Original Article

Genetic susceptibility to cow's milk allergy in Chinese children

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Background and Objectives: Cow's milk allergy (CMA) is the most common food allergy in young children. Previous studies have reported that single-nucleotide polymorphisms (SNPs) are associated with CMA. The extent to which SNPs contribute to the occurrence of CMA is unknown. The purpose of this study was to investigate the independent relevance of genetic predisposition to CMA in Chinese children. **Methods and Study Design:** 200 infants with CMA and 799 healthy controls aged 0–12 months were included. Five previously identified genetic variants (rs17616434, rs2069772, rs1800896, rs855791 and rs20541) were genotyped. Logistic regression was used to analyze the genetic associations or their interactions with a family history of allergy on CMA. **Results:** Among the five SNPs, only IL10 rs1800896 was significantly associated with CMA (odds ratio (OR) 1.60, p=0.042). Each 1-risk allele increase in the genetic risk score (GRS) was suggestively associated with an 11% higher risk of CMA (1.11: 0.99–1.27, p=0.069) and a 45% increased risk of CMA in the GRS high-risk group compared to the GRS low-risk group (1.45: 1.02–2.06, p=0.037). Furthermore, parental allergy also increased the risk of CMA among children (1.87: 1.46–2.39, p<0.001). Importantly, parental allergy exacerbated the genetic effect on the risk of CMA. **Conclusions:** The rs1800896 variant in the IL-10 gene is associated with CMA in Chinese children. In addition, the GRS had an interaction with parental history of allergy, implying that genetic risk for CMA was exacerbated among those with parental history of allergy.

Key Words: cow's milk allergy, single- nucleotide polymorphism, genetic susceptibility

INTRODUCTION

Cow's milk allergy (CMA) is the most common food allergy in infants and young children, with an estimated incidence ranging between 2% and 3.5%.[1-3] CMA can occur in infants who were exclusively breastfed or those who received mixed feeding (with introduction of milk protein).[3] There are 3 types of inflammatory mechanisms that can mediate CMA: "acute-onset" immunoglobulin E (IgE)-mediated allergies, "delayed-onset" non-IgE cell-mediated allergies, and mixed-type-mediated allergies.[4] A total of 82.5% of CMA babies develop allergic reactions in the first 3 months of life. The etiology of CMA is complex, and genetic risk factors have a strong influence. If one parent is allergic, the risk of allergic reactions rises to approximately 20% to 30%.[5] If both parents are allergic, their children have an approximately 40% to 70% chance of also developing it.[6] Patients with CMA and other food allergies have a heterogeneous clinical presentation, and the estimated heritability of food-specific IgE ranges from 0.15 (cow's milk) to 0.35 (wheat).[7,8] Although up to 90% of affected infants naturally develop tolerance to cow's milk proteins by 5 years of age,[9] children with CMA early in childhood seem to have a higher risk of developing asthma and other allergic diseases later in life. CMA is caused by the combined effect of genetic susceptibility and environmental influences, and exploring the genetic characteristics and related genes of CMA may provide valuable information for intervention and treatment.

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Manuscript received 08 January 2022. Initial review completed 13 January 2022. Revision accepted 04 February 2022.
doi: 10.6133/apjcn.202203_31(1).0016

