Jangala *et al.*
Egyptian Journal of Medical Human Genetics (2023) 24:22
https://doi.org/10.1186/s43042-023-00397-y

Egyptian Journal of Medical Human Genetics

RESEARCH

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Association of *CYP1A2* and *GST* gene variants with asthma in cases presenting with allergic chronic rhinosinusitis

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Abstract

Background Inter-individual differences in regulation and activity of xenobiotic metabolizing enzymes (XMEs) *CYP1A* and *GST* might cause distinct susceptibility to chronic rhinosinusitis (CRS) phenotypes that need to be explored. Therefore, the present study aimed to evaluate the role and risk of *CYP1A* and *GST* gene variants in allergic CRS subjects with and without asthma. A total of 224 allergic CRS cases with asthma, 252 allergic CRS cases without asthma, and 350 healthy control subjects were subjected to genetic analysis. Gene variants of cytochrome P450 (*CYP1A1* T3801 rs4646903, A2455G rs1048943, C2453A rs1799814 and *CYP1A2* G3858A rs2069514, T739G rs2069526, C163A rs762551) and glutathione S-transferase P (*GSTP1* A313G rs1605 & C341T rs1799811) were investigated by polymerase chain reaction-restriction fragment length polymorphism and *GSTM1null,* and *GSTT1null* by multiplex PCR methods.

Results TG genotype of *CYP1A2* rs2069526 (OR 1.73, 95% CI 1.20–2.50, $p < 0.002$), TC genotype of *CYP1A1* rs4646903 (OR 1.43, 95% CI 1.03–1.98, $p < 0.031$) and *GSTM1*del (OR 1.87, 95% CI 1.24–2.81, $p < 0.003$) and were found to be significantly associated with only allergic CRS cases. *CYP1A2* rs2069526 (OR 2.33, 95% CI 1.61–3.37, $p < 0.001$), GG genotype of *GSTP1* rs1605 (OR 4.75, 95% CI 2.62–8.63, $p < 0.001$), *GSTM1*del (OR 1.82, 95% CI 1.19–2.78, $p < 0.006$), *GSTM1/GSTT1* double null (OR 2.58, 95% CI 1.36–4.87, $p < 0.004$) and were found to be significantly associated with asthma in allergic CRS cases. Further, G-G-C haplotype of *CYP1A2* rs2069514, rs2069526 and rs762551 gene variants was found to increase the risk for asthma by 5 folds in allergic CRS subjects (OR 5.53, 95% CI 1.76–17.31, $p < 0.003$) while T-G-C haplotype of *CYP1A1* rs4646903, rs1048943, rs1799814 (OR 0.11, 95% CI (0.01–0.95, $p < 0.045$) and A-T haplotype of *GSTP1* rs1605, rs1799811 (OR 0.27, 95% CI (0.08–0.89, $p < 0.032$) showed protective effect in allergic CRS group.

Conclusion The present study reports the significantly increased association of *CYP1A2, GSTM,* and *GSTP* gene variants with asthma in allergic CRS.

Keywords Allergy, Asthma, Chronic rhinosinusitis, Cytochrome P450 1A2, Glutathione-S-transferase, Haplotype

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Background

Chronic Rhinosinusitis (CRS) accompanied by asthma drastically affects the quality of life and socioeconomic condition of millions of people worldwide [1].The antioxidant system counters oxidative stress by a complex network of phase I and phase II xenobiotic metabolizing enzymes (XMEs). The efficiencies of XMEs also balance pro-inflammatory, anti-inflammatory and mucosal hyperresponsiveness in allergic diseases [2]. CYP1A are the most important phase I biotransforming enzymes that constitute a superfamily of heme proteins responsible for the oxidative metabolism of a vast number of exogenous and endogenous compounds [3]. The Glutathione *S*-transferase (GST) superfamily consisting of phase II XMEs protect cells from the damage caused by reactive oxygen species and are also involved in the deactivation of allergens. Several families of soluble GSTs referred to as alpha, mu (GSTM), pi (GSTP), theta (GSTT), sigma and kappa have been identified in humans. Homozygosity for a nonfunctional allele (*GSTT1-null* and *GSTM 1* null genotype) results in the loss of enzyme activity [4, 5]. GSTP1 is more abundant in respiratory tissues than other GSTs and plays an important role in neutralising oxidative stress in response to allergen and environmental exposure [5].

Independent studies reported CRS to be associated with single and multiple nucleotide polymorphisms that modulate immunologic responses or airway inflammation to allergy and asthma [1]. Several important gene variants of *CYP1A1*, *CYP1A2* and *GST* genes have been identified to cause variability in the enzyme activity. The most common gene variants of *CYP1A1 are CYP1A1**m1 T3801C rs4646903, *CYP1A1*m*2 A2455G rs1048943, *CYP1A1*m*3 T3204C rs1048945 and *CYP1A1*m*4 C2453A rs1799814; *CYP1A2 are CYP1A2*1C* G3858A rs2069514, *CYP1A2*1E* T739G rs2069526 and *CYP1A2*1F* C163A rs762551 and *GSTP1 A*313G rs1605, *GSTP1 C*341T rs1799811, and null variants *GSTM1* and *GSTT1* [3–5]. Umamaheswaran et al., 2014 reported that the frequency of the mutant alleles of XME genes including CYP1A1 and GST genes were significantly different among populations and no studies have been conducted on *CYP1A2* polymorphism in South Indian population so far [6]. To the best of our knowledge, no study has related CYP1A1 and CYP1A2 gene polymorphism to allergic CRS and its endotypes. With regard to *GST* genes for their risk for respiratory disease and allergies, evidence of an association has been suggested but results are not concordant and further investigations were suggested in this direction [7, 8]. Also, studies on the impact of XME genes in the inter-individual susceptibility to the development of asthma in allergic CRS are very meager. In view of the above, the present study aimed to investigate the role of XME gene variants, (Cytochrome P450 1A1, Cytochrome 1A2 and Glutathione S transferase—*GSTT*, *GSTM* & *GSTP*), in the etiology with and without asthma in allergic CRS subjects.

