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Association between Genetic Polymorphisms in *DEFB1* and Susceptibility to Digestive Diseases

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Background: Aberrant expression of defensins is implicated in the pathogenesis of digestive diseases. However, the contribution of specific defensins and the influence of their genetic polymorphisms on the progression of digestive diseases remain controversial. In the present meta-analysis, we investigated the association between *DEFB1* SNPs and the susceptibility to digestive diseases.

Material/Methods: Case-control studies that reported the correlation between *DEFB1* SNPs and the susceptibility to digestive diseases were identified through electronic databases searches, and high-quality studies that satisfied our inclusion criteria were selected for this meta-analysis. Statistical analyses were performed utilizing STATA software version 12.0.

Results: The present meta-analysis revealed that patients with digestive diseases exhibited higher frequencies of the *DEFB1* genetic variants rs11362G>A, rs1800972C>G, and rs1799946G>A compared to healthy controls under the allele model. Subgroup analysis based on country showed that the rs1800972C>G variant under allele model and rs1799946G>A are associated with the susceptibility to digestive diseases in Hungarian and Italian populations, respectively. Subgroup analysis based on disease type showed that: (1) rs11362G>A variant was strongly associated with severe acute pancreatitis (SAP) and chronic gastritis, (2) frequency of rs1800972C>G variant was higher in SAP subgroup, and (3) frequency of rs1799946G>A variant was positively associated with the susceptibility to Crohn's disease (CD) under the allele model and with SAP.

Conclusions: Our meta-analysis provides evidence that *DEFB1* genetic polymorphisms rs11362G>A, rs1800972C>G and rs1799946G>A are important contributing factors to the development of digestive diseases.

MeSH Keywords: Digestive System Abnormalities • Disease Susceptibility • Meta-Analysis • Polymorphism, Genetic

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Background

Digestive diseases are described as the disorders of gastrointestinal (GI) tract, which includes esophagus, stomach, small intestine, large intestine and rectum, liver, gallbladder, pancreas and accessory digestive organs [1]. Cancers affecting the digestive system are the most frequent malignancies around the world and approximately 3 000 000 new digestive cancer cases are diagnosed each year, accounting for 30% of all cancers, with 2 200 000 deaths each year [2]. The prevalence of digestive cancers are on the rise globally largely due to the rapidly increasing trends in gastric, colorectal, and hepatocellular carcinoma, which are among the 5 most common cancers in the Asian region [3,4]. Non-malignant digestive diseases can have a very complex origin and course of development, with a strong involvement of both genetic and environmental factors [5,6]. Lifestyle factors such as tea consumption, smoking, and alcohol intake are implicated in the pathogenesis of digestive diseases, and other factors, including inflammation and bacterial and viral infections, also play crucial roles in the disease development [6,7]. Previous studies showed that genetic variations in interferon regulatory factor 5 (*IRF5*), toll-like receptor 4 (*TLR4*), and vitamin D receptor (*VDR*) are strongly associated with digestive diseases [8]. Recent evidence also suggests that genetic polymorphisms in genes encoding antimicrobial peptides, such as beta defensins, may also contribute to the etiology of digestive diseases [9,10].

The β -defensins exhibit a broad spectrum of activity against various bacteria, fungi, and enveloped viruses. They are a subgroup of cationic antimicrobial peptides that contain 6-cysteine motifs that form 3 intra-molecular disulfide linkages to provide stability against proteases, which presumably is important for their biological activity [11,12]. Further, the cationic nature of the β -defensins allows them to directly interact with the membranes of invading pathogens and dramatically alter their membrane stability. *DEFB1* is a member of the defensin family and possesses the ability to kill or inactivate a wide spectrum of bacteria and fungi directly and indirectly by triggering innate and adaptive immune responses [13,14]. Human *DEFB1* gene is located on chromosome 8p23.2-p23.1, contains 2 small exons and 1 intron and spans approximately 7.0 kb in length [15]. Three functional single nucleotide polymorphisms (-52 G>A, rs1799946; -44 C>G, rs1800972; -20 G>A, rs11362) were demonstrated to alter *DEFB1* gene expression in a variety of cellular models [16,17]. *DEFB1* is normally highly expressed in respiratory epithelium, gastric epithelium, intestinal epithelium, and in immune cells such as monocytes and macrophages [18]. It has been proposed that the antimicrobial response by host epithelial cells plays a crucial role in bacterial adherence to the epithelium exposed to environmental pathogens and in the development of *H. pylori*-induced gastritis. *DEFB1* is an important antimicrobial peptide in epithelial

tissues and functions as a primary and broad-spectrum response by the host innate defense system [5,19,20]. However, *DEFB1* genetic polymorphisms that impair the expression and function of *DEFB1* have been linked to the etiology of inflammatory bowel disease [9]. Multiple studies reported that the low expression of *DEFB1*, due to genetic polymorphisms, is associated with the pathogenesis of digestive diseases [5,10]. In contrast, other studies showed no such correlation between *DEFB1* genetic polymorphisms and digestive diseases [8,21]. In light of this debate, we investigated the association between *DEFB1* genetic polymorphisms and the susceptibility to digestive diseases using a meta-analysis framework.

