Original Article

Segregation analysis of mandibular prognathism in Korean orthognathic surgery patients and their families

Jeong-Min Ko^a; Young Ju Suh^b; Jongrak Hong^c; Jun-Young Paeng^d; Seung-Hak Baek^e; Young Ho Kim^t

ABSTRACT

Objective: To investigate the existence of genetic influences on the incidence of mandibular prognathism (MP) in Korean Class III patients.

Materials and Methods: The probands consisted of 100 Class III patients with MP (51 men and 49 women; mean age, 22.1 \pm 5.2 years; SNA, 81.2° \pm 3.2°; SNB, 84.1° \pm 3.9°) who underwent orthognathic surgery. Using three-generation pedigree charts, questionnaires, and clinical examinations, general information and information regarding MP for a total of 3777 relatives of the probands (1911 men and 1866 women) was ascertained. Familial correlations of MP between possible pairs in the pedigree were estimated. Heritability (*h*²) of MP under various models was estimated. Segregation analysis was conducted under the assumption of the nonpolygenic multivariate logistic model and finite polygenic mixed model. One-, two-, and three-susceptibility-type models were evaluated.

Results: Among 3777 relatives, 199 (97 men and 102 women) were affected with MP (5.3%). Correlation coefficients of MP incidence in full siblings and in parent-offspring were .2003 and .2036, respectively (all P < .001). The h^2 of MP was estimated as 21.5% after adjusting for sex and founder effects. Two- and three–susceptibility-type models showed that the general model fit better than the other models. MP incidence did not have a major gene transmission model and was influenced by numerous minor effect genes and their additive effects.

Conclusion: These results suggest that the inherited susceptibility to MP in Korean Class III patients might be due to the summation of minor effects from a variety of different genes and/or influence of environmental factors, rather than Mendelian transmission of major genes. (*Angle Orthod.* 2013;83:1027–1035.)

KEY WORDS: Segregation analysis; Mandibular prognathism; Class III malocclusion; Korean

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INTRODUCTION

Although a wide range of environmental factors can exist, Class III malocclusion is thought to mainly develop by genetic influence. Schulze and Weise¹ suggested a strong genetic role in mandibular prognathism (MP) in a twin study, which revealed that monozygotic twins have a sixfold higher chance of having MP than dizygotic twins.

There are several things to consider regarding the inherited susceptibility to MP in Class III malocclusion. First, the prevalence rate of MP is known to vary according to ethnicity. Hardy et al.,² in a meta-analysis, reported that East Asians have the highest prevalence

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		Probands	
Cephalometric Parameters	Men (n = 51)	Women (n = 49)	Total (n = 100)
Sagittal relationship			
Maxilla			
SNA, $^{\circ}$	80.8 ± 3.2	81.8 ± 3.1	81.2 ± 3.2
Mandible			
SNB, °	84.5 ± 3.8	83.6 ± 4.1	84.1 ±.3.9
Intermaxillary relationships			
ANB, °	-3.7 ± 2.2	-2.1 ± 3.5	-2.9 ± 3.0
Wits appraisal, mm	-12.5 ± 3.9	-10.8 ± 5.3	-11.7 ± 4.7
Vertical relationship			
FMA, °	27.6 ± 6.1	28.8 ± 6.4	28.2 ± 6.2

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Table I.	Cephalometric	Characteristics	OI	Probanusa