Methods

A case–control study was performed with a total of 826 adult subjects that includes 224 allergic CRS subjects with asthma, 252 allergic CRS subjects without asthma and 350 healthy controls from 2013 to 2020. All the study subjects were diagnosed and confirmed by ENT specialists at MAA ENT Hospital, Somajiguda, Hyderabad based upon the guidelines of European Position Paper on Rhinosinusitis and Nasal Polyps (EP^3OS) and Global Initiative for Asthma (GINA) [9, 10]. A special case proforma was prepared as per the Global Allergy and Asthma European Network (GA^2LEN) project. Patients with a high level of total IgE > 180 IU (ELISA) and allergic symptoms like nasal discharge, itching, and sneezing more than 5 times per day were classified as allergic CRS patients. Patients with symptoms of allergy, breathlessness and/or a cough were considered as allergic CRS subjects with asthma. The confirmation of asthma in allergic CRS subjects was also made by pulmonary function test. 12% increase in Forced Expiratory Volume 1 (FEV1) after 200 µg of salbutamol inhalation was considered as the cut-off criteria. Healthy age and sex matched subjects from the same geographical location, without any family history of allergy, asthma, and CRS were considered as controls. Cases with other syndromes such as cystic fibrosis, immunodeficiency diseases, immune-compromised conditions, nosocomial infections and allergic fungal sinusitis were excluded from the study. All patients provided informed written consent in accordance with the study protocol, and the study was approved by the institutional ethics committee.

Genotyping

Approximately 2 ml of whole blood was used for DNA extraction using salting out method [11]. Genotyping of SNPs of *CYP1A1* C3801T rs4646903, *CYP1A1* C2453A rs1799814, *CYP1A1* A2455G rs1048943, *CYP1A2* G3858A rs2069514, *CYP1A2* C163A rs762551, *CYP1A2* T739G rs2069526, *GSTP1 A*313G rs1605 and *GSTP1 C*341T rs1799811were performed by PCR–RFLP method and *GSTM1* and *GSTT1* null variants was done using the multiplex PCR [7, 8, 12–17]. PCR was carried out in a reaction mixture containing 1U of thermostable Taq DNA polymerase in a final volume of 25 µl. The purified DNA was used for RFLP using restriction enzymes (Fermentas, United Kingdom). The restriction digest products were run through 1.5–4% agarose

Table 1 Primers, restriction enzymes and PCR–RFLP conditions for the *CYP1A1*, *CYP1A2* and *GST* gene variants studied

Gene Variant	Primer Sequence 5'- 3'	Annealing	PCR Product Size	Restriction Endonuclease (5U)	Incubation Temp	Agarose Gel (%)	Fragment Pattern (bp)	References
Cytochrome P450 1A1								
rs4646903	F GGCTGAGCA ATCTGACCCTA R TAGGAGTCT TGTCTCATGCCT	63 °C for 1 min	899 bp	*Msp*I	37 °C	1.5%	TT: 899 bp CC: 693, 206 bp	[18]
rs1048943	F CTGTCTCCC TCTGGTTAC AGGAAGC R TTCCACCCG TTGCAGCAG GATAGCC	63 °C for 1 min	204 bp	*Bsr*DI	37 °C	3.0%	GG: 149, 55 bp AA: 204 bp	[19]
rs1799814	F CTGTCTCCC TCTGGTTAC AGGAAGC R TTCCACCCG TTGCAGCAG GATAGCC	63 °C for 30 s	204 bp	*Bsa*I	65 °C	4.0%	CC: 139, 65 bp AA: 204 bp	[20]
Cytochrome P450 1A2								
rs2069514	F GCTACACAT GATCGAGCT ATAC R CAGGTCTCT TCACTGTAA AGTTA	60 °C for 1 min	598 bp	*Dde*I	37 °C	2%	GG: 598 bp AA: 410,188 bp	[21]
rs2069526	F AAAGACGGG GAGCCTGGG CTAGGTGTA GGAG R AGCCAGGGC CAGGGCTGC CCTTGTGCT AAG	56 °C for 1 min	169 bp	*Stu*I	37 °C	3%	TT: 169 bp GG: 147, 22 bp	[21]
rs762551	F CAACCCTGC CAATCTCAA GCAC R AGAAGCTCT GTGGCCGAG AAGG	59 °C for 1 min	920 bp	*Apa*I	37 °C	1.5%	CC: 920 bp AA: 709, 211 bp	[22]
Glutathione S Transferase P								
rs1695	F GGCTCTATG GGAAGGACC AGCAGG R GCACCTCCA TCCAGAAAC TGGCG	66 °C for 1 min	445 bp	*Alw*26I	37 °C	2%	AA: 330, 115 bp GG: 270,115,60 bp	[23]
rs1799811	F CAGCAGAGG CAGCGTGTG TGC R CCCACAATG AAGGTCTTG CCTCC	64 °C for 1 min	485 bp	*Aci*I	37 °C	2%	CC: 365,120 bp TT: 485 bp	[24]
GSTM1/GSTT1								
*GSTM*1	F ACACAACTG TGTTCACTAGC R AACTTCATC CACGTTCACC	59 °C for 1 min	215 bp	NA	NA	2%	NA	[25]

Table 1 (continued)

Gene Variant	Primer Sequence 5'- 3'	Annealing	PCR Product Size	Restriction Endonuclease (5U)	Incubation Temp	Agarose Gel (%)	Fragment Pattern (bp)	References
*GSTT*1	F TTCCTTACT GGTCCTCAC ATCTC R TCACCGGAT CATGGCCAGCA		480 bp					
Albumin (Positive Control)	F ACACAACTG TGTTCACTAGC R CAACTTCAT CCACGTTCACC		350 bp					

gel electrophoresis with ethidium bromide and photographed under ultraviolet light. The PCR conditions, specific forward primer and reverse primer used and RFLP conditions are given in Table 1. Random PCR–RFLP retesting of approximately 10% of the samples per SNP was performed to find the concordance with the initial genotyping results. The genotyping results were scored by two independent investigators who had no idea whether the sample came from the cases or the control group.

