Copy Number Variation Analysis of IL22 and LCE3C in Different Subtypes of Psoriasis in a Chinese Han Population

Background: Psoriasis is a chronic, immune-mediated and hyperproliferative skin disease with both genetic and environmental components. Copy number variations (CNV) of IL22 and LCE3C-LCE3B deletion have been confirmed to be predisposed to psoriasis vulgaris (PsV) in several ethnic groups. However, it remains to be clarified whether CNVs of IL22 and LCE3C are associated with different subtypes of psoriasis (psoriatic arthritis, PsA; erythrodermic psoriasis, EP; and generalized pustular psoriasis, GPP).

Material/Methods: We enrolled 897 Han Chinese individuals, including 478 patients and 419 healthy controls, and detected CNVs of IL22 and LCE3C using the comparative CT method by real-time PCR, and Pearson’s χ² test was used to evaluate the copy number difference among subtypes.

Results: CNVs of IL22 were significantly higher in PsV than in healthy controls (P<0.001). CNV of LCE3C in PsV, PsA, and GPP groups were significantly lower compared to healthy controls. When linked with clinical parameters, mild psoriasis carried less IL22 copy numbers than that in severe psoriasis (P=0.043). Neither IL22 or LCE3C CNVs were associated with age of onset.

Conclusions: CNVs of LCE3C and IL22 might differentially contribute to subtypes of psoriasis. These findings suggest complex and diverse genetic variations in and among different clinical subtypes of psoriasis.

Keywords: Body Surface Area • DNA Copy Number Variations • Psoriasis

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Background

Psoriasis is an autoimmune-mediated disease that primarily affects the skin, nails, and joints [1,2]. The disease presents mainly in 4 presentations, and classifications have been proposed based on clinical course. PsV, characterized by erythematous and scaly plaques, is usually found on the elbows, knees, scalp, and back and affects 85-90% of patients with psoriasis [3-6]. PsA is a type of psoriasis that is associated with erosive polyarthritis and usually has a negative serologic test result for rheumatoid factor; it shares some common genetic background with psoriasis [6,7]. EP presents as widespread erythema with thick scales (exfoliation of the skin, which is quite different from the thick, adherent, and white scales of PsV) [5,6,8]. GPP is characterized by infiltration of neutrophil granulocytes in the epidermis to such an extent that clinically visible sterile pustules develop [5,6,9,10]. Both EP and GPP are severe subtypes of psoriasis that affect nearly the entire body surface. Approximately 30% of psoriasis patients develop PsA, EP, or GPP. Even though these clinical phenotypes share some common manifestations, their molecular mechanisms differ and remain to be classified further.

It was widely accepted that aberrant secretion of cytokines and skin barrier dysfunction are the 2 key features in psoriasis pathogenesis. Some cytokines, including IL22, IL17A, IL23, and beta-defensin 2 [11], and skin structural proteins such as S100A1 and LCE [12] were identified as critical risk factors in disease development. Thanks to the development of modern genetic technologies, great progress has been made in understanding the genetic landscape and pathogenesis of psoriasis. Linkage analysis and genome-wide association studies (GWASs), as well as next-generation sequencing studies, have further illuminated the genetic signatures of psoriasis. Notably, GWASs have identified more than 100 single-nucleotide polymorphisms (SNPs) and susceptibility genes. However, these markers explain only a small portion of the information in the hereditary susceptibility of psoriasis [13], indicating that other types of genetic loci beyond SNPs, such as CNVs, would add to the disease susceptible lists.

CNVs, defined as deletions or duplications of DNA segments longer than 1 kb, cover approximately 12% of the human genome and encompass more nucleotides than do SNPs [14]. CNVs can affect human phenotypes by directly affecting gene expression levels through duplication or deletion of a specific DNA sequence, or by indirectly altering gene expression, such as affecting the transcriptional regulatory elements of corresponding genes [15-18]. Several studies revealed that CNVs are important genetic factors that predispose to psoriasis [13,19-24]. CNVs of IL22 have been identified to be associated with PsV in the Estonian and other populations [24,25]. LCE3C-LCE3B deletion has been widely reported to be associated with PsV in several ethnic groups as well [21-23,25-28]. CNVs of the beta-defensin gene cluster and FCGR3B are reported to be associated with psoriasis in German and Chinese populations [19,20]. Unfortunately, all studies thus far have focused on psoriasis vulgaris. Whether CNVs of LCE3C and IL22 are associated with different subtypes of psoriasis (PsA, GPP, and EP) remains to be determined. In this study, we focused on the relationship between CNVs of IL22, LCE3C and PsV, PsA, EP, and GPP in a Chinese Han population.