^a This table was reorganized using the data from Kim et al.¹⁹

of MP, with approximately 18.0%, and are followed by Middle Easterners, Europeans, and South Asians, who have the lowest prevalence (1.2%). Second, skeletal Class III malocclusion can be divided into subtypes. Bui et al.³ classified skeletal Class III patients into five subtypes, which suggests that different genes might be involved in each subtype. Third, association between diverse genes and MP suggests that MP might be a complex disease. Recent advances in genetics and molecular biology have found several candidate loci for MP, such as 1p35-36, 6q25, 19p13, and 5p13 for Koreans and Japanese,⁴⁻⁸ 1p36, 4p16, and 14q24-31 for Han Chinese,⁹⁻¹² and 1p22, 3g26, 11g22, 12g13, and 12q23 for Hispanics.¹³ Some genes located within these loci are suspected to have a role in susceptibility to MP (perlecan, cartilage matrix protein 1, alkaline phosphatase, erythrocyte membrane protein band 4.1, growth hormone receptor, transforming growth factor beta 3, latent transforming growth factor beta binding protein 2, Ellis-van Creveld syndrome protein (EVC), EVC2, insulin-like growth factor 1, homeobox HOXC genes, and collagen type II alpha 1).4-13

Segregation analysis is useful for investigating the existence of major genes using the phenotype information gained from pedigrees of probands and for determining the best inheritance model that can explain the variation of phenotypes.^{14,15} Segregation analysis of MP has been conducted in only two ethnic groups: 37 Libyan families¹⁶ and 55 Brazilian families.¹⁷ These investigations suggested that MP has an autosomal dominant inheritance with or without incomplete penetrance. Interestingly, although Yamaguchi et al.⁵ reported that three markers (D1S234, D6S1689, and D19S566) were associated with MP in Koreans/ Japanese, a follow-up study of Cruz et al.¹⁸ showed that these markers did not have any evidence of linkage in the Brazilian population. These findings imply that different genes might be involved in the etiology of skeletal Class III malocclusion for between Brazilian and Korean/Japanese.

It is necessary to perform a complex segregation analysis of Korean MP patients and their families, who belong to a homogeneous ethnic group and have the highest MP prevalence compared to other ethnic groups. Some authors of this study performed a preliminary study to estimate the affected ratio of the families and the heritability in Korean orthognathic patients and their families (100 probands, 2729 relatives; affected ratio, 3.5%; heritability (h^2), 29.8%).¹⁹ However, it is still necessary to estimate familial correlations between possible pairs in the pedigree, to adjust sex and founder effect on heritability, and to perform segregation analysis. We also recruited additional pedigree members of the same probands to get more information from relatives and to increase the statistical power. Therefore, the purpose of this study was to investigate the existence of genetic influences on the epidemiologic incidence of MP in Korean Class III patients and their families using segregation analysis.

MATERIALS AND METHODS

Probands and Their Skeletal Characteristics

The probands of this study consisted of 100 skeletal Class III patients with MP (51 men and 49 women; mean age, 22.1 \pm 5.2 years) who underwent orthognathic surgery at Samsung Medical Center in Seoul, Korea. All probands were diagnosed by cephalometric analysis as severe MP with no or mild maxillary retrusion (Table 1). Although the anteroposterior position of the maxilla (SNA, 81.2° \pm 3.2°) and vertical pattern (FMA, 28.2° \pm 6.2°) were within the Korean norm, the mandible was positioned forward (SNB, 84.1° \pm 3.9°) beyond the Korean norm. The values of ANB (-2.9° \pm 3.0°) and Wits appraisal



Figure 1. Pedigree chart and questionnaire used in this study. It was reorganized using the Pedigree chart and questionnaire from Kim et al.¹⁹

 $(-11.7 \pm 4.7 \text{ mm})$ revealed skeletal Class III relationships. The general or medical conditions that are related to MP or that might have affected the outcome of this study were excluded.

Family Members

The participants included additional pedigree members of the same probands recruited in a previous preliminary study.¹⁹ As a result, 3777 relatives (1911 men and 1866 women) of the 100 probands belonging to at least three generations were included in the present study. Pedigree charts and questionnaires were designed to elicit information about probands and relatives (age, sex, and subtype of Class III malocclusion; Figure 1).¹⁹ Photographs and a clinical examination were used to determine whether each family member was affected with MP.