Statistical analysis

Using SPSS (version 21; IBM Corporation, Armonk, NY, USA) the genotype and allele frequencies of patients and controls were compared. Using an electronic calculator, genotype frequency distributions were tested for agreement with the Hardy–Weinberg equilibrium (HWE) [http://www.genes.org.uk/software/hardy-weinberg.html]. Statistical significance of the differences in frequency of alleles, genotypes and genotypic models of inheritance; dominant (wild homozygotes vs. heterozygotes plus variant homozygotes), recessive (wild homozygotes plus heterozygotes vs. variant homozygotes) and co-dominant (wild homozygotes vs. heterozygotes vs. variant homozygotes), were carried out using logistic regression analysis for all the SNPs individually. The Haploview software (version 4.1 Broad Institute, Cambridge) was used to create linkage disequilibrium (LD) plots [18]. The THESIAS software (version 3.1, INSERM U525, Paris, France) was used to generate haplotype frequencies and to perform logistic regression analysis on the haplotypes [19]. $p < 0.05$ was considered statistically significant. In the cumulative effect analysis of risk alleles for each SNP, the genotypes were coded as 0, 1, or 2 indicating the number of allergic CRS and asthma risk alleles. The unweighted cumulative genetic risk score (CGRS) of an individual is the total count of disease alleles from all SNPs obtained by adding coded genotypes. Benjamini–Hochberg adjustment procedure was applied to correct for multiple testing by setting false discovery rate (FDR) < 0.25 as the threshold for significance [20]. G*Power software (version 3.1, Universitat Dusseldorf, Germany) was used to calculate the study's power for individual SNPs.

Results

Male preponderance of 61.9% was seen in the aCRS and aCRS with asthma subjects under study. The mean age of the allergic CRS subjects without asthma [38.7 ± 13.30 years (18–65 years] was low when compared to allergic CRS subjects with asthma [41.53 ± 14.87 years (18–81 years)]. With regard to the mean age of onset of the disease for aCRS subjects was 21 ± 10.38 years whereas aCRS with asthma had early predisposition at mean age of 16 ± 10.05 years. The mean duration of the disease in aCRS with asthma (8.9 ± 3.65 years) was longer when compared to aCRS (3.50 ± 2.27 years). Increased frequency of smoking was seen in aCRS with asthma (25.6%) when compared to aCRS (14.7%). The frequency of aCRS subjects with asthma was seen to be high (73.3%) in urban population, while in aCRS it was 61.6% (Table 2). With respect to socio economic status, aCRS subjects with (20.1%) were mostly belonged to low socio economic status.

Hardy–Weinberg equilibrium test

Genotype frequencies for all the SNPs under study were in HWE in allergic CRS cases and controls (all $p > 0.05$, data not shown).

Genetic variant analysis

CYP1A1 and CYP1A2 gene variant analysis

In the present study *CYP1A1*2A* or m1 (3798 T > C) rs4646903, CYP1A1*2A, or m2 2455 A > G rs1048943 and CYP1A1*2C or m3 2453 C > A rs1799814 have been analyzed by PCR–RFLP (Table 1). The CYP*1A1*3798T > C, in the co-dominant model (TC vs TT + CC), were found to

Table 2 Demographic of subjects with allergic CRS, allergic CRS with asthma and controls

Characteristics of Study Subjects	aCRS only (n = 252)	aCRS with asthma (n = 224)	Controls (n = 350)	*p*-value
Sex				
Males	159 (62.3)	136 (68.9)	215 (59.8)	0.874
Females	93 (37.7)	88 (31.1)	135 (40.2)	
Marital status				
Unmarried	86 (34.1)	66 (28.9)	119 (33.9)	0.385
Married	166 (65.9)	158 (71.1)	231 (66.1)	
Age (Mean ± SD, years)	41.53 ± 14.87	38.7 ± 13.30	45.12 ± 13.86	< 0.001
Age at onset (Mean ± SD, years)	21 ± 10.38	16 ± 10.05		< 0.001
Duration of Disease (Mean ± SD, years)				
< 5 years	41 (16.2)	20 (8.9)		0.021*
5–10 years	92 (36.5)	75 (33.3)		
> 10 years	119 (47.3)	129 (57.8)		
Habitat				
Rural	97 (38.3)	60 (26.7)	180 (51.5)	< 0.001***
Urban	155 (61.1)	164 (73.3)	170 (48.5)	
Occupation				
Administration	27 (10.7)	21 (9.3)	29 (8.3)	0.521
Business	26 (10.3)	30 (11.9)	34 (9.7)	
Farmers	6 (2.4)	5 (2.2)	12 (3.4)	
Housewives	48 (19.02)	40 (17.8)	67 (19.1)	
Professional	53 (25.3)	51 (22.7)	76 (21.7)	
Students	69 (26.9)	56 (25.0)	86 (24.5)	
Unemployed	2 (0.8)	6 (2.7)	12 (3.5)	
Workers	21 (8.3)	15 (6.7)	34 (9.7)	
Alcohol				
No	220 (87.2)	182 (81.4)	305 (87.1)	0.071
Yes	32 (12.8)	42 (18.6)	45 (12.9)	
Smoking				
No	215 (85.3)	166 (74.4)	293 (83.7)	0.003**
Yes	37 (14.7)	58 (25.6)	57 (16.3)	

*p value less than 0.05, **p value less than 0.01, ***p value less than 0.001, values in parenthesis are SD values

be significantly associated with increased risk of in only aCRS subjects (OR 1.43, 95% CI 1.03–1.98) when compared to controls. With regard to CYP*1A1* 2455 A > G and CYP1A1*m4 2453C > A polymorphism no significant association was seen in the aCRS subjects with and without asthma when compared to controls. The frequency of 'G' allele (OR 2.11, $p \leq 0.0001$; OR 1.73, $p = 0.0009$) and GG genotype (OR 5.17, $p \leq 0.001$, OR 4.95, $p = 0.002$) of *CYP1A2* rs2069526 was found to show increased risk in allergic CRS with and without asthma when compared to controls. In the overdominant model, the frequency of TG genotype of *CYP1A2* rs2069526 was found to be predominant in allergic CRS subjects with asthma (OR 2.26, $p = 0.03$) when compared to allergic CRS without asthma (OR 1.73, $p = 0.0009$) and controls (Table 3).