Material and Methods

Subjects

We enrolled 897 Chinese Han individuals, including 478 patients (74 PsA, 69 EP, 52 GPP, and 283 PsV) and 419 healthy controls. None of the patients in the study had received systemic or physical therapy within the 2 weeks before a blood sample was drawn. All subjects were recruited from the First Affiliated Hospital of Anhui Medical University, China. Psoriasis patients with joint symptoms were confirmed with a diagnosis of PsA according to the Classification for Psoriatic Arthritis criteria [29]. The remaining patients with no joint symptoms were divided into PsV, EP, and GPP groups according to their clinical manifestations which state in the introduction section. All patients were diagnosed according to their individual clinical manifestation and/or histopathological performance by 2 experienced dermatologists (Table 1). Psoriasis patients were grouped as early- and late-onset psoriasis. Early-onset psoriasis is defined as onset before 40 years of age, while the rest are defined as late-onset psoriasis. Psoriasis severity is categorized as mild, moderate, and severe, which is guided by body surface area (BSA). BSA is preferential measurement in the US and other countries in both routine clinical practice and clinical trials [30,31]. BSA was assessed by a trained physician. The severity of psoriasis was classified as follows: mild: BSA ≤3%; moderate: 3% < BSA ≤10%, and severe: BSA >10%. Healthy controls were confirmed to have no personal or family history of autoimmune diseases such as psoriasis, rheumatoid arthritis, and systemic lupus erythematosus. This study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University. Each participant signed the informed consent form.

Sample Preparation

Genomic DNA was extracted from venous blood using the Qiagen Genomic Flexi Gene DNA Kit51206 (Qiagen, Germany). DNA templates used for CNV analysis were prepared as follows: DNA quality was assessed by gel electrophoresis to confirm no DNA degradation had occurred and was then diluted to 20 ng/μl and an OD260/280 ratio range of 1.8-2.0 for utilization.
Quantification of Copy Numbers

Copy number was determined using the 2^(-ΔΔC_T) method using TaqMan copy number targets and RNase P reference assays (assay ID: 4403328). TaqMan Copy Number Assays Hs00146600_cn (for IL22) and Hs02550639_cn (for LCE3C) (Applied Biosystems, Foster City, CA, USA) were used to detect CNVs of IL22 and LCE3C genes using real-time quantitative polymerase chain reaction (RT-qPCR) in an ABI PRISM 7900HT Fast Real-time PCR instrument. Cycling conditions were held at 95°C for 10 min, and 45 cycles of 2 steps (95°C for 15 s and 60°C for 1 min). Data were analyzed using the SDS2.2 software package (Applied Biosystems, Foster City, CA, USA).

Statistical Analysis

Statistical analysis was performed using the R 3.4.0 program for Windows (https://www.r-project.org). Categorical variables were compared using Pearson’s χ² test. Logistic regression was used to obtain the odds ratio (OR) and 95% confidence interval (CI) for copy numbers. Continuous variables were compared using the nonparametric Mann-Whitney and Kruskal-Wallis tests. Linear regression analysis was used to investigate the relationship between BSA and different CNV group. Statistical significance was assumed for P values <0.05.

Results

Clinical Data of All Participants

Patients were classified as PsV (n=283), PsA (n=74), EP (n=69), and GPP (n=52). The mean age of psoriasis patients and healthy controls was 39.6±16.1 and 35.7±16.6 years, respectively. The characteristics of subjects in the study are shown in Table 1. There was no significant difference in the distribution of male and female subjects between case and control cohorts (P>0.01).

CNV of IL22 in Psoriasis Subtypes

Copy numbers of the IL22 gene ranged from 2 to 7 (mean±SD, 2.31±0.6) in controls and 2 to 5 (mean±SD, 2.36±0.59) in patients. Mean copy numbers of IL22 were significantly higher in the PsV group compared to the control group (P=0.001, t test) (Figure 1A). No strong association was observed in comparisons between PsA, GPP, or EP and controls (Figure 1A). Allele frequency of IL22 copy numbers significantly differed in cases and controls, with 35% patients carrying 3 or more copies, while only 26.3% controls obtained more than 3 copies (P=0.021, Pearson’s χ² test; OR=0.036, 95% CI=0.18-0.82) (Figure 2A). Furthermore, those who had more than 2 copies of IL22 were more likely to develop PsV (P=0.028, Figure 2B), suggesting IL22 copy numbers increased risk of affecting psoriasis.

