Original Article

Epidemiology and genetics of hypodontia and microdontia: *A study of twin families*

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ABSTRACT

Objective: To identify genetic and environmental factors contributing to hypodontia and microdontia by using Korean twin family data.

Materials and Methods: A total of 1267 individuals (525 men and 742 women; 180 monozygotic twins [MZ] and 43 dizygotic twins [DZ] from 282 families) underwent an oral examination as part of the Healthy Twin Study in Korea. Dental anomalies classified as hypodontia or microdontia were diagnosed using radiographs and clinical examinations. In order to estimate genetic contributions to dental anomalies, we estimated the pairwise concordance rate (PCR), recurrence risk ratio (RRR), and heritability (h2).

Results: The prevalence of hypodontia and microdontia was 3.55% and 3.00%, respectively. MZ had the highest PCR and RRR (13.0–15.3). The PCR and RRR values for both anomalies were much higher for DZ (5.0–11.9) than for siblings (1.4–2.6), despite the fact that DZ pairs and sibling pairs share 50% genetic identity. Further genetic analysis revealed both an additive genetic effect (0.38 when hypodontia and microdontia were pooled) and a strong "twin effect" (0.52 when hypodontia and microdontia were pooled).

Conclusions: This twin-based study revealed that the formation of dental anomalies is affected by both genetic and environmental factors, and that the impact of these factors varies according to the specific dental anomaly. (*Angle Orthod.* 2015;85:980–985.)

KEY WORDS: Microdontia; Hypodontia; Korean twins; Genetics

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Accepted: November 2014. Submitted: May 2014.
Published Online: December 22, 2014

INTRODUCTION

Dental anomalies cause malocclusions by disturbing normal dental development.[1] Developmental dental anomalies such as hypodontia and microdontia are not uncommon in many populations, but little is known about their underlying causes.[2,3]

The prevalence rates of these anomalies varies across populations; previous studies have reported a prevalence as low as 2.3% and as high as 11.3%.[4–6] Substantial differences in frequency may at least partly be explained by study design, and a population-based study is more likely to determine the true frequency of these anomalies.[7–10]

Twins can be either identical or fraternal. Identical twins, or monozygotic twins (MZ), share 100% of their genetic information, whereas fraternal twins, or dizygotic twins (DZ), result from two egg cells each fertilized by a different sperm. Genetically, DZ are normal siblings, sharing approximately 50% of their genetic information.

The Healthy Twin Study of Korea has recruited families representing the general population of Korea.[11] Recruitment of both MZ and DZ as well as

nontwin siblings has endowed the study with the ability to perform high-resolution analysis of the contribution of genetic and environmental parameters to phenotypes of interest.

Because hypodontia and microdontia are the most common types of dental anomalies,[12–14] we assessed genetic contributions to these phenotypes by calculating the pairwise concordance rate (PCR), recurrence risk ratio (RRR), and heritability (h2); we assessed environmental contributions by evaluating the degree of shared environmental effects.

MATERIALS AND METHODS

Study Population

A total of 1267 individuals (525 men, 742 women, ranging in age from 17 to 81 years) who underwent dental examination as part of the Healthy Twin Study in Korea, participated in this study. The Healthy Twin Study, a nationwide, twin-family cohort study in Korea, recruited Korean adult twins and their family members who had no ascertained preexisting syndromic diseases.[11,15] The study population comprised 282 families with different types of relationships: 360 MZ (180 pairs), 87 DZ (42 pairs of twins and one pair of triplets), 304 nontwin siblings, and 278 spouses (139 pairs). A zygosity questionnaire and discriminating algorithms were used to determine MZ and DZ.[16]

Diagnosis of Dental Anomalies

Dental anomalies were diagnosed using radiographs, clinical examinations, and medical and dental histories. We investigated hypodontia, which was defined as congenital absence of at least one permanent tooth or tooth germ (third molars excluded).[7,17] We also investigated microdontia excluding third molars, which commonly affected the maxillary lateral incisor (incisal width mesiodistally narrower than the cervical width, including the peg lateral).[18,19] When teeth were missing, only those cases with positive history of microdontia or hypodontia were counted. All examinees had cephalograms and panoramic radiographs taken; when clinically diagnosed microdontia or hypodontia was consistent with radiographic findings, we made the final diagnosis of microdontia/hypodontia.