GSTP1, GSTT1 and GSTM1 gene variant analysis

In the present study, two SNPs of GSTP (GSTP A313G & GSTP C341T) have been analyzed by PCR–RFLP and deletion polymorphism of GSTT1 and GSTM1 has been identified by multiplex PCR. The GG genotype of *GSTP1* rs1605 was seen to be strongly associated with allergic CRS with asthma (OR 4.75, $p \leq 0.001$) while CT genotype of *GSTP1* rs1799811 polymorphism showed significant protective role only in allergic CRS without asthma (OR 0.48, p-value ≤ 0.001) (Table 3).

The *GSTT1* and *GSTM1* heterozygous null genotypes were 11.4% and 17.1% in controls, 13.5% and 25.8% in allergic CRS without asthma and 10.4% and 25.2% in allergic CRS with asthma. The double null genotype (i.e., the absence of both alleles) of *GSTM1* and *GSTT1* polymorphism was 11.3% and 7.5 in allergic CRS cases with and without asthma respectively while it was 5.4%

Table 3 Allelic and Genotypic association of *CYP1A1*, *CYP1A2* and *GST* gene variants in cases with allergic CRS, and allergic CRS with asthma and controls

SNP	Polymorphism	Control	Allergic CRS			Allergic CRS with asthma		
		n (n%)	n (n%)	OR (95% CI)	*p*-value	n (n%)	OR (95% CI)	*p*-value
CYP1A1								
rs4646903	Genotype							
	T/T	163 (46.3)	97 (38.5)	1 (Reference)	0.092	102 (45.5)	1 (Reference)	0.86
	T/C	149 (42.3)	129 (51.2)	1.46 (1.03–2.06)		99 (44.2)	1.06 (0.74–1.52)	
	C/C	40 (11.4)	26 (10.3)	1.09 (0.62–1.89)		23 (10.3)	0.91 (0.52–1.61)	
	T/C vs T/T + C/C	148 (42.3)	129 (51.2)	1.43 (1.03–1.98)	0.031*§	99 (44.2)	1.08 (0.77–1.52)	0.65
	Allele							
	T	468 (0.67)	322 (0.64)	1 (Reference)		298 (0.67)	1 (Reference)	
	C	232 (0.33)	182 (0.36)	1.16 (0.91–1.48)	0.241	146 (0.33)	0.99 (0.77–1.28)	0.948
rs1048943	Genotype							
	A/A	269 (76.9)	193 (76.6)	1 (Reference)	0.99	183 (81.7)	1 (Reference)	0.36
	A/G	78 (22.3)	57 (22.6)	1.02 (0.69–1.50)		39 (17.6)	0.73 (0.48–1.13)	
	G/G	3 (0.9)	2 (0.8)	0.93 (0.15–5.61)		2 (0.9)	0.98 (0.16–5.92)	
	Allele							
	A	597 (0.85)	430 (0.88)	1 (Reference)		408 (0.88)	1 (Reference)	
	G	103 (0.15)	74 (0.12)	1.01 (0.71–1.43)	0.999	36 (0.2)	0.78 (0.53–1.15)	0.211
rs1799814	Genotype							
	C/C	329 (94)	233 (92.5)	1 (Reference)	0.46	205 (91.5)	1 (Reference)	0.26
	C/A	21 (6)	19 (7.5)	1.28 (0.67–2.43)		19 (8.6)	1.45 (0.76–2.77)	
	Allele							
	C	668 (0.95)	428 (0.94)	1 (Reference)		402 (0.97)	1 (Reference)	
	A	32 (0.05)	76 (0.04)	1.27 (0.67–2.38)	0.515	42 (0.03)	1.43 (0.76–2.69)	0.322
CYP1A2								
rs2069514	Genotype							
	G/G	292 (83.4)	220 (87.3)	1 (Reference)	0.19	193 (86.2)	1 (Reference)	0.37
	G/A	58 (16.6)	32 (12.7)	0.73 (0.46–1.17)		31 (13.8)	0.81 (0.50–1.30)	
	Allele							
	G	625 (0.89)	462 (0.94)	1 (Reference)		398 (0.93)	1 (Reference)	
	A	75 (0.11)	42 (0.06)	0.75 (0.48–1.17)	0.223	46 (0.07)	0.82 (0.52–1.29)	0.429
rs2069526	Genotype							
	T/T	269 (76.9)	163 (64.7)	1 (Reference)	0.002**§	130 (58)	1 (Reference)	< 0.0001**§
	T/G	79 (22.6)	83 (32.9)	1.73 (1.20–2.50)		89 (39.7)	2.33 (1.61–3.37)	
	G/G	2 (0.6)	6 (2.4)	4.95 (0.99–24.82)		5 (2.2)	5.17 (0.99–27.02)	
	T/G vs T/T + G/G	79 (22.6)	83 (32.9)	1.68 (1.17–2.42)	0.0048*	89 (39.7)	2.26 (1.57–3.26)	< 0.0001**§
	Allele							
	T	609 (0.87)	400 (0.81)	1 (Reference)		340 (0.76)	1 (Reference)	
	G	91 (0.13)	104 (0.19)	1.73 (1.25–2.38)	0.0009**§	108 (0.24)	2.11 (1.53–2.90)	< 0.0001**§
rs762551	Genotype							
	C/C	164 (46.9)	110 (43.6)	1 (Reference)	0.73	103 (46)	1 (Reference)	0.98
	C/A	162 (46.3)	123 (48.8)	1.13 (0.81–1.58)		105 (46.9)	1.03 (0.73–1.49)	
	A/A	24 (6.9)	19 (7.5)	1.18 (0.62–2.26)		16 (7.1)	1.06 (0.54–2.09)	
	Allele							
	C	540 (0.77)	366 (0.68)	1 (Reference)		304 (0.69)	1 (Reference)	
	A	160 (0.23)	138 (0.32)	1.1 (0.86–1.40)	0.486	140 (0.31)	1.03 (0.80–1.35)	0.843
GSTP1								
rs1605	Genotype							
	A/A	186 (53.1)	122 (48.4)	1	0.39	100 (44.6)	1	< 0.0001**§

