al., 1995; Lachman et al., 1996; Tursen et al., 2002). The two alleles refer to COMT*H, the site-absent (G; Val) allele that encodes the thermostable, high-activity enzyme, and COMT*L, the site-present (A; Met) allele that encodes the thermolabile, low-activity enzyme. The allelic variant only affects the enzyme activity (Palmatter et al., 1999). A common single-nucleotide polymorphism (SNP) in codon 158 of the COMT gene (COMT-158 G > A, rs4680) codes for a substitution of valine (Val) by methionine (Met), resulting in the reduced thermostability and activity of the enzyme (Bertocci et al., 1991; Grossman et al., 1992; Lundstrom et al., 1995; Karayiorgou et al., 1997).

Erdal et al. (2004), based on a case-control analysis of a Turkish population, observed that the COMT-158 G > A polymorphism was significantly associated with genotype COMT AA and psoriasis cases. They speculated that low enzyme activity could be unable to prevent the formation of toxic o-quinones in psoriatics, and this oxidative stress of keratinocytes could trigger defective differentiation in psoriasis. No differences have been found in COMT polymorphism between psoriatics and control subjects, but the COMT-LL genotype was found significantly increased in the psoriasis patients (Karayiorgou et al., 1997). COMT is important in preventing the formation of toxic o-quinones during epidermal cell synthesis. Therefore, COMT also plays an important regulatory role in the oxidative damage of keratinocytes. Immuneocytes can degrade and inactivate CAks via MAO and COMT in the cells (Qiu et al., 2005).

Based on this concept, we genotyped the COMT-158 G allele and 322 bp for the COMT-158 A allele. These products were analyzed by 2% agarose gel electrophoresis and visualized with 0.5 μg/mL ethidium bromide staining under an ultraviolet illuminator. Genotypes were scored by two independent individuals, and any ambiguous genotypes were repeated or omitted. PCR products were identified by sequencing.

Chi-square tests were used to evaluate the differences in the frequency distributions of selected demographic variables between the cases and controls, including each allele and genotype of the COMT polymorphisms. Unconditional univariate and multivariate logistic regression analyses were performed to obtain the crude and adjusted odds ratios (ORs) for the risk of psoriasis and their 95% confidence intervals (CIs). The multivariate adjustment in-
cluded age and gender variables. Two-tailed tests of statistical significance were performed with SAS software (version 8.2; SAS Institute, Inc., Cary, North Carolina).

We found no significant differences in age and gender between the psoriasis patients and the control group: mean age was 32.1 ± 13.6 years in the psoriasis group and 31.5 ± 13.9 years in the control group (p = 0.232), while the gender distributions (M:F) were 54.8%:45.2% in the study group and 50.5%:49.5% in the control group (p = 0.157) (Table 1).

The genotype and allele frequencies of COMT 158 in the study and control groups are shown in Table 2. In the control group, the genotype frequencies of the COMT 158 polymorphism were in agreement with the Hardy-Weinberg equilibrium (p = 0.168). No significant differences were found between the psoriasis and control subjects regarding the frequencies of genotypes GG, GA, and AA (p = 0.759) (Table 2). Similarly, there was no significant difference between the two groups regarding the frequencies of allele A (p = 0.624).

To consider the single nucleotide polymorphism in codon 158 (G > A) of the COMT gene, which leads to a valine-methionine substitution resulting in the difference in COMT activity, we analyzed the association between combined genotypes (GG, GA+AA) and the risk of psoriasis vulgaris. We investigated whether the distributions of combined genotypes (GG, GA+AA) were different among type 1 and type 2 psoriasis patients and control subjects. However, as shown in Table 3, the frequency of the variant combined genotype (GA+AA) was not statistically different in the type 1 psoriasis (43.5%) and type 2 psoriasis (47.8%) cases compared to controls (43.0%).

The Psoriasis Area and Severity Index (PASI) is a widely used method to characterize the severity of the disease (de Rie et al., 2004). In our study, PASI was used to classify the psoriatic patients into two different levels: level 1 = PASI ≤ 20; level 2 = PASI > 20. As shown in Table 3, the frequency of the variant combined genotype (GA+AA) was 45.5% in level 1 and 41.5% in level 2 psoriasis patients. There was no statistical difference between the two levels of psoriasis and the controls.