Statistical Analysis

We examined the incidence of hypodontia, microdontia, and pooled cases according to sex, age, and zygosity status. PCR and RRR were estimated based on the type of family relationship: MZ or DZ twin pairs, siblings, parent-offspring, or spouse pairs.[20,21] We calculated the age and sex-standardized prevalence of each dental anomaly based on those of the study subjects.

Two different models were implemented to explain the variance in dental anomalies. Our first model was a polygenic model that included only additive genetic effects (A) and random errors (E). The second model included "shared environmental effects" (C) and comprised common environmental effects (C) that were not explained by covariates. Thus, for example, an AE model would be one that included both additive genetic effects and random errors. The symbol h2 was defined as the proportion of phenotypic variance explained by additive genetic effects.[22,23] A liability threshold model was implemented to analyze single discrete traits (affected or unaffected). This model assumes a certain genetic threshold according to population prevalence; when genetic risk is greater than the threshold, a specific disease is manifested.[24,25] We chose the best fitting model based on likelihood estimators.

Ethics Statement

The study protocol was reviewed and approved by the Institutional Review Board of Samsung Medical Center (IRB 2005-08-113-027). Informed consent was received from all subjects.

RESULTS

Demographics

Overall demographic data are shown in Table 1. Among 1267 individuals, 45 were diagnosed with hypodontia and 38 with microdontia. A total of 78 individuals had at least one of the two dental anomalies. The prevalence was 4.38% in men and 2.96% in women for hypodontia, and 1.90% in men and 3.77% in women for microdontia. The mean age (standard deviation) of participants was 43.04 $\pm$ 14.15 years (range, 17–81). There was a significant decrease in the prevalence of hypodontia ($P = .0001$) and pooled hypodontia/microdontia ($P = .0006$) according to age. Microdontia did not show meaningful trends according to age ($P = .21$). The distribution of dental anomalies according to relationship types (MZ, DZ, or other family members) was analyzed in two age groups (older or younger than 45 years) in order to reduce age effects.

Pairwise Concordance Rate and Recurrence Risk Ratio

PCR and RRR values are reported in Table 2.

Hypodontia

Six pairs of MZ had concordant hypodontia. Five pairs of MZ had discordant hypodontia. The PCR and

Table 1. Prevalence of Hypodontia and Microdontia According to Demographic Characteristics

Variables	Overall N, %	Hypodontia N, %	Microdontia N, %	Pooled N, %	Normal N, %
Overall	1267 (100)	45 (3.55)	38 (3.00)	78 (6.16)	1189 (93.84)
Sex					
Men	525 (41.44)	23 (51.11)	10 (26.32)	32 (41.03)	493 (41.46)
Women	742 (58.56)	22 (48.89)	28 (73.68)	46 (58.97)	696 (58.54)
Age group		*		*	*
15–29	213 (16.81)	13 (28.89)	5 (13.16)	16 (20.51)	197 (16.57)
30–39	400 (31.57)	20 (44.44)	17 (44.74)	35 (44.87)	365 (30.70)
40–49	223 (17.60)	7 (15.56)	7 (18.42)	13 (16.67)	210 (17.66)
50–59	233 (18.39)	5 (11.11)	7 (18.42)	12 (15.38)	221 (18.59)
≥60	198 (15.63)	0 (0.00)	2 (5.26)	2 (2.56)	196 (16.48)
Twin status (age ≤45)			*		
Singletons	366 (50.97)	18 (47.37)	9 (34.62)	25 (42.37)	341 (51.75)
Monozygotic twins	280 (39.00)	14 (36.84)	11 (42.31)	24 (40.68)	256 (38.85)
Dizygotic twins	72 (10.03)	6 (15.79)	6 (23.08)	10 (16.95)	62 (9.41)
Twin status (age >45)					
Singletons	454 (82.70)	4 (57.14)	12 (100.00)	16 (84.21)	438 (82.64)
Monozygotic twins	80 (14.57)	3 (42.86)	0 (0.00)	3 (15.79)	77 (14.53)
Dizygotic twins	15 (2.73)	0 (0.00)	0 (0.00)	0 (0.00)	15 (2.83)