Familial Correlation and Heritability

Intraclass correlation coefficients of MP were estimated to evaluate familial correlations between possible pairs in the pedigree using S.A.G.E. software version 6.1 (http://darwin.cwru.edu/sage/). There were 779 spouse pairs, 4318 parent-offspring pairs, and 3886 full sibling pairs.

Heritability (h^2) of MP was estimated from variance components models using the Sequential Oligogenic Linkage Analysis Routines (SOLAR) software package version 4.3.1 (http://www.txbiomed.org/departments/ genetics/genetics-detail?p=37). Estimated h^2 of MP was adjusted for sex and founder effects. The bestfitting model, whose variance was partitioned into additive genetic (A), unique environmental (E), or unmeasured shared environmental (C) components, was selected using the likelihood ratio test.

Segregation Analysis

To explore the mode of familial transmission of susceptibility to MP, complex segregation analysis of MP was conducted with the SEGREG program of the SAGE package. The segregation models can be classified according to the number of underlying susceptibility types in the model: one susceptibility type (no segregation), two susceptibility types (dominant or recessive, if there is Mendelian segregation), and three susceptibility types.²⁰

Two general analysis methods for segregating models were assumed. The first model was a nonpolygenic multivariate logistic model. This model is implemented for pedigree data by making the regressive model assumption that the likelihoods of the trait and the major type of individual for two nuclear families are independent. The second model was a finite polygenic mixed model, which assumes that the logit of susceptibility is influenced by a small number of additive diallelic loci in addition to possible segregation at a single major locus with a large effect.

Ethics Statement

The study protocol was reviewed and approved by the Institutional Review Board of Samsung Medical Center (IRB 2006-08-023). Informed consent was received from each subject.

RESULTS

Affected Ratios of Relatives of 100 Probands

Among 3777 relatives, 199 were affected with MP (5.3%). Sex distribution was 97 males (48.7%) and 102 females (51.3%).

Table 2.	Familial Correlations	of the Mandibular	Prognathism (MP) Between Possib	le Pairs of Famil	v Members ^a
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	Number of Pairs	ICC \pm SE (95% CI)	P Value
Full siblings Parent-offspring	3886 4318	.2003 ± .0254 (.1749–.2257) .2036 ± .0177 (.1859–.2213)	< .001 < .001
Spouse	779	0271 ± .0355 (06260084)	.4467

^a ICC indicates intraclass correlation coefficient; SE, standard error; CI, confidence interval.

Familial Correlation

The intraclass correlation coefficient values of MP (Table 2) in full sibling pairs and in parent-offspring pairs were .2003 and .2036, respectively (all P < .001). However, the correlation estimate of MP incidence in spouses was not significant.

Heritability

Although the ACE model fit better than the AE model (P < .05), the h^2 estimate of the ACE model (21.5%) was lower than that of the AE model (22.8%) after adjusting for sex and founder effects (Table 3).

One-Susceptibility-Type Models

The purposes of one-susceptibility-type analysis were to investigate whether covariates existed and which covariate should be included. According to the Akaike information criterion (AIC)²¹ value and the likelihood ratio test (Table 4), sex and founder status were included as covariates in subsequent segregation analyses.

In addition, one-susceptibility-type analysis can determine which kind of familial association exists. When compared to various other familial associations, the AIC value of the three separate familial association coefficients (father-offspring, mother-offspring, sibling-sibling; δ_{-} fo, δ_{-} mo, δ_{-} ss) was the lowest (1364.99; Table 5). Therefore, three separate familial associations were used in the subsequent segregation analyses.

Two-Susceptibility-Type Models

The purpose of the two-susceptibility-type model was to investigate whether Mandelian dominant or

recessive effects existed or not. All of the nonpolygenic multivariate logistic models (environmental-no-transmission, Mendelian dominant, and Mendelian recessive) and the finite polygenic mixed models (environmental-plus-polygenic, Mendelian dominant, and Mendelian recessive) were significantly different from the general model (all P < .001; Table 6). Since the general model showed a lower AIC than the other models, it can be regarded as a better fit model. These findings imply that the transmission of a potential major genetic effect for MP could not be confirmed.