Several studies have addressed the association of gene polymorphisms with CMA and have identified candidate genes, some of which are also associated with asthma. Peter et al analyzed six SNPs that have been described previously in relation to allergic diseases and found two SNPs, rs17616434 and rs2069772, to be significantly associated with CMA.[10] Rs17616434 is located near a cluster of Toll-like receptor (TLR1, 6, 10) genes. TLR is a member of the interleukin-1 receptor (IL-1R) superfamily and is a highly conserved molecular family in human evolution. It plays a key role in the innate immune response by identifying pathogen-associated molecular patterns (PAMPs).[11] Rs2069772 was previously reported to be associated with allergic rhinitis and is located near the IL2 and KIAA1109 genes.[12] In 2006, Ulla Christensen et al. reported for the first time that in the Danish population, IL-2 can be used as a candidate gene for asthma and found that two polymorphic sites in the IL-2 gene are related to mediating allergic diseases.[13] The other gene, KIAA1109, is known to be involved in celiac disease, a disease characterized by a strong immunological response to food proteins (gluten), found in wheat, rye and barley.[14] As an immunomodulatory factor, IL-10 plays an important role in the production of Th1 and Th2 cells and the secretion of cytokines. Studies have shown that the secretion of IL-10 is affected by genetic factors, and the level of IL-10 in the human body will directly affect the susceptibility and severity of diseases such as food allergies. Therefore, research on IL-10 gene polymorphisms has gradually attracted attention.[15-17] In a study, Koponen et al found that the IL10 rs1800896 SNP is associated with asthma after severe lower respiratory tract infections in preschool children and infants.[17] In their study, Korppi et al also found that the SNP site (rs1800896) is associated with repeated wheezing in children.[15] Iron homeostasis in the human body can affect the immune state of the body. Under iron deficiency, children are at increased risk of allergic diseases such as eczema and asthma.[18] The membrane-bound serine protease encoded by the TMPRSS6 gene is a negative regulator of hepcidin production, which can reduce the expression level of hepcidin. A small-sample-sized study of infants suggested that children with the TMPRSS6 rs855791 TT genotype had an increased risk of CMA (OR=3.47, p=0.011).[19] The IL13 pathway plays an important role in food allergies.[20] The SNP site of the IL13 gene rs20541 (+2044G→A) is related to an increase in IL13 levels.[21] Zitnik et al found that the rs20541 polymorphism is related to CMA.[22] However, whether previously identified genetic variants are associated with CMA and the extent to which these SNPs contribute to the occurrence of CMA in Chinese children are unknown.

Therefore, the present study aimed to investigate the extent to which genetic variants (previously reported CMA-related SNPs: rs17616434, rs2069772, rs1800896, rs855791 and rs20541) contribute to the occurrence of CMA in Chinese children and to further explore whether a family history of allergy modifies such a genetic association with CMA among two hundred infants with CMA and 799 healthy controls aged 0–12 months from seven hospitals in China.

METHODS

Study participants

This is a prospective cohort study involving 999 participants aged 0–12 months from 7 hospitals in China who were born between March 1, 2020, and December 31, 2020. The participants were recruited from a population of infants attending growth and development clinics or health clinics without supplemental food. Regarding the study groups, the CMA group comprised infants diagnosed with milk protein allergy according to the MAP Guidelines for Milk Allergy in Primary Care,[23] and the control group comprised infants who had been exposed to milk protein and had no allergic symptoms (follow-up to 1 year of age when there were no symptoms; patients with symptoms during follow-up were confirmed or excluded by avoidance testing).

A total of 200 children diagnosed with CMA in pediatric outpatient clinics from March 2020 to December 2020 were selected as the CMA group. The diagnostic criteria were based on the MAP Guidelines for Milk Allergy in Primary Care.[23] Children with suspected clinical symptoms of CMA were diagnosed by positive food avoidance and provocation tests. At the same time, 799 healthy infants were selected as the healthy control group.

The study was approved by the Clinical Research Ethics Committee of People's Hospital of Peking University (protocol #2019PHB192-01). Written informed consent for both the study and genetic sampling was obtained from a parent or a legal guardian of all individual participants included in the study.

Epidemiologic and clinical information collection

Trained research nurses conducted face-to-face interviews using structured questionnaires, collecting information on parity, previous pregnancy, gestational age, date of birth, delivery mode, infant sex, birth weight, antenatal complications and parental age and atopy. Atopy was referred to as asthma, allergic rhinitis or atopic dermatitis.

Specimen collection: The sponge head in the saliva collector (children's version) was used to scrape the inner wall of the oral cavity 10 times, and then, it was placed in the preservation solution for storage.

Genotyping using an Illumina ASA gene chip: The ASA (Asian Screening Array) chip is Illumina's first whole-genome SNP chip designed based on 9000+ East Asian whole-genome sequencing data. The chip contains 700,000 markers. The chip was used to clarify the differences in gene polymorphisms between the CMPA group and the control group.

Calculation of the genetic risk score

The genetic risk score (GRS) is the sum of the number of risk alleles of five SNPs. The number of risk alleles for each individual was weighted according to the effect size of the SNP–trait associations. We categorized GRS into a low-genetic-risk group (≤5) and high-genetic-risk group (6 to 10).