Based on previous research, we hypothesized that polymorphism COMT 158 (G > A) might be associated with the risk of psoriasis vulgaris. Our study, however, found no significant association between COMT 158 (G > A) and psoriasis vulgaris, and also no significant difference between COMT 158 (G > A) and different types of psoriasis vulgaris. Our study included only statistical research, not functional investigation of the association between the COMT polymorphism and psoriasis vulgaris, so this hypothesis needs to be tested by further functional studies.

In conclusion, we found no significant difference regarding the COMT-158 (G > A) polymorphism between psoriasis vulgaris patients and control subjects in a Han Chinese population. The difference between these results and those of Erdal et al. (2004) may be due to differences in the ethnic composition of the populations and in the number of investigated subjects. Our findings suggest that polymorphism COMT 158 may not be associated with the risk of psoriasis.

Table 1 - Frequency distributions of selected variables in the psoriasis cases and psoriasis-free controls.

| Variables | Cases (n = 524) | Controls (n = 549) | p* |
|-----------|----------------|--------------------|----|
| Age (years) |                |                    |    |
| ≤ 10      | 18             | 22                 | 0.232 |
| 11-20     | 102            | 136                |      |
| 21-30     | 138            | 140                |      |
| 31-40     | 133            | 114                |      |
| > 51      | 50             | 58                 |      |
| Gender    |                |                    | 0.157 |
| Male      | 287            | 277                |      |
| Female    | 237            | 272                |      |

*Two-sided χ² test for the frequency distributions of selected variables between the cases and controls.

Table 2 - Genotype and allele frequencies of polymorphism COMT and associations with psoriasis risk.

| Genotype | Cases (N = 524) | Controls (N = 549) | p* | Crude OR (95% CI) | Adjusted OR (95% CI) |
|----------|----------------|--------------------|----|-------------------|---------------------|
| GG       | 294            | 313                | 1.00 | 1.00              |                     |
| GA       | 201            | 211                | 0.759 | 1.02 (0.79-1.31) | 1.00 (0.78-1.29)    |
| AA       | 29             | 25                 | 1.24 (0.71-2.16) | 1.23 (0.70-2.15) |                     |
| GA+AA    | 230            | 236                | 0.765 | 1.04 (0.82-1.33) | 1.02 (0.80-1.31)    |
| A allele | 0.247          | 0.237              | 0.624 |                   |                     |

*The genotype frequencies observed in the control subjects were in agreement with the Hardy-Weinberg equilibrium (χ² = 1.900, p = 0.168).

*Two-tailed χ² test for either genotype distributions or allele frequencies between the cases and controls.

*Odds ratios (ORs) were obtained from a logistic regression model with adjustment for age and gender; 95% confidence interval (CI).
of psoriasis vulgaris. Larger population-based studies, different clinical subgroups and studies among different ethnic groups are needed to confirm these findings.

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Table 3 - Association and stratification analyses of the combined genotypes of polymorphism COMT and risk of psoriasis.

| Variables | N (case/control) | Combined genotypes (case/control)* | Crude OR (95% CI) | Adjusted OR (95% CI) b | p^c |
|-----------|-----------------|-----------------------------------|------------------|------------------------|-----|
| GG        | 294/313         | 230/236                           | 1.04 (0.82-1.33) | 1.02 (0.80-1.31)       | 0.765 |
| GA+AA     | 207/236         | 43.9/43.0                          | 1.02 (0.80-1.31) | 1.03 (0.80-1.32)       | 0.865 |
| Onset age |                |                                   |                  |                        |     |
| ≤ 40      | 270/313         | 208/236                           | 1.22 (0.67-2.22) | 0.81 (0.40-1.63)       | 0.525 |
| > 40      | 24/313          | 22/236                            | 1.11 (0.84-1.47) | 1.09 (0.82-1.44)       | 0.468 |
| PASI      |                |                                   |                  |                        |     |
| ≤ 20      | 173/294         | 144/254                           | 0.95 (0.69-1.31) | 0.94 (0.68-1.30)       | 0.735 |
| > 20      | 122/313         | 87/236                            | 1.04 (0.82-1.31) | 1.03 (0.80-1.32)       | 0.865 |

*The observed genotype frequencies of the controls were in agreement with the Hardy-Weinberg equilibrium (χ² = 1.900, p = 0.168).

^Odds ratios (ORs) were obtained from a logistic regression model with adjustment for age and gender; 95% confidence interval (CI).

^Two-tailed χ² test for either genotype distributions or allele frequencies between cases and controls.
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