Three-Susceptibility-Type Models

All of the nonpolygenic multivariate logistic models (environmental-no-transmission and Mendelian additive transmission) and the finite polygenic mixed models (environmental-plus-polygenic transmission and Mendelian additive transmission) were significantly different from the general model (all P < .001; Table 7). These findings indicate that the general model was a better fit (with a lower AIC) than the other models. However, when considering the AIC values, the Mendelian additive transmission was better than the environmental-no-transmission and the environmental-plus-polygenic transmission.

In conclusion, two- and three-susceptibility-type models showed that the general model was a better fit than the other models. Korean MP incidence did not have a major gene transmission model and was influenced by numerous minor effect genes and their additive effects.

DISCUSSION

The affected ratio of the relatives of Korean MP patients in this study was 5.3% (199/3777), which is

Table 3. Heritability (h^2) Estimates of the Mandibular Prognathism^a

<i>h</i> ² ± SE (95% CI)			Variance Component				
Crude (95% CI)	P Value	Adjusted for Gender and Founder Effects	P Value	А	С	E	Model
0.2116 ± 0.0148 (0.1968–0.2264)	<.0001	$0.2146\pm0.0154(0.19920.2300)$	<.0001	0.2146	0.0256	0.7598	ACE⁵
0.2250 ± 0.0135 (0.2115–0.2385)	<.0001	$0.2283\pm0.0140\;(0.21430.2423)$	<.0001	0.2283	—	0.7717	AE

^a SE indicates standard error; CI, confidence interval. Components of the variance component model after adjusting for gender and founder effects: A indicates additive genetic component; C, unmeasured shared environmental component; E, unique environmental component.

^b Selected between ACE and AE models using likelihood ratio test.

	Covariates in the Model				
Parameter	No Covariate	Sex	Founders	Sex and Founders	
β (SE)	-2.87 (0.07)	-2.88 (0.07)	-3.23 (0.12)	-3.24 (0.12)	
ξ_sex (SE) ^ь	_	0.05 (0.15)		0.06 (0.15)	
ξ_founders (SE)°	_	_	-2.11 (0.34)	-2.11 (0.34)	
$-2 \ln(L)$	1498.60	1498.50	1427.22	1427.07	
d.f.	1	2	2	3	
P value*	<i>P</i> < .001	P < .001	0.699		
AIC	1500.60	1502.50	1431.22	1433.07	

Table 4. Parameter Estimates in the One-Susceptibility-Type Models with and Without Covariates

^a The logit of the susceptibility formula, $y = \beta + \xi_1 x_1 + \xi_2 x_2 + ... + \xi_p x_p$, where β is the intercept value and ξ is the covariate regression coefficients. AIC indicates Akaike information criterion,²¹ which is defined as $2 \ln(L) + 2k$ (where *L* is the maximum of the likelihood function for the estimated model and *k* is the number of parameters estimated in the model). The model with the smallest AIC is determined to be the best-fit model. d.f. indicates degrees of freedom. *L* in $-2 \ln(L)$ is the maximum of the likelihood function for the estimated model.

^b Sex value for male is 0 and for female is 1.

 $^{\circ}$ Founder value for founder is 1 and for nonfounder is 0.

* Compared with the full model including both sex and founder as covariates.

similar to that in Lee et al.²² (4.5%; Table 8). However, these affected ratio values are lower than those of Japanese MP relatives (34.5% in Suzuki23 and 11.2% in Watanabe et al.24; Table 8). Although Koreans and Japanese are both East Asians, Koreans have lower affected ratios than Japanese. Since these Japanese studies had a relatively smaller number of relatives compared to probands than the present study (relatives vs probands: 1119 vs 243 for Suzuki,23 1480 vs 105 for Watanabe et al.,²⁴ 3777 vs 100 for this study; Table 8), this might account for the higher values of the affected ratio than that of Korean patients. In addition, Brazilian MP patients showed a 14.3% affected ratio (Table 8),17 which is higher than the 5.3% of this study. These results imply that different ethnic backgrounds can result in different affected ratios and prevalence of MP.