Statistical analysis

Stata 15.1 was used for statistical analysis. Measurement data are expressed as the mean ± standard deviation (x±s), and count data are expressed as the frequency and per-

centage (%). Comparisons of the measurement data of two groups were analyzed by means of the t test, and comparisons of count data were analyzed by means of the chi-square test. Hardy–Weinberg genetic balance tests were used to determine whether samples were from the same population. Logistic regression was used to analyze the correlation between genes and clinical phenotypes. Logistic regression analysis was performed to compare the incidence of CMA. The following covariates were included in the statistical model: mode of delivery, sex, parental history of allergies, and gestational age. Additionally, the statistical model included the interactions between the SNPs and parental allergies. All values were 2-sided, and $p<0.05$ was considered statistically significant.

RESULTS

Demographic and clinical features

All five SNPs were in Hardy–Weinberg equilibrium ($p>0.05$). The main demographic and clinical characteristics of the study population are shown in Table 1. Among the 999 study subjects, 200 were in the CMA group, and the rest were in the control group. The differences in preterm birth rate, low-birth-weight rate, average birth weight and average gestational age of the two groups were statistically significant. Compared with the control group, the CMA group had a higher preterm birth rate (17.5% and 9.6%, respectively), a higher rate of low-birth-weight infants (11.0% and 6.6%, respectively), a lower average birth weight, and a lower average gestational age. In the CMA group, the proportions of first babies and first pregnancies were higher, and the differences were statistically significant. The difference in the ratio of birth season between the two groups was also statistically significant ($p<0.001$), with the rate of children born in spring in the CMA group being significantly higher than that in the control group (20% vs 9.4%). However, there were no significant differences in sex, average parental age, mother's method of conception, delivery method, or whether amniotic fluid was contaminated between the two groups ($p>0.05$). Regarding the feeding method, the rate of exclusive breastfeeding in the CMA group was lower than that in the control group (26.5% and 36.7%, respectively, $p=0.015$). In the comparison of the two groups with a family history of allergies, the proportion of parents with allergies in the CMA group

Table 1. Demographic and clinical characteristics of patients and control subjects

Parameters	Patients (n=200)	Control (n=799)	*p* value
Sex			
Male	113 (56.5%)	398 (49.8%)	0.091
Female	87 (43.5%)	401 (50.2%)	
Gestational age	38.6±2.29	38.9±1.84	0.026
Premature	35 (17.5%)	77 (9.6%)	0.002
Low-birth-weight infant	22 (11.0%)	53 (6.6%)	0.036
Birth weight (kg)	3.15±0.62	3.26±0.51	0.018
Parental age			
Maternal age	31.9±3.96	32.0±4.02	0.679
Paternal age	33.3±4.34	33.4±4.77	0.732
Fertilization method			
Natural conception	185 (92.5%)	748 (93.6%)	0.570
Assisted reproduction	15 (7.5%)	51 (6.4%)	
Delivery mode			
Vaginal	115 (57.5%)	449 (56.2%)	0.739
Cesarean section	85 (42.5%)	350 (43.8%)	
Amniotic fluid pollution	15 (7.5%)	47 (5.9%)	0.396
Previous pregnancy			
None	129 (64.5%)	439 (54.9%)	0.015
≥1	71 (35.5%)	360 (45.1)	
Parity			
None	160 (80%)	537 (67.2%)	<0.001
≥1	40 (20%)	262 (32.8)	
Season of birth			
Spring (Mar.–May)	40 (20.0%)	75 (9.4%)	<0.001
Summer (Jun.–Aug.)	86 (43.0%)	266 (33.3%)	
Autumn (Sep.–Nov.)	60 (30.0%)	348 (43.6%)	
Winter (Dec.–Feb.)	14 (7.0%)	110 (13.8%)	
Parents allergy			<0.001
Absent	76 (38.0%)	480 (60.1%)	
Paternal (P)/Maternal (M)	100 (50.0%)	271 (33.9%)	
P+M	24 (12.0%)	48 (6.0%)	
Symptoms			
Urticaria/atopic eczema	155 (77.5)	445 (55.7)	<0.001
Oral allergy syndrome	102 (51.0)	107 (13.4)	<0.001
Feeding patterns			
Breast feeding	53 (26.5%)	293 (36.7%)	0.015
Mixed feeding	135 (67.5%)	476 (59.6%)	
Artificial feeding	12 (6.0%)	30 (3.8%)	

was significantly higher(p<0.001).