Table 1. Demographic and clinical data of study participants.

| Phenotypes | Severity | No. | Average (range) | P< | Male | Female | P< |
|------------|----------|-----|-----------------|----|------|--------|----|
| Healthy controls | | 419 | 35.7 (4-84) / | 268 (63.9%) | 151 (36.0%) | / |
| All patients | | 478 | 39.6 (6-90) <0.001 | 280 (58.6%) | 198 (41.4%) | 0.11 |
| PsV | | 283 | 36.9 (7-78) 0.16 | 161 (56.8%) | 122 (43.1%) | 0.07 |
| Mild | | 45 | 40.6 (13-76) / | 29 (64.44%) | 16 (35.56%) | / |
| Moderate | | 203 | 36.2 (7-78) 0.07(P<) | 114 (56.16%) | 89 (43.84%) | <0.001(P<) |
| Severe | | 35 | 36.2 (13-58) 0.184(P<) | 18 (51.43%) | 17 (48.57%) | 0.001(P<) |
| PsA | | 74 | 45.1 (14-90) <0.001 | 46 (62.2%) | 28 (37.8%) | 0.86 |
| GPP | | 52 | 31.4 (6-71) 0.09 | 24 (46.2%) | 28 (53.8%) | 0.02 |
| EP | | 69 | 51.0 (11-85) <0.001 | 49 (83.1%) | 20 (33.8%) | 0.32 |

1 Clinical phenotypes of controls and psoriasis patients. PsV – psoriasis vulgaris; PsA – psoriatic arthritis; GPP – generalized pustular psoriasis; EP – erythrodermic psoriasis. 2 Age (in years) values are given as the mean and range (minimum–maximum). 3 Mann-Whitney test (each subgroup of patients versus controls). 4 Pearson’s chi-square test (each subgroup of patients versus controls). 5 Mann-Whitney test (each subgroup of patients versus Mild group). 6 Pearson’s chi-square test (each subgroup of patients in the Mild group).
Figure 1. Frequency distributions of IL22 and LCE3C CNVs. (A) Associations of IL22 gene copy number with PsV. (B) LCE3C CNVs are associated with PsV, PsA and GPP. ** P<0.001, * P<0.05. HC – healthy control; PsV – psoriasis vulgaris; PsA – psoriatic arthritis; EP – erythrodermic psoriasis; GPP – generalized pustular psoriasis. (The figure was created by Microsoft Excel 2019 software, Microsoft, USA).

Figure 2. Distribution of IL22 in PsV, PsA and HC. (A) IL22 copy numbers were significantly different between PsV and HC. (B) More than 2 copies of IL22 increased the risk of developing PsV. (C) PsA has lower IL22 copy number compared to PsV. (D) The PsV group had wider IL22 copy number spectrums than the PsA group. HC – healthy control; PsV – psoriasis vulgaris; PsA – psoriatic arthritis. (The figure was created by Microsoft Excel 2019 software, Microsoft, USA).
We then looked at copy number alterations among psoriasis subtypes. Mean copy numbers of IL22 were higher in PsV than that in PsA groups (P=0.0025), but not in other subtypes (Figure 1A). Interestingly, PsV group presented wider copy number spectrums than PsA group, with 2-6 copies in PsV and 2-3 copies in PsA (Figure 2D). A distinct distribution was observed between the PsV and PsA groups (P=7.75E-10, OR=0.089, 95% CI=0.26-2.83, Figure 2C). These findings revealed IL22 copy numbers might differentially associated with psoriasis subtypes.