The estimated heritability of MP in our subjects ($h^2 = 21.5\%$) is lower than the 84.3% reported by Watanabe et al.²⁴ and the 31.6% reported by Cruz el al.¹⁷ (Table 8), which suggests that MP might have a weak heritability in the families of Korean MP patients. Not only the difference in sample selection criteria and ratio of probands and relatives but also the variation of genetic traits and transmission pattern may affect the estimation of this value. In addition, since the relatives of MP patients might consider mild MP as normal, a more accurate classification method for MP and training of both investigators and participants are required for further studies.

Most of the complex diseases influenced by multiple genes can be classified into several subtypes. Various subtypes in skeletal Class III malocclusion occur because of the anteroposterior position of the maxilla,

 Table 5.
 Parameter Estimate in the One-Susceptibility-Type Models, Incorporating Various Residual Familial Associations by the Multivariate Logistic Model multivariate logistic model^a

		Familial Association Components					
Parameter	$\delta_fo = \delta_mo = \delta_ss = 0$	$\delta_fo = \delta_mo = \delta_ss$	$\delta_{fo} = \delta_{mo}, \delta_{ss}$	$δ_{fo}$, δ_{mo} , δ_{ss}			
β	-3.24 (0.12)	-3.13 (0.12)	-3.12 (0.12)	-3.13 (0.12)			
ξ_sex ^b	0.06 (0.15)	0.07 (0.15)	0.07 (0.14)	-0.02 (0.15)			
ξ_founders°	-2.11 (0.34)	-2.01 (0.34)	-2.05 (0.35)	-2.11 (0.36)			
δ_fo	0	1.58 (0.20)	1.35 (0.34)	0.30 (0.46)			
δ_mo	0	1.58 (0.20)	1.35 (0.34)	1.90 (0.38)			
δ_ss	0	1.58 (0.20)	1.74 (0.28)	1.81 (0.27)			
$-2 \ln(L)$	1427.07	1359.17	1358.53	1352.99			
d.f.	3	4	5	6			
P value*	<.001	0.046	0.019	—			
P value**	<.001	0.726		_			
AIC	1433.07	1367.17	1368.53	1364.99			

^a Father-mother association ($\delta_{fm} = 0$) was set to 0 because of insufficient data for estimation; δ_{fm} indicates father-mother residual association; δ_{f0} , father-offspring; δ_{m0} , mother-offspring; δ_{ss} , sibling-sibling. See the footnote to Table 4 for descriptions of the remaining parameters.

^b Sex value for male is 0 and for female is 1.

 $^\circ$ Founder value for founder is 1 and for nonfounder is 0.

* Compared with model ($\delta_{fo}, \delta_{mo}, \delta_{ss}$).