Genotype and allele distribution of SNPs in the CMA group and control group

Five SNPs, namely, rs17616434, rs2069772, rs855791, rs1800896 and rs20541, were summarized. As shown in Table 2, SNP rs1800896 was solely associated with CMA. The T allele of rs1800896 (OR=1.60, p=0.042) was significantly higher in the CMA group than in the control group. After adjusting for environmental and perinatal factors (sex, gestational age, birth weight, feeding patterns, season of birth, delivery mode, previous pregnancy, parity and parental age), further study was conducted to determine whether there were differences in 5 single-nucleotide polymorphisms (SNPs) and GRSs between the CMA group and the control group. Logistic regression analysis found that rs1800896 was more significantly associated with the CMA (OR=1.68, p=0.033). Each 1 risk allele, and an increase in the GRS was suggestively associated with an 11% higher risk of CMA (1.11: 0.99-1.27, p=0.069). When the GRS was classified as low genetic risk (grs5 ≤5) or high genetic risk (grs5 >5) as a dichotomous variable, a 45% increased risk of CMA was found in the GRS high-risk group compared to the GRS low-risk group (1.45: 1.02–2.06, p=0.037), as shown in Table 3.

The impact of parental allergy on offspring and interaction analyses

Logistic regression analysis indicated that if one parent is allergic, the offspring's risk of CMA will increase 1.87 times (1.46–2.39, p<0.001), as shown in Table 3. For the interaction analyses, a product term of 5 SNPs and parental allergy (yes, no) was added into the logistic regression models, and we found that only rs1800896 interacted with parental allergy history (p=0.0097). To clarify the interaction between GRS and parental allergy, a further stratified analysis of the effect of parental allergy on offspring CMA was conducted based on different GRS groups (≤5, >5). As shown in Figure 1, in the GRS ≤5 group, the risk of offspring CMA increased 1.97 times (95% CI: 1.11–3.51) for each additional parent with allergies. In the GRS >5 group, the risk increased 2.63 times (95% CI: 1.78-3.90) for each additional parent with allergies. The effect of parental allergy on offspring CMA was greater in the high genetic risk group (GRS >5) than in the low genetic risk group (GRS ≤5). In addition, the participants were

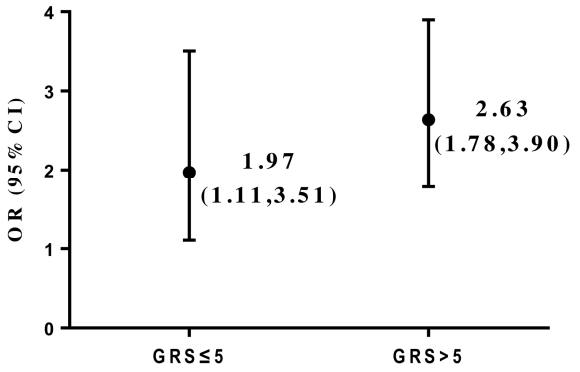

Figure 1. Parental allergy for CMA risk.

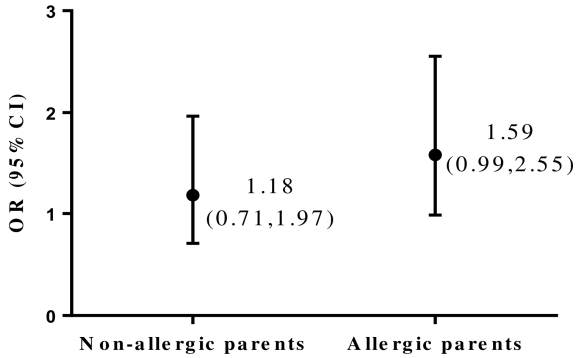

Figure 2. GRS for CMA risk.

stratified by whether the parents had allergies to study the influence of high genetic risk (GRS >5) and low genetic risk (GRS ≤5) on the occurrence of CMA in infants. The results show that the effect of high genetic risk of CMA in offspring was increased by 18% and 59% in the parental nonallergic group and parental allergic group, respectively (Figure 2). We found a positive additive interaction between the GRS of CMA and parental allergy. Figures 3(a) and 4(a) show the population distribution of the different GRSs in the CMA and control groups, respectively. The cumulative percentage for GRS ≤5 was 29.5% in the CMA group (Figure 3(b)) and 36.4% in the control group (Figure 4(b)). Figure 5 show a decision-making diagram for Chinese infants suspected with CM.