Table 3 (continued)

SNP	Polymorphism	Control	Allergic CRS			Allergic CRS with asthma		
		n (n%)	n (n%)	OR (95% CI)	*p*-value	n (n%)	OR (95% CI)	*p*-value
	A/G	146 (41.7)	112 (44.4)	1.17 (0.84–1.64)		78 (34.8)	0.99 (0.69–1.43)	
	G/G	18 (5.1)	18 (7.1)	1.52 (0.76–3.05)		46 (20.5)	4.75 (2.62–8.63)	
	Allele							
	A	518 (0.74)	356 (0.69)	1 (Reference)		278 (0.64)	1 (Reference)	
	G	182 (0.26)	148 (0.31)	1.09 (0.85–1.40)	0.482	166 (0.36)	1.25 (0.97–1.61)	0.088
rs1799811	Genotype							
	C/C	238 (68)	204 (81)	1 (Reference)	< 0.001**§	158 (70.5)	1 (Reference)	0.80
	C/T	108 (30.9)	44 (17.5)	0.48 (0.32–0.71)		64 (28.6)	0.89 (0.62–1.29)	
	T/T	4 (1.1)	4 (1.6)	1.17 (0.29–4.72)		2 (0.9)	0.75 (0.14–4.16)	
	Allele							
	C	584 (0.83)	452 (0.9)	1 (Reference)		376 (0.85)	1 (Reference)	
	T	116 0.17)	52 (0.1)	0.98 (0.72–1.33)	0.937	68 (0.15)	0.96 (0.70–1.33)	0.87

OR Odds ratio, *CI* Confidence interval. OR obtained after Multinomial logistic regression analysis

*Significance of *p*-value ≤ 0.05

***p*-value ≤ 0.001

§ *p*-value significant after Benjamini–Hochberg correction

in controls. *GSTM1* null was found to be statistically significant in allergic CRS with asthma (OR 1.82, $p=0.006$) and without asthma (OR 1.87, $p=0.003$) subjects when compared with controls. *GSTM1* and *GSTT1* double null genotypes was significant only in allergic CRS with asthma (OR 2.58, $p=0.004$). The allelic and genotypic frequency distribution, as well as their associated risk with allergic CRS and asthma, is shown in Table 4.

Haplotype analysis in CRS phenotypes

In the present study, haplotypes were constructed based on three polymorphic sites of *CYP1A1* gene, three polymorphic sites of *CYP1A2* gene on Chr 15 and two polymorphic sites of *GSTP1* rs1605 & *GSTP1* rs1799811 situated on Chr11 in the study subjects and controls. Haplotype G-G-C at *CYP1A2* G3858A rs2069514, T739G rs2069526, and C163A rs762551 has increased the risk of asthma in allergic CRS subjects (OR 5.53, *p*-value = 0.003) while A-T haplotype of *GSTP1* rs1605 & *GSTP1* rs1799811 (OR 0.27, $p=0.045$) and T-G-C of *CYP1A1* rs4646903, rs1048943and rs1799814 had a protective effect in allergic CRS subjects without asthma (OR 0.11, $p=0.045$) (Table 5).

Linkage disequilibrium analysis in CRS phenotypes

It is well understood that associations between alleles at different loci can aid in the identification of disease susceptibility genes. In the present study, linkage disequilibrium among the SNPs of *CYP1A2* rs2069514, rs2069526 & rs762551is high (D' = 99) in allergic CRS with asthma. *CYP1A1* rs4646903, rs1048943 and rs1799814 (D' = 99) were linked in allergic CRS cases without asthma. Further, *CYP1A2* gene variants were also linked with exonic variants of *CYP1A1* rs1048943

Table 4 Interaction of GSTM and GSTT genes in cases with allergic CRS, and allergic CRS with asthma and controls

Genotype	Control	Allergic CRS without asthma			Allergic CRS with asthma		
	n (n%)	n (n%)	OR (95% CI)	*p*-value	n (n%)	OR (95% CI)	*p*-value
GSTM present/ *GSTT* Present	231 (66.0)	134 (53.2)	1 (Reference)		118 (53.2)	1 (Reference)	
GSTM present /GSTT null	40 (11.4)	34 (13.5)	1.46 (0.88–2.43)	0.138	23 (10.4)	1.13 (0.64–1.97)	0.332
GSTM null /GSTT present	60 (17.1)	65 (25.8)	1.87 (1.24–2.81)	0.003**§	56 (25.2)	1.82 (1.19–2.78)	0.006**§
GSTM null/ GSTT null	19 (5.4)	19 (7.5)	1.72 (0.88–3.37)	0.111	25 (11.3)	2.58 (1.36–4.87)	0.004**§

OR Odds ratio, *CI*-Confidence interval

OR obtained after Multinomial logistic regression analysis

Significance of ***p*-value ≤ 0.0001

§ *p*-value significant after Benjamini–Hochberg correction

Table 5 Haplotype Frequencies of *CYP1A1*, *CYP1A2* and *GSTP* genes in cases with allergic CRS, and allergic CRS with asthma and controls