** Compared with model ($\delta_{fo} = \delta_{mo}, \delta_{ss}$).

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Parameter	Environmental-No- Transmission	Mendelian Dominant Transmission	Mendelian Recessive Transmission	General
Nonpolygenic Multivari	ate Logistic Model multivariate log	gistic model		
βΑΑ	-3.24	1.25	-3.74	-15.08
β_ AB	-3.24	1.25	1.25	-15.08
β_ BB	-3.24	-3.74	1.25	20.68
ξ_sex	0.06	0.09	0.09	0.39
ξ_founders	-2.11	-2.71	-2.71	-36.73
g A	_	$8.27 imes10^{-3}$	$3.40 imes10^{-3}$	$5.61 imes 10^{-3}$
τ_ΑΑ	_	1	1	0.3
τ_AB	_	0.5	0.5	0
τ_BB	_	0	0	1
$-2 \ln(L)$	1427.07	1349.44	1349.44	1012.93
d.f.	3	5	5	8
P value*	<.001	<.001	<.001	_
AIC	1433.07	1359.44	1359.44	1024.93
	Environmental-Plus-	Mendelian Dominant	Mendelian Recessive	
	Polygenic	Transmission	Transmission	
Finite Polygenic Mixed	Model finite polygenic mixed mod	del		
β_ AA	3.09	1.30	-3.85	2.65
β_ AB	3.09	1.30	1.30	2.65
β_BB	-8.45	-3.85	1.30	-11.79
ξ_sex	0.76	0.09	0.09	0.18
ξ_founders	-7.28	-2.78	-2.78	9.74
σ_3^2	0	0.22	0.22	0
q_A	$3.49 imes10^{-2}$	$8.20 imes10^{-3}$	$9.92 imes10^{-1}$	$1.70 imes10^{-3}$
τ_ΑΑ	—	1	1	1
τ_AB	—	0.5	0.5	1
τ_BB	—	0	0	0.05
$-2 \ln(L)$	1426.24	1349.27	1349.27	1251.42
d.f.	6	6	6	9

Table 6. Analysis of MP with Two Susceptibility Types^a

^a q_A indicates the frequency of the allele A in the population when Hardy-Weinberg equilibrium is assumed; τ , transmission parameter (the probability that a parent transmits allele A to offspring); σ_3^2 , the variance of the polygenic effect incorporating three polygenic loci. See the footnote to Table 4 for descriptions of the remaining parameters.

<.001

1361.27

* Compared with the general model.

P value' AIC

mandible, or combination of the maxilla and mandible, and differences in the vertical components.25 The ratios of these subtypes are expected to be different according to family and ethnic groups. Moreover, similar Class III malocclusion subtypes could have originated from different etiologies. The typical inheritance example of a certain Class III malocclusion subtype is the so-called "Habsburg Jaw." Analysis of the skull of Joanna of Austria, a member of the Habsburg Royal family, revealed that a retrognathic maxilla rather than a prognathic mandible is a transmitted trait of this family.²⁶ This finding suggests that different genes can be involved in the distinct subtypes of Class III malocclusion. Therefore, it is preferable to use the classified subtypes of Class III malocclusion to reveal the effects of genetic and environmental influences and their interactions on the cause of MP.

<.001

1436.24

In segregation analysis of Class III malocclusion on 37 Libyan families, El-Gheriani et al.¹⁶ concluded that the autosomal-dominant model is the best fit. However, they did not differentiate the subtypes of Class III malocclusion (for example, MP and maxillary retrusion; Table 8). Therefore, their results could have originated from a mixture of Class III subtypes that might have different etiologic factors. In contrast, this study evaluated only the MP subtype of Class III malocclusion, and included more than 3.5 times the number of probands than El-Gheriani et al.¹⁶ (Tables 2 and 8). Nevertheless, we could not find any significant major gene inheritance model after analysis of 3777 relatives (Tables 4–7).

<.001

1361.27

Cruz et al.¹⁷ also performed a segregation analysis on 55 Brazilian families with 2562 relatives. Their study was similar to this study in terms of the subject number and the recruited subtype of Class III malocclusion

Table 7.	Analysis	of MP	with	Three	Susce	otibility	Types
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Parameter	Environmental-No-Transmission	Mendelian Additive Transmission	General	
Nonpolygenic Multivariate L	ogistic Model multivariate logistic model			
β_ΑΑ	-3.24	6.14	-14.58	
β_ AB	-3.24	1.20	-62.73	
β_BB	-3.24	-3.73	20.77	
ξ_sex	0.06	0.09	0.39	
ξ_founders	-2.11	-2.70	-36.86	
q_A	_	$3.40 imes10^{-3}$	$2.95 imes10^{-3}$	
τ_ΑΑ	_	1	$4.21 imes10^{-5}$	
τ_AB	_	0.5	$5.80 imes10^{-3}$	
τ_BB	_	0	$5.84 imes10^{-3}$	
-2 ln(<i>L</i>)	1427.07	1349.37	987.55	
d.f.	3	5	8	
P value*	<.001	<.001	—	
AIC	1433.07	1359.37	1001.55	

