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Research paper

Association of *IL18* genetic polymorphisms with increased risk of Biliary atresia susceptibility in Southern Chinese children

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ABSTRACT

Biliary atresia (BA) has complex genetic etiology, characterized by different levels of hepatic fibrosis after the Kasai procedure and immune responses to the bile duct. As an activator of the two most important inflammatory cells in Biliary atresia (T cells and NK cells), *IL-18* is significantly increased in BA patients. This study aims to investigate the association of Interleukin 18(*IL-18*) with the susceptibility to BA. We examined the association of three polymorphisms (rs549908, rs187238 and rs1946518 in *IL-18*) and BA susceptibility in a Southern Chinese population composed of 506 cases and 1473 controls. SNP rs187238 and rs1946518 were identified as associated with BA. Interestingly, we also observed that the intragenic synergistic epistasis between SNPs rs187238 and rs1946518 boosting the risk to BA by logistic regression and Multifactor dimensionality reduction (MDR) analysis. This study provides for the first time a direct evidence to support IL-18 as a susceptibility gene for the disease in southern Chinese children.

1. Introduction

Biliary atresia (BA) is a neonatal biliary disease with poor prognosis and high fatality, which leads to persistent jaundice and progressive destruction of the biliary system in infants, as well as subsequent cirrhosis and liver failure. It is the most common cause of infant end-stage liver disease. Without treatment, most patients would die within two years after birth. By now, except for liver transplantation, Kasai surgery is the most common solution for this disease which bridges the remaining bile ducts in the portal area with jejunum. Unfortunately, although the symptoms could be partially ameliorated by the successful surgical intervention, the majority of patients would still evolve into liver cirrhosis and liver failure due to the progressive intrahepatic bile ducts injury. It is higher in Asia with the incidence of 1:9600 live births comparing with 1:15,000 live births in the USA (Gallo and Esquivel, 2013).

The etiology of Biliary atresia is unknown. Current studies suggested BA might be based on genetic components and inspired by the virus infection, resulting in immune response to the bile duct, followed by a series of pathological changes, including bile duct inflammatory cells infiltration, biliary epithelial cell apoptosis and bile duct obstruction (Lakshminarayanan and Davenport, 2016; Asai et al., 2015) (Mezina and Karpen, 2015). A number of family cases suggest the possibility of Biliary atresia as an inherited disease (Fallon et al., 2013). Genome-wide association study (GWAS) has confirmed several genetic susceptibility genes including ADD3 (Cheng et al., 2013), *XPNPEP1* (Kaewkiattiyot et al., 2011) and *GPC1* (Smith, 2013) through case-control study.

Interleukin 18(*IL-18*) was found as an inducible factor of *IFN*-γ to promote the production of *IFN*-γ, following by activating the inflammatory response of T cells and NK cells, which have been shown to be two most important inflammatory cells in Biliary atresia. Hence, *IL-18* may play an important role in Biliary atresia. Studies have already shown the significantly higher expression of *IL-18* in the serum of Biliary atresia patients when compared with healthy matched control group, suggesting that it plays an important role in the pathogenesis of

Abbreviations: ADD3, adducin 3; BA, Biliary atresia; CEU, Caucasians; CHB, Han Chinese; CV, cross-validation; GPC1, glypican-1; GWAS, genome-wide association study; GZ, Guangzhou; HWE, Hardy Weinberg equilibrium; IFN-γ, interferon-γ; IL-18, interleukin 18; LD, linkage disequilibrium; MDR, Multifactor dimensionality reduction; OR, odds ratio; SNP, single nucleotide polymorphism; XPNPEP1, Xaa-Pro aminopeptidase 1

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Table 1
Replication results on three SNPs in IL-8 in Southern Chinese children using 506 cases and 1473 controls.

SNP	Chr	Position	Gene	Feature	Left_gene	Right_gene	A1/A2	AFF	UNAFF	P	OR
P_hwe = 0.61							G/T				
rs549908	11	111526126	*IL18*	Reference[NM_001562.2]	*SDHD*	*TEX12*	ALLELIC	118/870	339/2583	0.773	1.03(0.83–1.29)
							GENO	5/108/381	17/305/1139	0.870	NA
							ADD	118/870	339/2583	0.802	0.94(0.57–1.55)
							DOM	113/381	322/1139	0.700	1.05(0.82–1.34)
							REC	5/489	17/1444	0.783	0.87(0.32–2.37)
P_hwe = 0.10							C/G				
rs187238	11	111540198	*IL18*	Near-gene-5[NM_001562.2]	*IL18*	*TEX12*	ALLELIC	454/72	1926/406	**0.039**	**1.33(1.01–1.74)**
							GENO	199/56/8	787/352/27	0.015	NA
							ADD	454/72	1926/406	0.699	0.92(0.62–1.38)
							DOM	255/8	1139/27	0.493	0.76(0.34–1.68)
							REC	199/64	787/379	**9.99E−03**	**1.50(1.10–2.04)**
P_hwe = 0.35							G/T				
rs1946518	11	111540668	*NA*	NA	*IL18*	*TEX12*	ALLELIC	481/429	1401/1511	**0.012**	**1.21(1.04–1.40)**
							GENO	119/243/93	346/709/401	0.011	NA
							ADD	481/429	1401/1511	0.012	1.22(1.04–1.42)
							DOM	362/93	1055/401	**2.63E−03**	**1.48(1.15–1.91)**
							REC	119/336	346/1110	0.300	1.14(0.89–1.45)