DISCUSSION

Our study found for the first time that the rs1800896 variant in the IL-10 gene is associated with CMA in Chinese children. A GRS constructed based on genetic variants that have been previously identified in the Western population was additively associated with the risk of CMA and had an interaction with a parental history of allergy, implying that genetic risk for CMA was exacerbated among those with a parental history. Our findings underscore the importance of early targeted therapeutic interventions for children with a parental history.

CMA is the most common allergic disease in infancy, accounting for 1/4 of childhood food allergies.[24] CMA can involve various systems throughout the body, with digestive system and skin symptoms, such as vomiting, reflux, diarrhea, blood in the stool, intestinal colic, eczema, and urticaria, as the main manifestations. Indeed, a growing body of literature has shown that FA significantly diminishes quality of life among affected patients and their caregivers,[25] who live in constant fear of accidental ingestion and potentially life-threatening reactions. To date, the mechanism of CMA remains unclear, but it is generally believed to be the result of a combination of environmental and genetic factors. Therefore, to explore the genetic characteristics of milk protein allergies, early diagnosis and treatment can allow infants to eliminate the intrusion of milk protein allergies early, reduce the impact of CMA on the growth and development of infants and young children, eliminate parental anxiety, reverse abnormalities in early immune status, avoid the develop-

Table 2. Comparison of SNPs between cow's milk allergy (CMA) and controls

SNP	Group	Risk allele	Frequency, n (%)	*p* value	OR (95% CI)	Genotype frequency AA/AB/BB, n (%)			‡*p* value
rs17616434						CC	CT	TT	0.903
	CMA	T	142 (35.5)	0.650	1.06 (0.838-1.33)	85 (42.5)	88 (44.0)	27 (13.5)	
	Control		548 (34.3)			351 (43.9)	348 (43.6)	100 (12.5)	
rs2069772						CC	CT	TT	0.684
	CMA	T	352 (88.0)	0.442	1.14 (0.816-1.59)	3 (1.50)	42 (21.0)	155 (77.5)	
	Control		1383 (86.8)			12 (1.50)	191 (23.9)	596 (74.6)	
rs855791						GG	AG	AA	0.493
	CMA	G	177 (44.3)	0.873	1.02 (0.817-1.70)	37 (18.5)	103 (51.5)	60 (30.0)	
	Control		700 (43.8)			163 (20.4)	374 (46.8)	262 (32.8)	
rs1800896						CC	CT	TT	0.107
	CMA	T	377 (94.3)	0.042	1.60 (1.01-2.52)	0 (0.00)	23 (11.5)	177 (88.5)	
	Control		1456 (91.1)			3 (0.40)	136 (17.0)	660 (82.6)	
rs20541						GG	AG	AA	0.305
	CMA	A	139 (34.8)	0.184	1.17 (0.93-1.47)	81 (40.5)	99 (49.5)	20 (10.0)	
	Control		500 (31.3)			372 (46.6)	354 (44.3)	73 (9.10)	

SNP: single-nucleotide polymorphism; OR: odds ratio; CI: confidence interval.
†*p* values for risk allele.
‡*p* values for genotype frequency.

Table 3. Genetic effects of SNP and parental allergies on cow milk allergies

Parameters	Model 1†		Model 2‡		Model 3§	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
rs17616434	1.05 (0.834–1.31)	0.692	1.05 (0.830–1.32)	0.706	1.05 (0.834–1.33)	0.664
rs2069772	1.13 (0.809–1.59)	0.470	1.15 (0.816–1.63)	0.420	1.16 (0.816–1.63)	0.417
rs855791	0.990 (0.796–1.23)	0.928	1.01 (0.809–1.26)	0.924	1.02 (0.810–1.27)	0.897
rs1800896	1.67 (1.050–2.69)	0.031	1.61 (1.01–2.59)	0.046	1.68 (1.04–2.71)	0.033
rs20541	1.19 (0.921–1.48)	0.201	1.15 (0.900–1.46)	0.267	1.16 (0.911–1.49)	0.225
grs5	1.11 (0.983–1.25)	0.092	1.11 (0.983–1.26)	0.091	1.11 (0.991–1.27)	0.069
GRS	1.40(0.996–1.96)	0.053	1.39 (0.983–1.97)	0.062	1.45 (1.02–2.06)	0.037
Parents allergy	1.94 (1.53–2.47)	<0.001	1.97 (1.55–2.50)	<0.001	1.87 (1.46–2.39)	<0.001