Material and Methods

Data sources and keywords

Scientific articles published before April 1st, 2014, which assessed the correlation between *DEFB1* genetic polymorphisms and the susceptibility to digestive diseases, were identified through electronic database search using PubMed, Embase, Web of Science, China BioMedicine (CBM), and China National Knowledge Infrastructure (CNKI). The common keywords used were: ("DEFB1 protein, human" or "DEFB1" or "beta-defensin-1" or "hBD-1 protein" or "hBD-1" or "beta defensin 1" or "beta-defensin 1" or "beta defensin-1" or " β -defensin 1") and ("Polymorphism, Genetic" or "polymorphism" or "polymorphisms" or "variants" or "SNP" or "mutation" or "genetic variants"). We also manually searched cross-references to identify additional relevant studies.

Selection criteria

The studies included in this meta-analysis fulfilled the following selection criteria: (1) contained patients with digestive diseases; (2) were human case-control studies reporting the role of *DEFB1* genetic variants in the risk of digestive diseases; (3) provided genotype data for *DEFB1* genetic variants; (4) reported the adjusted odd ratios (ORs) and 95% confidence intervals (CI) for *DEFB1* genetic polymorphisms; (5) supplied the sample numbers; (6) conformed with Hardy-Weinberg equilibrium (HWE) in the control group; and (6) the sample size was greater than 120. Additionally, if 2 or more studies were published by the same authors, only the latest or the most comprehensive study was included.

Data extraction

Two investigators (Zhou WH and Zhang YF) separately extracted the required data from the 6 selected papers. The extracted data included: first author, time of publication, source of publication, study design, source of controls, age, sex, study type, disease type, sample size, ethnicity and country of subjects,

Table 1. Baseline characteristics of included studies. Six case-control studies were included in this meta-analysis.

First author	Year	Country	Disease	Sample size		Gender (M/F)		Age (years)		Genotyping methods	SNP
				Case	Control	Case	Control	Case	Control		
Wilson TJ [10]	2014	Brazil	IBD	149	200	75/74	100/100	–	–	DS	rs11362 G>A rs1800972 C>G rs1799946 G>A
Li P [8]	2013	China	UC	300	302	161/139	157/145	40.4±13.8	42.0±14.6	Mass Array	rs1799946 G>A
Zanin V-a [9]	2012	Italy	CD	108	130	–	–	36.5±14.0	31.3±12.4	DS	rs11362 G>A rs1800972 C>G rs1799946 G>A
Zanin V-b [9]	2012	Italy	UC	37	130	–	–	38.2±15.7	31.3±12.4	DS	rs11362 G>A rs1800972 C>G rs1799946 G>A
Tiszlavicz Z [30]	2010	Hungary	SAP	124	100	75/49	65/35	58.0±6.9	45.0±8.9	TaqMan assay	rs11362 G>A rs1800972 C>G rs1799946 G>A
Kocsis AK [5]	2009	Hungary	Chronic gastritis	150	100	–	53/47	–	26.0±15.0	PCR-RFLP	rs11362 G>A rs1800972 C>G rs1799946 G>A
Kocsis AK [29]	2008	Hungary	CD	190	95	108/82	50/45	36.4±12.9	26.0±15.0	PCR-RFLP	rs11362 G>A rs1800972 C>G rs1799946 G>A

M – male; F – female; IBD – inflammatory bowel disease; UC – ulcerative colitis; CD – Crohn's disease; SAP – severe acute pancreatitis; a and b represent two different diseases in one study; DS – direct sequencing.

genotyping method, available genotype, genotype and mutation frequencies, and HWE evidence in controls.

Quality assessment

Two investigators (Zhou WH and Zhang YF) used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) score system to independently assess the quality of the studies [22]. The STROBE consists of 40 assessment items associated with quality appraisal, with scores ranging from 0 to 40. Based on the STROBE scores, the included studies were assessed as: low quality (0–19), moderate quality (20–29), or high quality (30–40). Discrepancies in STROBE scores of the enrolled publications between the 2 investigators were resolved through discussion involving all authors.