CNV of LCE3C in Psoriasis Subtypes

The mean LCE3C copy number in the PsV group was significantly lower when compared to the control group (P<0.001) (Figure 1B). The copy number distribution difference was observed between PsV and control groups (P=0.0018, OR=1.4, CI=0.91-2.18, Figure 3A). Furthermore, those who had 2 copies of LCE3C were more likely to develop PsV (P=0.0018, Figure 3B). The mean LCE3C copy number in PsA and GPP groups was lower compared to the control group (P=0.0046 and P=1.56E-04, respectively) (Figure 1B). The same distribution trend was observed when comparing the GPP and control groups (P=0.078, OR=0.13, 95% CI=0.06-0.31) (Figure 3C). Those who had 2 copies of LCE3C were more probably to develop GPP (P<0.05, Figure 3D). The copy numbers of LCE3C tended to be associated with EP, although the comparison did not reach significance (P=0.076).

CNV of IL22 Linked with Psoriasis Severity

Given the critical roles of IL22 in psoriasis development, we evaluated the relationship between CNV of IL22 and clinical parameters of psoriasis. We found patients with different IL22 copy numbers obtained varied severity scores (mild, moderate, and severe) (Figure 1B). We also found the mean BSA scores were dramatically higher in patients with 2 copy numbers than that in 3 or more carriers, and the CNV of IL22 was inversely
correlated with the severity of psoriasis ($P=0.0348$, $R^2=0.9316$, Figure 4A). CNV of \textit{IL22} in the mild group were significantly higher than in either the severe group or healthy controls (Mild: 2.53±0.694, Severe: 2.33±0.581, Control: 2.31±0.598, $P_{\text{Mild vs Severe}}=0.043$, $P_{\text{Mild vs Control}}=0.019$, respectively, Figure 4C). We also evaluated the relationship between CNV in the \textit{LCE3C} gene and the clinical parameters of psoriasis. Similar to \textit{IL22} copy numbers, BSA scores varied in patients with different \textit{LCE3C} copy numbers (Figure 4B). But the correlation between CNV of \textit{LCE3C} and the trends of BSA score were not found (Figure 4B). However, we noticed that CNV of \textit{LCE3C} in mild, moderate and severe psoriasis being lower compared to healthy controls ($P_{\text{mild}}=0.007$, $P_{\text{moderate}}=0.002$, $P_{\text{severe}}<0.001$, respectively, Figure 4D).

For genetic background would be associated with early onset of psoriasis [32]. We assessed whether CNVs of \textit{IL22} and \textit{LCE3C} were risk factors for early onset, by comparing the copy number allele frequencies in early and late-onset 4 subtypes of psoriasis. No significant relationships were observed, indicating CNVs of \textit{IL22} and \textit{LCE3C} are not the key predisposing factors for early onset of psoriasis.

**Discussion**

Psoriasis is a common skin disorder with strong environmental and genetic components. Genome variation studies have revealed at least 100 disease-associated risk loci or genes, including CNVs in \textit{IL22} and \textit{LCE3C} [21-28]. Our group previously identified \textit{LCE3C} copy numbers were strong risk factors in PsV predisposition. Several gene copy numbers have been associated with PsV in European, African, and other ethnic populations. For the phenotype difference among PsV, PsA, EP and GPP, we raised the question of whether copy number alteration of these genes might be involved in etiology of disease development. We selected \textit{IL22} and \textit{LCE3C} as candidates, mainly for 2 reasons. Firstly, \textit{IL22} and \textit{LCE3C} have been confirmed to be risk alleles in both Chinese and other populations, but have not been evaluated in psoriasis subtypes. Secondly, psoriasis was tightly associated with immune


dysfunction and epidermal hyperproliferation. *IL22* and *LCE3C* are good candidates because of their fundamental roles in modulating immune microenvironment and barrier function of human skins respectively. This study will help better understanding the common and different aspect of psoriasis subtypes, from the perspective of *IL22* and *LCE3C* copy number alterations.

*IL22* is a cytokine member of the *IL10* family. *IL22* targets external epithelial barriers and maintains immune homeostasis at barrier surfaces through the induction of regulatory genes [33]. As an important component of the cytokine network, *IL22* has long been implicated in driving psoriatic skin inflammation [24,34-36]. The concentration of *IL22* in serum was significantly higher in psoriasis patients than in healthy controls [37]. In psoriatic skin lesions, increased *IL22* pathway signaling (*IL20* subfamily members including *IL10*, *IL19*, *IL20*, *IL22*, *IL24*, and *IL26*) induces characteristic histological features, such as skin infiltration by various immune cell types and keratinocyte differentiation [36]. Furthermore, serum levels of *IL22* were positively correlated with the severity scores of GPP [38].