SNP: single nucleotide polymorphism; Chr: chromosome; Gene.refgene: The gene where the SNP located to; A1/A2 indicates the risk allele and protective allele to disease; AFF: cases with IL18; UNAFF: control subjects unaffected by IL18; GENO:genotypic. ADD, DOM and REC terms refer to analysing the SNP under an additive, dominant or recessive genetic model. The P value indicates the significance based on allelic association tests. The calculation of odds ratio (OR) is also based on the risk allele of each SNP. Significant associations with P value less than 0.05 were bolded.

Biliary atresia. *IL-18* is located on 11q22.2-q22.3 (Nolan et al., 1998), SNPs rs549908, rs187238 and rs1946518 in the promoter region were associated with differential levels of gene transcription and protein production (Giedraitis et al., 2001; Sánchez et al., 2009). The above variants have been replicated as associated with acute and chronic immune-related complex diseases. A study using 50 BA patients and 1117 controls failed to identify the association of above SNPs in *IL-18* with BA (Lee et al., 2011). With the aim of further investigating the association of *IL-18* with BA, we conducted a case-control study to verify the association of these three polymorphisms (rs549908, rs187238 and rs1946518 in *IL-18*) with BA susceptibility in a Southern Chinese population composed of 506 cases and 1473 controls.

2. Materials and methods

2.1. Subjects

506 BA patients and 1473 healthy controls were collected from Guangzhou Women and Children's medical center in the present study. Mean age of the patients was 2.088 ± 1.934 months (range: 1–7 months).The cases were diagnosed as BA by clinical manifestations, laboratory tests, imaging examinations and cholangiography. Unrelated subjects visiting the same hospital for routine health check were selected as control group. This study was approved by the institutional review board of the hospital. The written informed consents were provided by guardians of all subjects. The research was carried out according to the World Medical Association Declaration of Helsinki.

2.2. SNP Genotyping and quality control

Three SNPs (rs549908, rs187238 and rs1946518) in *IL18* were chosen for replication. They were genotyped by MassARRAY iPLEX Gold system (Sequenom). Quality control of the three SNPs was performed as shown below: 1)1 SNPs with > 10% missing data were removed. 2) SNPs which violated the Hardy-Weinberg equilibrium ($P < 0.05$) were removed. After quality control of all three SNPs were kept for further analysis consisted of 506 cases and 1473 controls. PLINK1.9 was used to perform the association analysis in current study. Linkage disequilibrium patterns were obtained using HaploView. SNPTEST v2.5b was applied to perform the independence test in this study.

2.3. Intragenic epistatic effect with BA

Epistasis test (case-control analysis) by logistic regression was adopted for the parametric analysis of genetic interaction using PLINK1.9 (Purcell et al., 2007). PLINK used a model according to allele dosage ranging from 0 to 2 indicating the number of risk alleles for each SNP, A and B, and fits the model in the form of Y = b0 + b1 SNPA + b2 SNPB + b3 SNPA ∗ SNPB + e. The parameters b1, b2 and b3 indicate the contribution of SNP A and SNP B and interaction between A and B. The test for interaction is based on the coefficient b3. *P* values < 0.05 were considered statistically significant. Multifactor dimensionality reduction (MDR) was used to determine the non-parametric genetic epistatic model that could mostly predict the disease status or phenotype at several loci (Hahn et al., 2003). The MDR analysis was carried out using version 2.0 of the open-source MDR software package that is freely available online (http://www.epistasis.org) (Zhang et al., 2013).

3. Results

3.1. Association of IL18 with the risk to BA

Three SNPs in *IL18* including SNP rs549908, rs187238 and rs1946518 were genotyped. The genotype distributions for all the SNPs were examined, they all did not violate the Hardy Weinberg equilibrium (HWE) in the control subjects ($P = 0.61$ for rs549908, $P = 0.10$ for rs187238 and $P = 0.35$ for rs1946518). As shown in Table 1, we identified two SNPs as associated to BA including rs187238 ($P = 0.039$, OR = 1.33) and rs1946518 ($P = 0.012$, OR = 1.21) respectively. The association was calculated based on the risk allele to disease. For rs187238, the major allele (C/82.6% in controls) served as the risk allele to the disease. Inconsistent with rs187238, for rs1946518, the minor allele (G/48.1% in controls) was the risk allele to BA. To better understand the genetic inherited patterns for the two associated SNPs, we tested the association following different models including genotypic, additive, dominant and recessive patterns. We observed that the main association to disease for the two SNPs was based on different models. SNP rs187238 followed the recessive model indicating a 1.50-folds risk to BA ($P = 9.99E-03$). Rs1946518 followed the dominant model with a 1.48-folds risk to disease ($P = 2.63E-03$).

In order to further distinguish whether the association was derived from one signal or multiple signals, we examined the linkage

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