Statistical analysis

STATA 12.0 (Stata Corp, College Station, TX, USA) software was used for meta-analysis. The summary ORs with its 95% CI were used under allele model ([M] allele versus [W] allele) and dominant model (WW + WM versus MM) with the utilization of Z test. A random-effects model or a fixed-effects model was used to evaluate the correlation between *DEFB1* genetic polymorphisms and the susceptibility to digestive diseases among the included studies. The Cochran's Q-statistic and

I^2 test were also applied to reflect the heterogeneity among studies [23,24]. Heterogeneity on non-threshold effects was performed by quantitative evaluation of I^2 test, the value of which ranged between 0% and 100% and was positively correlated to heterogeneity. If significant heterogeneity was observed ($P < 0.05$ or $I^2 > 50\%$), a random-effect model was employed, otherwise a fixed-effect model was utilized [25,26]. The meta-regression analysis and subgroup meta-analyses by country and disease type were conducted to explore potential influencing factors. Sensitivity analysis was conducted by deleting each enrolled study to estimate the effect of a single study on the overall results. The funnel plot and Egger's linear regression test were implemented to assess whether publication bias existed to further confirm the original result [27,28].

Results

Included studies

Our present meta-analysis was based on a total of 6 selected studies, published between 2008 and 2014, that supplied sufficient information on the association of *DEFB1* genetic polymorphisms with the susceptibility to digestive diseases [5,8–10,29,30]. Demographic information of the subjects, study characteristics, and methodological quality of the extracted

Figure 1. Flow chart shows the study selection procedure. Six case-control studies were included in this meta-analysis.

studies are presented in Table 1. Five studies were performed in whites and 1 study was performed in Asians. The 6 studies included a combined total of 2115 subjects (1058 digestive diseases cases and 1057 healthy controls). The studies were conducted in Brazil (n=1), China (n=1), Italy (n=1), and Hungary (n=3). In relation to the disease types, 5 digestive disease types were reported in the studies included in our meta-analysis: inflammatory bowel disease (IBD), ulcerative colitis (UC), Crohn's disease (CD), severe acute pancreatitis (SAP), and chronic gastritis. The source of the control subjects in this meta-analysis was population-based (PB) sample. Genotyping methods included PCR-RFLP (n=2), Mass Array (n=1), direct sequencing (n=2), and TaqMan assay (n=1). The available SNPs of *DEFB1* gene in this meta-analysis were rs11362 G>A, rs1800972 C>G, and rs1799946 G>A. The procedure for the selection of studies for this meta-analysis is displayed in Figure 1. A total of 177 papers were initially identified from electronic database searches, which was followed by excluding 2 duplicates; 26 letters, reviews, or meta-analyses; 37 non-human studies; and 40 studies unrelated to the research topic. After further review of the remaining 72 studies, an additional 63 studies were excluded for not being case-control studies (n=15), not relevant to *DEFB1* gene (n=19), and not relevant to digestive tract diseases (n=29). A thorough examination of the remaining 9 studies led to the elimination of 3 studies for insufficient information. Thus, a total of 6 studies were finally enrolled in the meta-analysis. The quality scores of these selected eligible studies were all higher than 30 (high quality).

Association between *DEFB1* genetic polymorphisms and susceptibility of digestive diseases

As shown in Figure 2, the major finding of the present meta-analysis was a significantly higher frequency of *DEFB1* genetic

variants rs11362G>A, rs1800972C>G, and rs1799946G>A in patients with digestive diseases compared to healthy controls under the allele model (rs11362G>A: OR=1.33, 95%CI: 1.07~1.65, $P=0.011$; rs1800972C>G: OR=1.26, 95%CI: 1.08~1.46, $P=0.003$; rs1799946G>A: OR=1.18, 95%CI: 1.06~1.32, $P=0.003$). However, the same association was not observed under the dominant model (all $P>0.05$).

Subgroup analysis by country showed no correlation between the frequency of rs11362G>A genetic polymorphism and the risk of digestive diseases among Brazilian, Italian, or Hungarian populations under both the allele model and the dominant model (all $P>0.05$). Interestingly, rs1800972C>G variant was associated with a significantly higher risk for digestive diseases in the Hungarian population under the allele model (OR=1.41, 95%CI: 1.11~1.80, $P=0.006$), but a similar association did not exist in the Brazilian or Italian populations under the allele model, as well as the Brazilian, Italian, or Hungarian populations under the dominant model (all $P>0.05$). Subgroup analysis by country also suggested that the frequency of rs1799946G>A polymorphism was significantly higher in patients with digestive diseases, compared to the controls, in the Italian population (allele model: OR=1.39, 95%CI: 1.11~1.74, $P=0.004$; dominant model: OR=1.62, 95%CI: 1.15~2.29, $P=0.006$), but a similar relationship was not seen in Brazilian, Chinese, or Hungarian populations under both the allele model and the dominant model (all $P>0.05$) (Figure 3).