In this study, CNVs of *IL22* were found to be significantly associated with PsV but not with other subtypes. A protective effect of lower *IL22* copy number was observed, indicating that a higher copy number leads to increased risk of developing psoriasis vulgaris, while a lower copy number results in reduced disease risk [24], which was consistent with the Estonian study. A previous study has demonstrated the mRNA expression of *IL22* in the samples with >2 copies was significantly higher than that in those with 2 copies [39]. Thus, we speculate that CNV of *IL22* may directly affect the expression of *IL22* and thus participate in the pathogenesis and clinical manifestations of psoriasis. Interestingly, *IL22* copy number was inversely correlated with disease severity. This phenomenon might be due to our relatively small sample size in high copy number groups or the different distribution of sex ratio in patients with varying severity of psoriasis, but we raised the possibility that *IL22* might be just a trigger factor that ignited the inflammatory circuit. We speculated that expression level of *IL22* can be modulated by several mechanisms such as promoter methylation, miRNA, and/or intergraded with some undetermined factors. *IL22* CNVs is a genome variation that stably induces gene expression and lasts for a relatively long time. The disease severity was also determined by some other cytokines like *IL17*, *IL22*, and *IL23*. This hypothesis was confirmed by the fact that biological therapy targeted to *IL22* was less effective than to *IL17* or *IL23* [40,41].

We also identified differential distribution of *IL22* CNV between PsA and PsV subtypes. *IL22* is expressed at a high level in the synovial fluid of PsA patients and can regulate synoviocyte proliferation [35]. The inverse correlation between *IL22* CNV and PsA in our study suggested *IL22* alone was insufficient to drive synovial inflammation, but needs additional cytokines, such as *IL17A*. There also some other possibilities such as inadequate sample size or bias in sample selection in the PsA group. These findings suggest that CNV of *IL22* has diverse roles in different subtypes and severities of psoriasis. It is reasonable to speculate that different subtypes and severities of psoriasis stem, at least in part, from differences in their *IL22* CNV.

The *LCE3C* gene is located in the *LCE* gene cluster, encoding stratum corneum proteins, within the epidermal differentiation complex on chromosome 1q21.3. Stratum corneum proteins are indispensable in the differentiation and disruption of the terminal epidermis [22]. *LCE3C* mRNA expression is detected in psoriasis lesions but not in normal skin [22]. Mutations in LCE3B/LCE3C confer a nearly 40% increased risk of development of plaque psoriasis [42]. Reduced CNVs in the *LCE* gene cluster were associated with psoriasis in Chinese, European, and American populations. Consistent with previous studies, we found that lower copy numbers of *LCE3C* were associated with PsV [23,43]. Our study also demonstrated associations between *LCE3C* CNV and PsA/GPP. In each group, except for EP, subjects with fewer *LCE3C* copies were more prone to developing psoriasis. This suggests that PsV, GPP, and PsA share a partially similar disease pathogenesis. We also found the CNV of *LCE3C* in mild, moderate, and severe psoriasis were lower than in healthy controls, suggesting *LCE3C* CNV may play a consistent role in patients with different severities of disease.

**Conclusions**

In conclusion, we observed that CNV of *IL22* contributes to the occurrence of PsV and might play different roles during the development of PsV and PsA. Reduced CNV of *IL22* increases the risk of developing severe psoriasis. CNV in *LCE3C* contributes to the risk of PsV, PsA, and GPP. Both CNV of *IL22* and *LCE3C* affect the severity of psoriasis. Our study reveals the complexity in associations of different CNVs with different subtypes of psoriasis. We demonstrate that CNVs have a profound effect on human genomic diversity and may cause disease or confer risk to complex disease traits. This information will aid in identifying new and suitable targets for diagnosis and therapy in different subtypes and different severities of psoriasis according to different CNV of *IL22* and *LCE3C*. In addition, information about CNV of *IL22* and *LCE3C* may help to define populations with high susceptibility to different subtypes of psoriasis.

Further research is needed to determine whether CNVs of *IL22* and *LCE3C* are predictors of psoriasis and the severity or clinical classification of psoriasis. *IL22* and *LCE3C* are located far apart, and the relations between the 2 genes are poorly understood. Therefore, the correlation between the 2 genes needs further analysis before combined analysis, which will be the focus of our future research.
Declaration of Figures’ Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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