* *P*-value < .05 by chi-squared test.

RRR of hypodontia in MZ were 0.55 and 13.00 (95% confidence intervals, 7.13–23.69), respectively; this means that if one twin had hypodontia, the cotwin had a 13-fold increased risk of hypodontia. Among DZ, there were two concordant pairs and two discordant pairs; accordingly, the PCR was 0.50. The RRR of hypodontia in DZ was 11.92 (4.32–32.89), which was slightly lower than that of MZ. When we pooled DZ and nontwin siblings, both of whom share the same degree of genetic influences, there were three concordant and 25 discordant pairs, which led to a PCR of 0.11 and an RRR of 2.62 (range, 0.87–7.87). The last concordant pair was between one DZ twin and another sibling. There were no concordant pairs among parent-offspring or spouse pairs, so RRR could not be estimated for these familial groupings.

Microdontia

MZ showed highly aggregated patterns of microdontia manifestation. There were four concordant and three discordant pairs, resulting in a PCR of 0.57 and

Table 2. Pairwise Concordance and Recurrence Risk Ratios

	Concordant	Discordant	None	PCR[a]	RRR[b] (CI[c])
Hypodontia					
MZ[d] twin (pairs)	6	5	169	0.55	13.00 (7.13–23.69)
DZ[e] twin (pairs)	2	2	41	0.50	11.92 (4.32–32.89)
DZ/Siblings (pairs)	3	25	328	0.11	2.62 (0.87–7.87)
Siblings (pairs)	0	15	225	0	N/A
Parent-offspring (pairs)	0	58	849	0	N/A
Spouse (pairs)	0	4	135	0	N./A
Microdontia					
MZ twin (pairs)	4	3	173	0.57	15.29 (7.60–30.79)
DZ twin (pairs)	1	4	40	0.20	4.99 (0.85–29.40)
DZ/Siblings (pairs)	2	32	322	0.06	1.72 (0.43–6.81)
Siblings (pairs)	1	21	218	0.05	1.44 (0.21–10.04)
Parent-offspring (pairs)	2	44	861	0.04	1.63 (0.40–6.58)
Spouse (pairs)	0	6	133	0	N/A
Pooled Hypodontia/Microdontia					
MZ twin (pairs)	10	7	163	0.59	7.92 (5.09–12.34)
DZ twin (pairs)	3	4	38	0.43	5.57 (2.32–13.38)
DZ/Siblings (pairs)	6	49	301	0.11	1.55 (0.70–3.39)
Siblings (pairs)	2	32	206	0.06	0.86 (0.22–3.35)
Parent-offspring (pairs)	4	91	812	0.04	0.77 (0.29–2.06)
Spouse (pairs)	0	10	129	0	N/A

[a] PCR indicates pairwise concordance rate; [b] RRR, recurrence risk ratio; [c] CI, confidence interval; [d] MZ, monozygotic; [e] DZ, dizygotic.