Subgroup analysis based on the disease type revealed that rs11362G>A genetic polymorphism was strongly associated with severe acute pancreatitis (SAP) (allele model: OR=2.17, 95%CI: 1.48~3.17, $P<0.001$; dominant model: OR=3.09, 95%CI: 1.68~5.69, $P<0.001$) and chronic gastritis (allele model: OR=2.54,

Figure 2. Frequency of *DEFB1* genetic variants (rs11362G>A, rs1800972C>G, rs1799946G>A) in patients with digestive diseases compared with the healthy controls.

95%CI: 1.75~3.70, $P<0.001$; dominant model: OR=4.19, 95%CI: 2.37~7.39, $P<0.001$, but not with Crohn disease (CD), ulcerative colitis (UC), and inflammatory bowel disease (IBD) under both the allele model and the dominant model (all $P>0.05$), as shown in Figure 3. In addition, subgroup analysis based on the disease type (Figure 3) showed that the frequency of rs1800972C>G genetic variant is positively correlated with the susceptibility to SAP (allele model: OR=1.77, 95%CI: 1.12~2.79, $P=0.014$; dominant model: OR=6.03, 95%CI: 1.27~28.60, $P=0.024$), but a similar association was not found with CD, UC, IBD, and chronic

gastritis under both the allele model and the dominant model (all $P>0.05$). Furthermore, the positive association between the frequency of rs1799946G>A variant and the susceptibility to digestive diseases, as shown in Figure 3, was evident in the CD subgroup under the allele model (OR=1.28, 95%CI: 1.04~1.58, $P=0.022$) and SAP subgroup (allele model: OR=1.62, 95%CI: 1.11~2.35, $P=0.012$; dominant model: OR=2.20, 95%CI: 1.17~4.15, $P=0.014$), but not in the CD subgroup under dominant model or in UC, IBD, or chronic gastritis subgroups under both the allele model and the dominant model (all $P>0.05$).

Figure 3. Subgroup analyses by country and the frequency of *DEFB1* genetic variants by disease type (rs11362G>A, rs1800972C>G, rs1799946G>A) under both allele model and dominant model.

Figure 4. Sensitivity analysis of the correlations between digestive diseases and the frequency of *DEFB1* genetic variants (rs11362G>A, rs1800972C>G, rs1799946G>A) under both allele model and dominant model.

Figure 5. Evaluation of publication bias for the correlation between digestive diseases and *DEFB1* genetic variants (rs11362G>A, rs1800972C>G, rs1799946G>A) under both allele model and dominant model.

Sensitivity analysis and publication bias

Sensitivity analysis results illustrated that all included studies had no influence on the pooled ORs of relationship of *DEFB1* gene polymorphism and the susceptibility to digestive diseases (Figure 4). The graphical funnel plots of the 6 studies involving

DEFB1 rs11362G>A, rs1800972C>G and rs1799946G>A genetic variants were symmetrical and Egger's test showed no publication bias (all $P>0.05$) (Figure 5).