Haplotype	Controls	Allergic CRS without asthma			Allergic CRS with asthma		
	Frequency	Frequency	OR (95% CI)	*p*-value	Frequency	OR (95% CI)	*p*-value
CYP1A1 rs4646903, rs1048943, rs1799814							
T-A-C	0.472	0.553	1 (Reference)		0.584	1 (Reference)	
T-A-A	0.115	0.124	0.90 (0.39–2.12)	0.816	0.057	0.40 (0.07–2.26)	0.301
T-G-C	0.063	0.010	0.11 (0.01–0.95)	0.045*§	0.096	1.36 (0.43–4.30)	0.599
C-A-C	0.339	0.237	0.67 (0.29–1.56)	0.358	0.286	0.57 (0.27–1.21)	0.142
CYP1A2 rs2069514, rs2069526, rs762551							
G-T-C	0.582	0.483	1 (Reference)		0.461	1 (Reference)	
G-G-C	0.062	0.136	2.43 (0.81–7.28)	0.113	0.183	5.53 (1.76–17.31)	0.003**§
A-T-C	0.109	0.068	0.72 (0.24–2.13)	0.555	0.081	1.02 (0.30–3.46)	0.973
G-T-A	0.186	0.234	1.72 (0.82–3.64)	0.153	0.197	1.54 (0.61–3.87)	0.362
G-G-A	0.062	0.080	2.06 (0.64–6.70)	0.228	0.078	2.23 (0.62–8.05)	0.222
GSTP1 rs1605, rs1799811							
A-C	0.574	0.693	1 (Reference)		0.479	1 (Reference)	
A-T	0.144	0.052	0.27 (0.08–0.89)	0.032*§	0.199	2.12 (0.64–6.98)	0.217
G-C	0.260	0.238	0.76 (0.37–1.57)	0.469	0.271	1.38 (0.60–3.20)	0.446
G-T	0.023	0.016	NA	NA	0.051	1.91 (0.20–18.15)	0.572

Haplotypes with a frequency ≥ 1% were tested

OR Odds ratio, *CI* Confidence interval

Significance of **p*-value ≤ 0.05

***p*-value ≤ 0.005

§ *p*-value significant after Benjamini–Hochberg correction

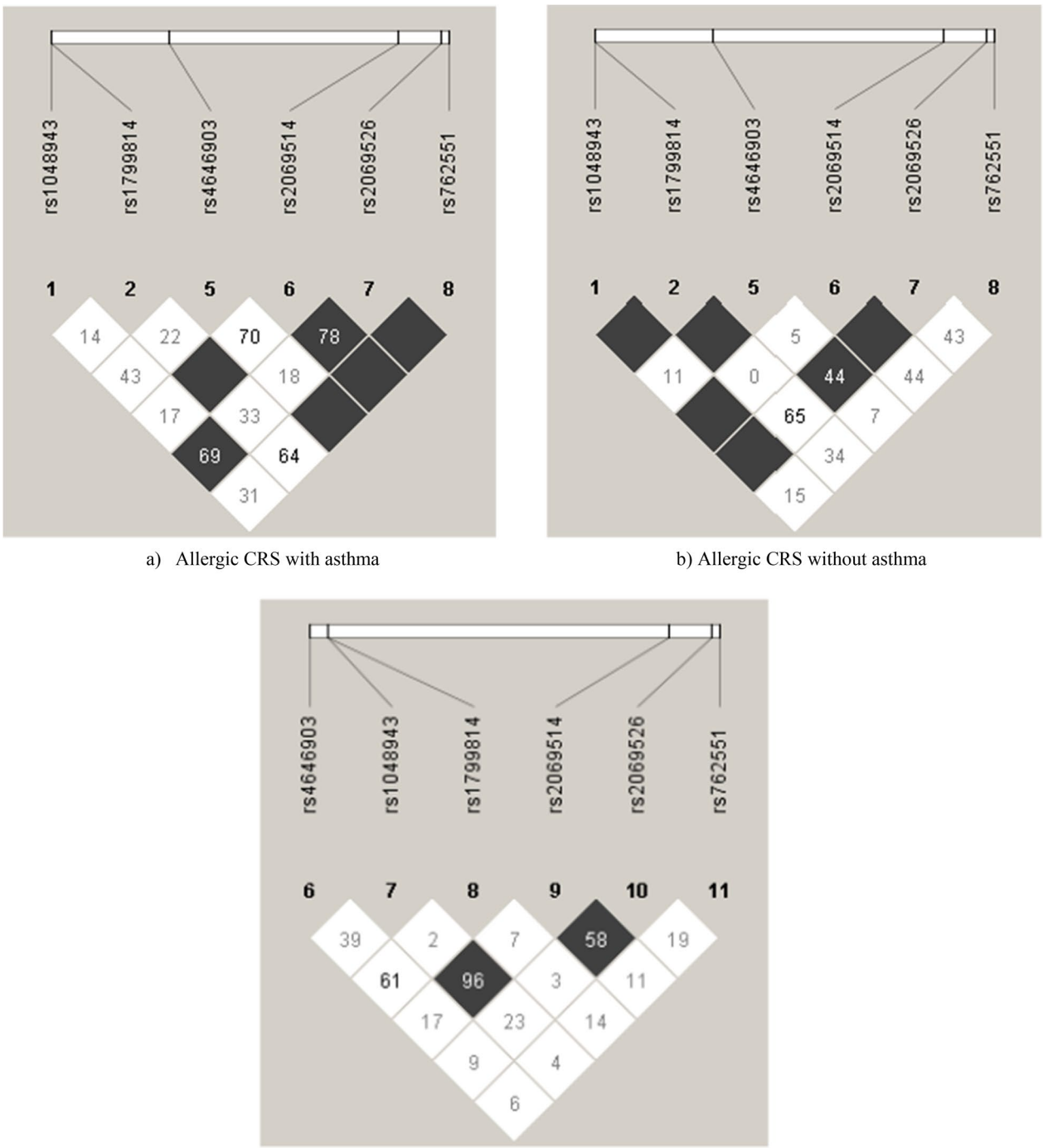
and rs1799814 in allergic CRS with and without asthma (Fig. 1). The total number of risk alleles present in allergic CRS was more when compared to controls. Risk contributed by the more than 6 risk alleles in allergic CRS subjects with asthma was high (OR 11.25, $p = 0.004$) when compared to allergic CRS without asthma (OR 5.35, $p = 0.056$) (Table 6).

Discussion

Genetic studies are promising and may offer insights into the pathophysiology of CRS, asthma and allergy, a strong and consistent association has not been established so far. Earlier, need for studies pertaining to clinically relevant phenotypes of airway diseases have been suggested. However, a few sporadic studies have reported that phenotypic manifestations of CRS depend on a complex interplay between multiple genes of the innate and adaptive immunity [21–24]. Further, the reports indicate the oxidative stress caused by environmental factors such as air pollutants, inhalant, and food allergens activates inflammatory cells, bronchial epithelial cells, and endothelial cells and lead to host susceptibility to the development of asthma, sinonasal inflammation and allergic symptoms [25–27]. Hence, it was pertinent to understand the genes and their interactions involved in oxidative stress leading to CRS phenotypes.