Table 3. Estimates of Additive Genetic (A), Shared Environmental With a Twin (C), and Nonshared Environmental (E) Influences

	Model	A	C	E	Log Likelihood
Hypodontia	AE	0.86 (0.77, 0.95)		0.14 (0.05, 0.23)	−170.03
	ACE	0.16 (0.06, 0.26)	0.72	0.12 (0.02, 0.22)	−164.53
Microdontia	AE	0.87 (0.75, 0.99)		0.13 (0.01, 0.25)	−159.45
	ACE	0.43 (0.31, 0.55)	0.47	0.11 (0, 0.23)	−157.59
Pooled hypodontia/ microdontia	AE	0.87 (0.79, 0.95)		0.13 (0.05, 0.21)	−263.82
	ACE	0.38 (0.30, 0.46)	0.52	0.10 (0.02, 0.18)	−259.71

an RRR of 15.29 (range, 7.60–30.79); DZ had a PCR of 0.20 and an RRR of 4.99 (0.85–29.40), calculated from one concordant and four discordant pairs. Pooling the DZ and siblings yielded two concordant pairs and 32 discordant pairs, leading to a PCR of 0.06 and an RRR of 1.72 (0.43–6.81). There was one concordant pair and 21 discordant pairs of nontwin siblings, resulting in a PCR of 0.05 and an RRR of 1.44 (range, 0.21–10.04). There were two concordant and 44 discordant parent-offspring pairs, with a PCR of 0.04 and an RRR of 1.63 (0.40–6.58). No concordant pairs were found between spouses.

Pooled Hypodontia/Microdontia

When we pooled hypodontia and microdontia, we found 10 concordant and seven discordant pairs among MZ; the PCR was 0.59 and the RRR was 7.92 (5.09–12.34). For DZ, we observed three concordant and four discordant pairs, resulting in a PCR of 0.43 and an RRR of 5.57 (2.32–13.38). Pooled DZ and siblings and parent-offspring pairs resulted in PCRs of 0.11, 0.06, and 0.04, respectively, corresponding to RRRs of 1.55, 0.86, and 0.77. No concordant pairs were detected among MZ spouse pairs.

Heritability Estimates

The h2 estimates of hypodontia, microdontia, and presence of either anomaly are presented in Table 3. In the AE model, the h2 estimates of hypodontia, microdontia, and pooled hypodontia or microdontia were 0.86, 0.87, and 0.87, respectively. In the ACE model, the h2 estimates were 0.16, 0.43, and 0.38 for hypodontia, microdontia, and pooled hypodontia or microdontia, respectively. Twin common environmental effect estimates were 0.72, 0.47, and 0.52 for hypodontia, microdontia, and pooled hypodontia or microdontia, respectively. The ACE model with twin common environmental effects had a lower log likelihood ratio than did the AE model, indicating that the ACE model had a better fit.

DISCUSSION

Prevalence

Several studies have reported the prevalence of dental anomalies in different populations.[7,8,26–28] Differences in prevalence among populations have been attributed to racial differences, different sampling techniques, and different diagnostic criteria. In east Asian populations, including Koreans, one of the distinct characteristics of dental anomalies is a higher prevalence of mandibular incisor hypodontia than in other populations.[7,8,17,26,27]

The prevalence of hypodontia (3.55%, Table 1) is consistent with previous studies (2.3% to 11.3%).[4–6] A higher prevalence of dental anomalies has been reported in studies that have examined orthodontic patients vs those that have examined the general population.[4–9,17,26,27,29] Because the twin study population in this study was community based, the prevalence of hypodontia that we calculated is likely to be an accurate estimate of the prevalence of hypodontia in the Korean general population, and is therefore much lower than that reported in previous studies that examined orthodontic patients.[17,27]

The prevalence of hypodontia in orthodontic patients and the general population are reported in Table 4.[7–10] In adolescents, the prevalence of hypodontia was 8.50% for orthodontic patients and 4.50% for the general population. The wider age range of Turkish orthodontic patients sampled (9–46 years) is the most likely explanation for the lower prevalence of hypodontia in this population compared with that of Japanese orthodontic patients (5–15 years). In our study, the prevalence of hypodontia decreased with

Table 4. Prevalence of Hypodontia

	Country	N	Age, y	Total, %	Men, %	Women, %
Orthodontic patients	Japan[7]	3358	5–15	8.50	7.50	9.30
	Turkey[8]	2761	9–46	6.77	5.44	7.63
General population	Norway[9]	9532	18	4.50	4.00	5.10
	Israel[10]	21,384	12–18	4.60	4.38	4.80

increasing age. This may be due to orthodontic or prosthetic treatment for missing teeth.