Discussion

In this study we investigated the association between *DEFB1* gene polymorphisms and the susceptibility to digestive diseases using a systematic meta-analysis-based approach. Our main result indicates a significant correlation between rs11362G>A, rs1800972C>G, and rs1799946G>A polymorphisms in *DEFB1* gene and the susceptibility to CD, chronic gastritis, and SAP. Defensins are small, acid-stable, amphipathic, antimicrobial peptides with a largely β -sheet structure, which is important for their activities against bacteria, fungi, viruses, and some parasites [31]. *DEFB1* was the first defensin to be discovered and is an important member of the defensin family. *DEFB1* has 3 conserved disulfide bonds, which apparently is important for the structural stability and its stability against proteases, and exhibits broad-spectrum activities against infectious agents [10]. *DEFB1* is expressed in multiple cell types of the immune system such as macrophages, monocytes, dendritic cells, and leukocytes. More importantly, epithelial cells in many organs such as pancreas, skin, kidney, respiratory system, and digestive tract express high levels of *DEFB1* [32,33]. Initially, *DEFB1* was thought to be constitutively expressed in the body, but subsequent evidence suggested that its expression is regulated under specific conditions. Additionally, *DEFB1* has strong chemoattractant properties towards memory T cells and dendritic cells, through the CC chemokine receptor, suggesting an important role for *DEFB1* in inflammation [19,34]. *DEFB1* is also implicated in the activation of cellular apoptosis, and several cancers such as prostate and renal cancer down-regulate defensin gene expression to inhibit apoptosis and promote cancer progression. Therefore, *DEFB1* gene expression and the role of *DEFB1* polymorphisms are of significant importance to human health [35,36]. Not surprisingly, *DEFB1* gene polymorphisms are linked to other infection and inflammatory diseases such as chronic obstructive pulmonary disease (COPD), asthma, oral candida infections, periodontitis, and atopic dermatitis [18]. *DEFB1* expression in the digestive tract epithelium protects against intestinal pathogens and *DEFB1* gene polymorphisms influencing *DEFB1* expression have been previously implicated in digestive tract diseases [8]. Accordingly, SNPs located within the *DEFB1* regulatory region have been associated with chronic gastritis, CD, and SAP, particularly the 3 SNPs at the 5'-untranslated region, rs11362 (G-20A), rs1800972 (C-44G), and rs1799946 (G-52A) [37]. A higher frequency of GA and AA genotypes of the G-52A SNP was found in chronic active gastritis patients, and both inducible and constitutive forms of human defensins are involved in the development of *H. pylori*-induced gastritis, with *DEFB1* expression induced by infection of AGS cells with cagPAI strain [5]. Further, a lower frequency of GG genotype in *DEFB1* C-44G SNP, which harbors a nuclear factor- κ B binding site, is reported in CD patients, suggesting that a change from C allele to G allele may increase antimicrobial activity of *DEFB1* and that the GG phenotype may be

a protective factor for CD [29]. In agreement with our analysis, Tiszlavicz et al. found higher frequencies of AA genotype of G-20A and G-52A SNPs and lower frequency of GG genotype of C-44G SNP in SAP patients compared to the control group, showing that *DEFB1* polymorphisms at different sites might influence SAP differently [30].

We also considered the influence of country and disease types on our results involving rs11362, rs1800972, and rs1799946 *DEFB1* gene polymorphisms and the susceptibility to digestive diseases. In a stratified analysis based on country, the rs11362 polymorphism was not significantly associated with digestive diseases among Brazilian, Italian, and Hungarian populations, while the rs1800972 polymorphism was associated with the increased risk for digestive diseases in the Hungarian population in the allele model, and rs1799946 SNP was linked with digestive disease susceptibility in the Italian population. It is possible that different lifestyles, diet, pathogen exposure, and access to health care in different countries might influence the results seen with these genetic variants. Importantly, in our disease-stratified analysis, we observed a significant association of rs11362 *DEFB1* polymorphism with the susceptibility to SAP and chronic gastritis, along with a strong association between rs1800972 and SAP progression, and an association of rs1799946 with the pathogenesis of CD and SAP.

It is important to highlight the strengths of our meta-analysis and acknowledge its weaknesses. The central advantage of this meta-analysis is the rigorous statistical review of data from the literature that cannot be achieved by any single study [38–40]. An unambiguous and strong association between *DEFB1* SNPs and digestive diseases cannot be drawn from the results of a single study, but our approach confirmed this relationship by analyzing the results from multiple studies. Our meta-analysis has several weaknesses. First, the enrollment of a relatively small sample size (only 6 studies) may lack sufficient statistical power to assess the results. Second, of the 6 eligible studies, most were performed in whites, and only 1 study was conducted in Asians, indicating a selection bias. Third, the origin and progression of digestive diseases depends on the interaction of a variety of genetic factors such as *IRF5*, *TLR4*, *DEFB1*, and *VDR*, and *DEFB1* is only 1 of the main factors contributing to the pathological course of these digestive diseases. Thus, the conclusions drawn from this study should not be viewed as if *DEFB1* is the sole contributor in disease pathogenesis. In this context, we could not ascertain the potential clinical value of *DEFB1* SNPs as biomarkers and this will require further studies. Lastly, the genotyping methods used in the 6 selected studies were different, which may influence our study results.

Conclusions

In summary, our results provide evidence that the *DEFB1* genetic polymorphisms rs11362G>A, rs1800972C>G, and rs1799946G>A are strongly associated with the susceptibility to digestive diseases, indicating that *DEFB1* is an important player in the pathogenesis of digestive diseases and may be a target for therapeutic intervention. However, further studies with larger sample sizes and diverse populations are required to confirm our findings.

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Competing interests

The authors declared no interest conflicts and the authors alone are accountable for the writing and content of the paper.

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