†Model 1 Adjusted for sex and gestational age.
‡Model 2 Adjusted for sex, gestational age, birth weight, feeding patterns and season of birth.
§Model 3 Adjusted for sex, gestational age, birth weight, feeding patterns, season of birth, delivery mode, previous pregnancy, parity and parental age.
¶grs5 =rs17616434+rs2069772+rs855791+rs1800896+rs20541.
††GRS was classified as low genetic risk (grs5 ≤5) or high genetic risk (grs5 >5), as a dichotomous variable.

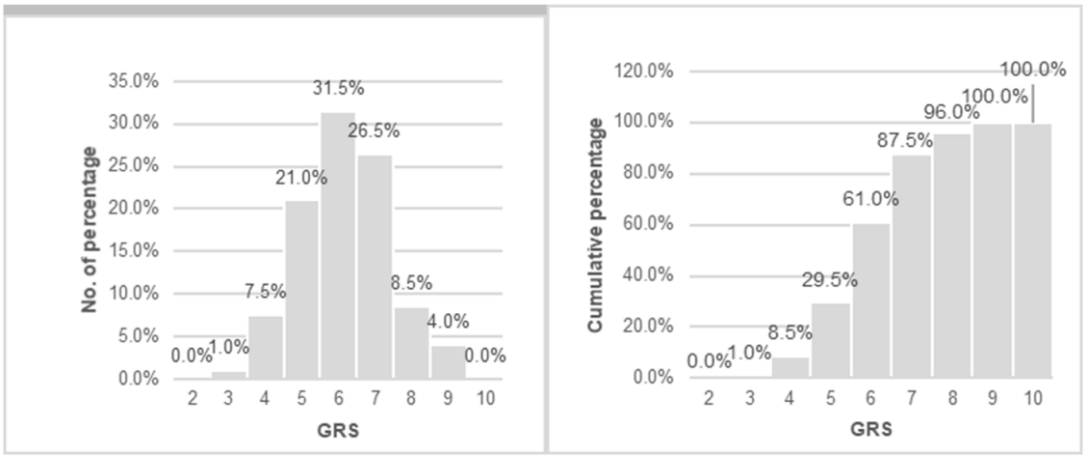

Figure 3. Distribution of GRS (a) population percentage and (b) population cumulative percentage in CMA group.

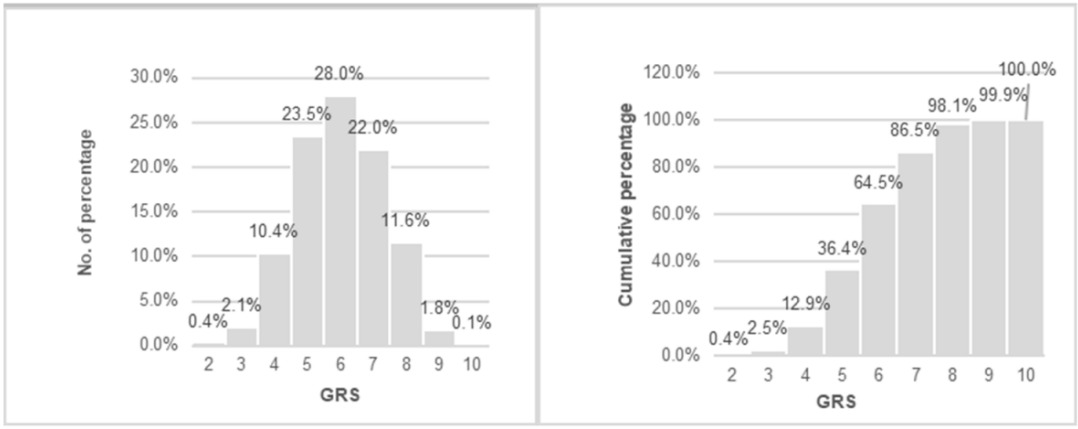

Figure 4. Distribution of GRS (a) population percentage and (b) population cumulative percentage in the control group.