Environmental-Plus-Polygenic Mendelian Additive Transmission

Finite Polygenic Mixed Model finite polygenic mixed model				
β_ΑΑ	45.40	6.34	7.61	
β_ AB	1.78	1.25	-18.03	
β_ BB	-41.45	-3.85	-116.49	
ξ_sex	0.89	0.09	0.21	
ξ_founders	-5.75	-2.76	24.35	
σ_3^2	0	0.23	0	
q_A	$3.69 imes10^{-2}$	$8.30 imes10^{-3}$	$1.96 imes10^{-2}$	
τ_ΑΑ	—	1	1	
τ_ΑΒ	_	0.5	1	
τ_ΒΒ	—	0	0.22	
-2 ln(<i>L</i>)	1426.24	1349.19	1214.58	
d.f.	6	6	9	
P value*	<.001	<.001	—	
AIC	1438.24	1361.19	1228.58	

^a See Tables 4–6 for parameter descriptions.

* Compared with the general model.

(only MP; Table 8). They reported that the autosomal dominant inheritance model with incomplete penetrance can explain the familial transmission of MP traits. However, they did not investigate three susceptibility

type models and multiple additive polygenic effects. Therefore, the variation in inheritance patterns between their study and ours may be partly due to different statistical approaches.

Table 8. Summary of the Results from Previous Studies on Class III Malocclusion^a

References	Ethnicity	Number of Relatives/ Probands ^b	Class III Subtype	e Affected Ratio	Heritability	Inheritance Model	Remarks
Suzuki ²³	Japanese	1119/243	Class III	34.3%	_	_	_
Watanabe et al.24	Japanese	1480/105	MP only	11.2%	84.3%	_	_
Lee et al.22	Korean	3485/103	Class III	4.5%	_	_	_
El-Gheriani et al.16	Libyan	976/37	Class III	_	_	Autosomal dominant model	Segregation analysis
Cruz et al. ¹⁷	Brazilian	2507/55	MP only	14.3%	31.6%	Autosomal dominant (incomplete penetrance)	Segregation analysis
This study	Korean	3777/100	MP only	5.3%	21.5%	No major gene model	Segregation analysis

^a MP indicates mandibular prognathism.

^b These values are recalculated from the original articles.

According to the subsequent linkage analysis of Cruz et al.,¹⁸ the loci that are mapped to be connected with Korean/Japanese MP had no evidence of linkage with Brazilian families. Because they reported that Brazilian MP can be transmitted with the autosomal dominant mode in their previous study,¹⁷ this may suggest that Koreans and Brazilians have different genes, leading to different modes of transmission for MP, which caused the divergence in inheritance models.

The findings that the Korean population had a low affected ratio (5.3%) and relatively weak heritability (21.5%) of MP compared to other ethnic groups (Tables 2 and 8) and that no major gene transmission model was proven (Tables 4–7) might imply that the inheritance of MP in Korean Class III patients is likely influenced by numerous minor effect genes and their additive effects. Further studies are needed to verify these findings.

This study using segregation analysis of Korean MP patients and their families did not support the results from the studies of Libyans and Brazilians, which reported Mendelian autosomal dominant inheritance of MP.^{16,17} Increase in the sample size, establishment of the distinct subtypes in probands and relatives, comparison with different ethnic groups, and application of more sophisticated statistical methods may help to reveal genetic backgrounds underlying the etiology of skeletal Class III malocclusion more clearly. These investigations can provide more plausible models for inheritance and susceptibility genes of skeletal Class III malocclusion, and may help to find a prediction method, biologic marker, and cure for MP.

CONCLUSION

• The inherited susceptibility to MP in Korean Class III patients might be due to the summation of minor effects from a variety of different genes and/or influence of environmental factors, rather than Mendelian transmission of major genes.

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