Genetic variants of phase I and II xenobiotic metabolism genes might change the enzymatic activity and the kinetics of reactions involved in detoxification of numerous toxic compounds and lead to oxidative stress [27, 28]. Pollutants in the environment, which frequently coexist with allergens, may synergistically elicit allergic inflammation and aryl hydrocarbon receptor (AhR) activation [29]. The aryl hydrocarbon receptor (AhR) regulates the expression of *CYP1A1* and *1A2* and maintains the homeostasis by increasing the clearance of metabolic substrates such as PAHs and heterocyclic aromatic amines/amides and is involved in the pathogenesis and exacerbation of allergic and inflammatory diseases such as bronchitis, asthma, and chronic obstructive pulmonary disease (COPD) [5, 30]. As XMEs share overlapping substrate specificities it is suggested to analyze the gene gene variants simultaneously for better correlation with clinical outcome [31]. The present study on XME gene variants (*CYP1A1*, *CYP1A2*, *GSTP1*, *GSTM1* and *GSTT1*) revealed significant association with asthma in allergic CRS.

CYP1A1 and *CYP1A2* genes are highly inducible by a number of environmental factors including diet and



a) Allergic CRS with asthma

b) Allergic CRS without asthma

c) Control

Fig. 1 Linkage disequilibrium (LD) plots of *CYP1A1* and *CYP1A2* genes variants in cases and controls. Pattern of Linkage Disequilibrium (LD) in CYP1A region using the Four Gamete Rule implemented in HaploView software program. Standard color scheme of Haploview was applied to display LD. The different shades of gray indicate different D values. The darker the grey shading, the larger the ID'I. D' × 100 are shown in each cell. D' values of 100 are taken as the strongest and the value will get displayed

exhibit variations in expression caused by genetic and epigenetic mechanisms [32–36]. Vrzal et al., (2004) and Congiu et al., (2009) reported that under pathophysiological conditions, such as inflammation processes, the level and activity of *CYP1A2* is decreased [37, 38]. The CYP1A gene cluster was discovered on

Table 6 Distribution of cumulative risk alleles of *CYP1A1*, *CYP1A2* and *GSTP* genes in cases with allergic CRS, and allergic CRS with asthma and controls

Risk alleles	Controls	Allergic CRS without asthma			Allergic CRS with asthma		
	n (n%)	n (n%)	Odds Ratio (95% CI)	*p*-value	n (n%)	Odds Ratio (95% CI)	*p*-value
0	21 (6)	12 (4.8)	1 (reference)		8 (3.6)	1 (reference)	
1–2	137 (39.1)	59 (23.4)	0.74 (0.34–0.60)	0.447	40 (17.9)	0.77 (0.32–1.86)	0.557
3–4	163 (46.6)	116 (46.0)	1.22 (0.58–2.59)	0.597	86 (38.4)	1.38 (0.59–3.26)	0.455
5–6	25 (7.1)	53 (21.0)	3.64 (1.55–8.56)	0.003**	72 (32.1)	7.56 (2.97–19.21)	≤ 0.001***
> 6	4 (1.1)	12 (4.8)	5.25 (1.38–19.96)	0.015*	18 (8.0)	11.81 (3.04–45.80)	≤ 0.001***

OR Odds ratio, *CI* Confidence interval, OR obtained after Multinomial logistic regression analysis

Significance of ****p*-value ≤ 0.001

***p*-value ≤ 0.01, **p*-value ≤ 0.05

chromosome 15q24.1, with a close relationship between the CYP1A1 and 1A2 genes. *CYP1A1* and *1A2* are highly inducible at both mRNA and protein levels by a number of environmental factors such as chemicals, drugs, smoking, and several dietary factors and may lead to the development of respiratory diseases [3]. Human CYP1A2 is a key hepatic metabolising enzyme, accounting for roughly 13% of all CYP proteins that metabolise a variety of drugs, natural substances, and other compounds. According to a recent pathway-based analysis in human liver samples, CYP1A2 genetic variation may account for catalytic activity, protein expression, and mRNA levels [4, 5].

CYP1A1 T3801C rs4646903 located in the 3′ noncoding region is reported to influence gene function and *CYP1A1* rs1048943 and *CYP1A1* rs1799814 located in exon 7 resulted in elevated enzymatic activity. *CYP1A2* rs762551 polymorphism was also reported to increase enzyme activity and inducibility while *CYP1A2* rs2069514 and *CYP1A2* rs2069526 gene variants were associated with the decreased CYP1A2 activity [4, 6]. Findings of the present study have revealed a significant association of *CYP1A2* rs2069526 in allergic CRS subjects with and without asthma. Further, the haplotype analysis also revealed that G-G-C combination of *CYP1A2* rs2069514, rs2069526 and rs762551 to increase the risk of asthma (5.5 folds) in allergic CRS subjects which might be due to decreased enzymatic activity. Hence, promoter variants of *CYP1A2* seem to play a vital role in the development of asthma in allergic CRS subjects. With regard to *CYP1A1* rs4646903, rs1048943 rs1799814 variants, no association was observed with asthma in allergic CRS subjects. Similarly, studies carried out on Caucasians, Japanese and Serbians also failed to confirm its role in COPD [35–38]. However, earlier studies on Japanese and Indian populations have shown CYP1A1 rs1048943 variant to be associated with COPD [39, 40] indicating discrepancy in the role of CYPIA1 polymorphism in respiratory disorders.