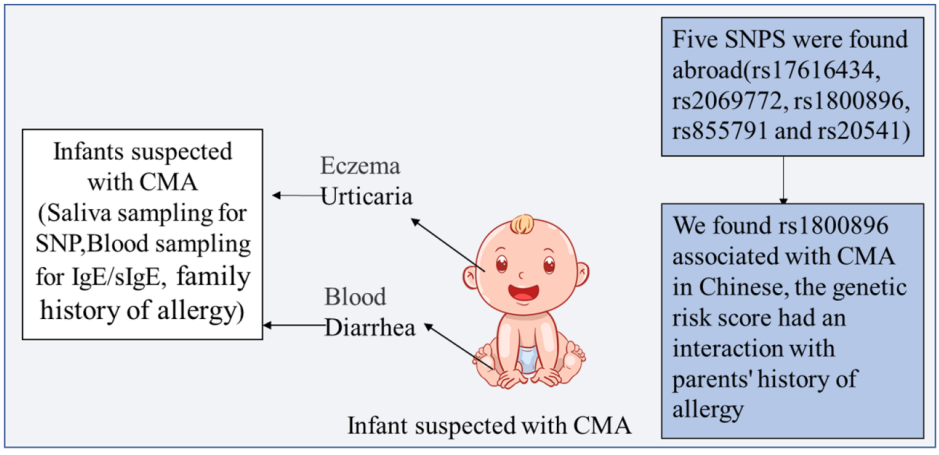

Figure 5. Decision-making diagram. Genetic susceptibility of cow's milk allergy.

ment of allergic processes, and lay the foundation for the health of infants and children.

The natural history of CMA is unique because in most patients, the symptoms resolve spontaneously. This complicates the evaluation of the prevalence of the disease. CMA usually occurs in the first 2 years of life and especially within the first year.[24,26,27] Therefore, this study selected infants aged from 0–12 months, and they were followed up to 12 months to determine whether they had allergies. The development of all food allergies is affected by genetics, environment, and genome-environmental interactions, including epigenetic effects.[27,28] Many risk factors for CMA have been identified or proposed to cause allergies or sensitization. The currently discovered CMA-related risk factors include sex, and males have a near twofold higher risk among children; however, the opposite is true in adulthood, with 80% of CMA patients being women.[3] We did not find sex-related differences in our previous study. Additionally, there are differences between races. McGowan et al compared the racial sensi-

tization rate of NHANES (National Health And Nutrition Examination Survey) participants (6 to 19 years old) and found that white participants had the lowest CMA allergy rate compared with black and Mexican-American participants.[29] It is generally believed that parental atopy significantly increases the risk of atopic diseases in the developing baby. It is one of the strongest risk factors, similar to other atopic diseases. Koplin et al[30] found that among one-year-old infants, compared with infants with no family history of allergic disease, infants who had one immediate family with an allergic disease had a 40% higher risk of allergies, and among infants with two relatives who had allergic disease, the risk of allergies rose to 80%. This study found that for every parent who has an allergy, the offspring's risk of allergies increases by approximately 1.9 times. In addition, preterm birth is a risk factor for CMA. Sardeecka et al reported that the risk of CMA in preterm newborns is increased,[31] which may be caused by the greater intestinal permeability of premature infants.[32] This study found that compared with the control group, the CMA group had a higher preterm birth rate (17.5% versus 9.6%), a higher rate of low-birth-weight infants (11.0% versus 6.6%), a lower average birth weight, and a lower average gestational age, which is consistent with the conclusions of previous reports. The mode of delivery may also affect the occurrence of CMA. The incidence of CMA among infants born by cesarean section may be higher because of the lack of the neonatal microbiota obtained by vaginal delivery, which in turn affects the infant's immune system.[32,33] However, no relationship between CMA and delivery type was observed in this study.