Genes and Environment

A higher PCR and RRR in MZ than in other relatives, such as DZ, nontwin siblings, parent-offspring pairs, and spouses, suggests a strong genetic contribution to dental anomalies (Table 2). A close relationship between hypodontia and microdontia has been reported, and genetics plays an important role in dental development.[2,3,5,6,14,18,30,31] However, the details differ based on the type of dental anomaly.

Overall, PCR, RRR, and h2 estimation revealed genetic contributions to dental anomalies. PCR and RRR decreased when comparing MZ with spouses; h2 estimates also supported a considerable genetic contribution to overall dental anomalies.

PCR and RRR of hypodontia in MZ and DZ were similar, implying a twin common environmental effect as well as a genetic effect (Table 2). The h2 estimates of hypodontia also indicate a strong contribution from the twin common environment (Table 3). The h2 estimates showed that the twin common environmental effect (0.72) was stronger than the additive genetic effect (0.16; Table 3). Because DZ, nontwin siblings, and parent-offspring pairs share an average of 50% of their genetic information, the difference between PCR and RRR (Table 2) of DZ twin pairs and other relative pairs indicates environmental as well as genetic contributions to hypodontia.

Strong genetic and twinning effects were evident when the two dental anomalies were pooled. PCR and RRR values of MZ and DZ were much higher than those of other first-degree relative types. In addition, MZ had slightly higher PCR and RRR values than did DZ (Table 2). RRR values of MZ and DZ for pooled anomalies were more stable than separate analysis (Table 2). In the h2 estimation, the additive genetic effect was 0.38, which was larger than that for hypodontia, but smaller than that for microdontia. The twin common environmental effect was 0.52, which was larger than that of microdontia, but smaller than that of hypodontia (Table 3). Therefore, both genetic and twin common environmental effects contribute to the presence of these dental anomalies, although the contribution of a twin common environment was larger than that of the genetic contribution.

Genetic and Environmental Influences in Twins and Siblings

Our results are consistent with those of previous studies reporting that dental anomalies have a high h2 estimate; if one twin in a pair is affected by a dental anomaly, the risk of the other having that anomaly is increased.[32,33] Nontwin siblings share half their genetic information with each other, as do DZ; however, concordance and RRR values for nontwin siblings were much lower than for DZ. Conventional genetic theory assumes that the degree of environmental sharing is the same between DZ and nontwin siblings. However, one of our most important findings is the difference between DZ and siblings. In Table 3, official testing for twinning effects (ie, the influence of being a twin, whether MZ or DZ) was 0.72, exceeding that of additive genetic effects (0.16). The marked difference between twin effects and shared sibling effects indicates that the influence of very early environmental effects, such as intrauterine effects or factors in early infancy, are not usually shared by siblings.

CONCLUSIONS

- Both genetic and environmental factors contribute to the development of dental anomalies.
- Although hypodontia and microdontia showed some differences in genetic vs environmental effects, pooled analysis showed consistent results.
- Pooled analysis for microdontia/hypodontia suggests strong shared environmental effects only between twins that are not seen in siblings, indicating the possible importance of early life influences (such as intrauterine environment or nutrition in early infancy).

ACKNOWLEDGMENTS

This study was supported by grants from the National Research Foundation of Korea (2012K2A1A2032536) and the Global Research Network Program (2011-220-E00006). We would like to thank all twin families for their participation and also Eung Min Kim and Won Hee Cho (Department of Orthodontics, Institute of Oral Health Science, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea) for assistance with data collection and analysis.

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