The *GSTM1*, *GSTT1*, and *GSTP1* genes are mapped to chromosome 1p13.3, 22q11.23 and 11q13 respectively. The *GSTP1* A313G and C341T gene variants leads to the substitution of Ile105Val and Ala114Val amino acids located near the substrate-binding site and alter catalytic activity of the *GSTP1* [4, 5]. GSTP plays an important role in neutralizing oxidative stress in response to environmental and allergen exposures. GSTP1 is more abundant in alveoli, alveolar macrophages, and respiratory bronchioles, and it may play an important role in lung detoxification [41, 42]. Missense mutations in the GSTP1 gene (Ile105Val and Ala114Val) can result in decreased detoxification of airway irritants, which increases inflammation and oxidative stress and causes airway dysfunction [43]. Previous research indicates that patients with the GSTP1 rs1605 AA genotype can quickly eliminate reactive oxygen species and have lower levels of oxidative DNA damage [41]. A protective effect of the Val105 *GSTP1* rs1605 polymorphism in allergic inflammation has been reported in Korean population [44]. No correlation was observed between *GSTP1* rs1605 polymorphism and CRS with and without nasal polyps and COPD [44–49]. Interestingly, in the present study, the *GSTP1* rs1605 Val105 allele showed a significant risk of asthma in allergic CRS subjects. Similarly, studies on COPD in Indian, Tunisian and Russian populations also reveled 105Val allele as a significant risk factor for COPD [40–42].

The inability of the GSTM1 null genotype to detoxify polycyclic aromatic hydrocarbons has been linked to lung cellular and tissue damage caused by an excess of oxidants and free radicals [41]. According to Cheng

et al. (2006), GSTM1-null genotype is an independent risk factor for developing severe COPD [44]. The present study, also finds *GSTM1* to show a strong significant association in both allergic CRS subjects with and without asthma but could not find any association of *GSTT 1* null genotype. The study is also in agreement with the studies carried out by Arbag et al., 2006 in the Turkish population and Fruth et al., 2011 in German population which did not find any significant association of *GSTT1* null genotype with and without nasal polyposis in CRS [45, 46]. However, a significant protective effect of *GSTT1* null genotype was reported in allergic rhinitis patients in a study conducted by Iorio et al., (2012) while Mak et al., (2007) reported *GSTM1* null genotype to be protective in the development of atopic asthma [50, 51]. Combined deletion variants of the GSTM1 and GSTT1 genes were found to be a risk factor for the development of asthma in children and adults, as well as a risk factor for the development of nasal polyposis and hyposmia in allergic individuals [52]. Similarly, in the present study the *GSTM1*/*GSTT1* double null genotype was found to be significantly associated with asthma in allergic CRS subjects. Also, risk contributed by double null genotype was higher (2.8 vs 1.9 folds) than the risk attributed by *GSTM1* null indicating its additive contribution for risk of asthma in allergic CRS subjects. However, no association between *GSTM1* and *GSTT1* double null genotype was observed with allergy, CRS, asthma, and COPD [45, 46, 53].

Interactions of several XME genes were reported to be associated in the present study with risk of asthma indicating the polygenic basis of asthma [54]. The results of cumulative genetic risk allele score predicted a high number of risk alleles in both the allergic subgroups when compared to controls indicating genetic susceptibility to allergic CRS with and without asthma. The cumulative risk contributed by risk alleles in allergic CRS with asthma was higher when compared to CRS without asthma. Also, the absence of protective alleles and allelic combinations might have promoted for the development of asthma. It is also reported that each locus could also be in linkage disequilibrium with an unknown casual gene(s) [45]. Further, it is reported that inter-individual differences due to genetic variation, linkage disequilibrium (LD), gene–gene and gene-environment interactions may be responsible for the complexity of allergic phenotypes. Further, the LD analysis in the present study has also revealed close linkage between *CYP1A1* and *CYP1A2* which is in agreement with earlier studies in Asian population [55–58]. However, LD of these gene variants varied between the allergic CRS subjects with and without asthma which might contribute to the altered enzyme activity.

Conclusion

The allelic, genotypic, haplotype frequencies and linkage disequilibrium of *CYP1A2* gene are the first to be reported in South Indian population and allergic CRS in particular. Findings of the present study revealed a significant association of CYP1A2 and GST gene variants with asthma in allergic CRS individuals. Future studies are warranted to delineate on the functional analyses of these genes and gene–gene and gene environment interactions leading to asthma in allergic CRS.

Abbreviations

aCRS	Allergic chronic rhinosinusitis
CGRS	Cumulative genetic risk score
COPD	Chronic obstructive pulmonary disease
CRS	Chronic rhinosinusitis
CYP1A1	Cytochrome P450 1A1
CYP1A2	Cytochrome P450 1A2
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunoassay
EDTA	Ethylene diamine tetraacetic acid
EP^3OS	European position paper on rhinosinusitis and nasal polyps
FDR	False discovery rate
FEV1	Forced expiratory volume 1
GA^2LEN	Global Allergy and Asthma European Network
GINA	Global Initiative for Asthma
GST	Glutathione-S-transferase
HWE	Hardy–Weinberg equilibrium
LD	Linkage disequilibrium
NAT	*N*-Acetyl transferase
PCR	Polymerase chain reaction
RFLP	Restriction fragment length polymorphism
XME	Xenobiotic metabolizing enzymes

Acknowledgements

The authors would like to thank MAA Research Foundation for the funding and Ms. B. Sunita G Kumar, CMD, MAA ENT Hospitals, Hyderabad for her support and cooperation in carrying out the work. We would also thank B.Bharathwaj, B.Rajesh, J.V. Ramakrishna, D. Dinesh, Kevin and I. Krishna Kishore in providing valuable support in carrying out the work. The author Madhavi Jangala thank ICMR for funding in the form of SRF.

Author contributions

MJ has designed the work and was involved in acquisition, analysis and interpretation of data. SKM was involved in acquisition and analysis of the data. MMK has assisted with the preparation of the manuscript content. RMK has contributed to the conception and drafted the work. JA has contributed to the conception and substantively revised and approved the submitted version of the manuscript. All authors read and approved the final manuscript.

Funding

Author JM has received Senior Research Fellowship from ICMR, New Delhi, India.

Availability of data and materials

The data that support the findings of this study are not openly available as the data will be used for further studies being carried out at the MRF and are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by Institutional Ethics Committee at Institute of Genetics and Hospital for Genetics Diseases and the consent for participation was taken from all the study subjects.

Consent for publication
Consent to publish was obtained.

Competing interests
The author declares that they have no competing interests.

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Received: 26 July 2022 Accepted: 14 February 2023
Published online: 07 March 2023

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