IL-10 is an immunomodulatory and anti-inflammatory cytokine that regulates the production of Th1 and Th2 cells and the secretion of cytokines during the immune response. Studies have found that the IL-10 gene polymorphism is associated with eczema, wheezing in infants and young children, childhood asthma, and the number of circulating eosinophils and IgE levels.[34,35] Rs1800896 is a single-nucleotide variant in the promoter region of the IL10 gene on chromosome 1.[36] Biologically relevant changes in promoter regions often alter the anchoring of different transcription factors, leading to differences in gene transcription. In their study of 125 children of Finnish descent, Holster et al found that the AA allele at locus rs1800896 was associated with an increased incidence of asthma, duration of asthma, and use of inhaled glucocorticoids compared to the AG or GG genotypes.[35] The meta-analysis published in 2014 included 4716 adults and children with asthma and 5093 controls and found that the IL-10 rs1800896 polymorphic locus was associated with asthma susceptibility in atopic children and adults.[37,38] A meta-analysis published in 2016 including 2494 asthmatic children and 2160 control children concluded that the IL-10 rs1800896 polymorphism may be a risk factor for childhood asthma.[39] The secretion of IL-10 is affected by genetic factors, and the level of IL-10 in the human body directly affects the susceptibility to and severity of diseases such as food allergies. A Brazilian study including 50 children with IgE-mediated CMA and 224 healthy controls found that the homozygous rate of the G allele at locus rs1800896 (IL10-1082A/G) was higher in the CMPA group than in the control group (19% versus 12%, p=0.027).[40] Our data show that the IL-10 rs1800896 gene polymorphism site is related to CMA and that there is an interaction with parental allergy history. Previous studies suggest that IL-10 rs1800896 is related to other late-onset allergic diseases (allergic rhinitis, asthma),[41,42] and Alduraywish found that food sensitization in the first two years of life increased the risk of subsequent asthma and allergic rhinitis.[43] These results indicate that CMA, allergic rhinitis and asthma have a common genetic cause, which also supports the "allergic march" hypothesis and the role of early-life food sensitization in the atopic march.

We found a positive additive interaction between the GRS of CMA and parental allergies. Genetic factors associated with a high risk of the GRS and parental allergies have a greater impact on offspring CMA. Additionally, the presence of parental allergies have a more pronounced effect of the GRS on CMA occurrence than lack of parental allergy. The cumulative percentage distribution in the low genetic risk (GRS <5) was higher in the control group than in the CMA group. These findings suggested that GRS has predictive significance for CMA and will inform the development of CMA risk prediction models in the future. In this study, no associations between other genetic models and CMA were found. This may be partly due to the short-term follow-up of the cohort and the assessment of allergic diseases based on the symptoms reported by the parents. Therefore, in the future, long-term follow-up and disease assessments through symptom evaluations and objective measurements (such as the skin prick test or serum allergen-specific IgE measurement) will be necessary.

This study has several limitations in this study. First, only five SNP loci (rs17616434, rs2069772, rs1800896, rs855791, and rs20541) were selected as candidate genes. There are few candidate genes, and these genes should include more allergy-related genes and SNPs. Second, genetic risk is classified according to the number of homozygous risk alleles. Failure to fully consider the single effect of each risk allele on the disease may weaken its effect. The GRS is an emerging method that integrates the weak effects of each risk allele and enables effective causal estimation of a large number of genetic variants. It has been widely used in genetic research of complex diseases. However, the GRS in this study had an interaction only with a parental history of allergy and did not obtain other positive results, which may be related to the small number of positive SNPs. Third, in this study, 999 children completed the 1-year follow-up and were evaluated for allergic diseases based on the symptoms reported by their parents. In future studies, larger samples, long-term follow-up, symptoms plus objective measurements, and repeated findings in other cohorts are needed.

Conclusion

In summary, our results show that the rs1800896 variant in the IL-10 gene is associated with CMA in Chinese children and that there is an interaction between this site and a parental allergy history on CMA, suggesting that genetic risk for CMA is exacerbated among those with a parental history. Our results underscore the importance of early targeted therapeutic intervention in children with a parental history. Moreover, our findings inform the future

development of CMA risk prediction models. In the future, long-term follow-up and functional and replication studies of this gene model are still needed.

AUTHIR DISCLOSURES

The authors declare no conflict of interest. This research was supported by the Foundation of 2018 Beijing Key Clinical Specialty Construction Project-Pediatrics (2199000726).

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