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Genome-wide linkage analysis for ocular and nasal anthropometric traits in a Mongolian population

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Abbreviations: BMI, body mass index; MIBD, multipoint identity by decent; QTL, quantitative trait locus; STR, short tandem repeat (microsatellite)

Abstract

Anthropometric traits for eyes and nose are complex quantitative traits influenced by genetic and environmental factors. To date, there have been few reports on the contribution of genetic influence to these traits in Asian populations. The aim of this study was to determine the genetic effect and quantitative trait locus (QTL) of seven traits eyes- and nose-related anthropometric measurements in an isolated Mongolian population. Frontal and lateral photographs were obtained from 1,014 individuals (434 males and 580 females) of Mongolian origin. A total of 349 short tandem repeat markers on 22 autosomes were genotyped for each individual. Heritability estimates of the seven ocular and nasal traits, adjusted for significant covariates, ranged from 0.48 to 0.90, providing evidence for a genetic influence. Variance-component linkage analyses revealed 10 suggestive linkage signals on 5q34 (LOD = 3.2), 18q12.2 (LOD = 2.7), 5q15 (LOD = 2.0), 9q34.2 (LOD = 1.9), 5q34 (LOD = 1.9), 17q22 (LOD = 1.9), 13q33.3 (LOD = 2.7), 1q36.22 (LOD = 1.9), 4q32.1 (LOD = 2.1) and 15q22.31 (LOD = 2.9). Our study provides the first evidence that genetics influences nasal and ocular traits in a Mongolian population. Additional collaborative efforts will further extend our understanding of the link between genetic factors and human anthropometric traits.

Keywords: anthropometry; eye; genetic linkage; nose; quantitative trait loci

Introduction

Many congenital diseases, such as Down syndrome (Antonarakis *et al*., 2004), Noonan syndrome (Allanson, 1987) and Robinow syndrome (Patton and Afzal, 2002), are associated with particular facial deformities. However, few of the genes that cause facial anomalies in these diseases have been identified. Studying how genetics governs facial morphogenesis will broaden our understanding and inform future research on congenital diseases.

Popular methods to measure craniofacial anthropometry include direct measurements on the surface of skin, radiographic cephalometry and photographic approaches. The direct measurement method has several advantages, such as non-invasiveness, technical simplicity and low cost. However, because it is carries the risk of examiner subjectivity, it can result in poor reproducibility and reliability, especially when conducted by examiners with insufficient training (Hunter, 1996). Furthermore, repeated measures are often impractical because subjects may not be available for follow-up. Radiographic cephalometry is suitable for the observation of hard tissue such as bone, and can assess many points, angles and planes (Allanson, 1997). Its costs, however, are relatively high, and it exposes subjects to radiation (albeit minute levels) during measurement. For these reasons, the photographic approach remains a very useful method for measuring facial anthropometric parameters. Photographs can be quickly and easily obtained, after which they can be permanently stored for repeated measures (Allanson, 1997). This approach is suitable for the analysis of facial features, and is adaptable to

Table 1. Mean and SD values on age, height, weight, BMI and body fat of the subjects by sex.

Parameters	Total (1,014)		Male (434)		Female (580)	
	Mean	SD	Mean	SD	Mean	SD
Age	29.5	18.0	27.9	18.1	30.6	17.9
Height (cm)	151.5	15.9	154.1	18.7	149.5	13.2
Weight (kg)	51.7	17.5	52.4	19.7	51.2	15.7
BMI (kg/m^2)	21.8	4.8	21.1	4.5	22.4	5.0

meet the specific measurement needs of different investigators (Bishara *et al*., 1995). The measurements taken by these means not only provide standard data for each population, but also contribute to defining the biological mechanisms that determine facial morphology.

It is generally accepted that facial features are inherited from the parent generation. Genetic studies have reported a heritable component in the facial anthropometry of twins, as well as other family members (Susanne, 1975; Byard *et al*., 1985; Hauspie *et al*., 1985). Various face-related measurements have also been reported to display heritability, with values ranging from 0.25 to 0.61 (Raposo-do-Amaral *et al*., 1989; Arya *et al*., 2002; Ermakov *et al*., 2005). Using segregation analysis, Ermakov and colleagues have shown that various measurements related to craniofacial traits, when divided in two components via principal component analysis, are each linked to one major gene (Ermakov *et al*., 2006). Understanding the genetic factors involved in determining the craniofacial shape of humans and defining the underlying mechanisms requires genome-wide gene mapping studies on a large, general population. To our knowledge, such a report has not yet been published. In this first of its kind study, we measured seven ocular and nasal anthropometric traits in a Mongolian population, estimating heritability and performing a genome-wide linkage analysis in an effort to clarify the influence of genetics in defining craniofacial features.

Results

A total of 1,014 (434 male and 580 female) individuals were analyzed with respect to genotypes and phenotypes. The physical features of these individuals are summarized in Table 1. In general, males tended to be taller and heavier than females, whereas females had a higher body mass index (BMI) than males.

We selected 13 landmarks in the eyes and nose area for measuring seven different ocular and nasal traits: ex-ex, en-en, en-ex, ps-pi, al-al, n-sn, and sn-prn (Supplemental Data Figure S1 and Table S1, and Figure 1). The mean and standard deviation (SD) of eye and nose sizes of adults ($\geq$ 18 years of age) are summarized in Table 2. The overall values for most traits were significantly higher in males than in females ($P < 0.05$), with the exception of the trait ps-pi, which was not significantly different between males and females. This lack of significance may be due to variability in emotional states or personal habits of individuals during sampling sessions. Previous studies on the differences in ps-pi between sexes have reported a similar pattern (Yuen and Hiranaka, 1989; Ngeow and Aljunid, 2009).

Heritability estimation and genome-wide linkage analyses were performed using SOLAR (Sequential Oligogenic Linkage Analysis Routines) with a variance-component algorithm. Because the size of body parts, including eyes and nose, can be proportional to other individual size variables, such as height, we adopted a multiple regression method to identify significant covariates among age, sex, age*sex, age2, age2*sex, height, weight and BMI, and adjusted the values of each phenotype for significant covariates in heritability estimation and linkage analysis. The results are summarized in Figure 1 and Table 3. After correcting for significant covariates, the heritability estimates of the phenotypes ranged from 0.48 to 0.90.

Based on the theoretical LOD (logarithm of odds) score threshold of genome-wide significance for QTL mapping (Lander and Kruglyak, 1995), we found 10 suggestive linkage signals (LOD $>$ 1.9). The highest LOD score was 3.2 on 5q34 ($P < 0.0001$) for en-ex. Other regions were 18q12.2 (LOD = 2.7, $P = 0.0006$), 5q15 (LOD = 2.0, $P = 0.0015$), 9q34.2 (LOD = 1.9, $P = 0.0017$) and 5q34 (LOD = 1.9, $P = 0.0018$) for ex-ex; 17q22 (LOD = 1.9, $P = 0.0017$) for en-en; 13q33.3 (LOD = 2.7, $P = 0.0002$) and 1q36.22 (LOD = 1.9, $P = 0.002$) for ps-pi; 4q32.1 (LOD = 2.1, $P = 0.0011$) for n-sn; and 15q22.31 (LOD = 2.9, $P = 0.0002$) for sn-prn. The trait en-ex displayed the highest heritability and also showed the strongest evidence of linkage on 5q34. In this region, we also found evidence of linkage for ex-ex (Figure 2).

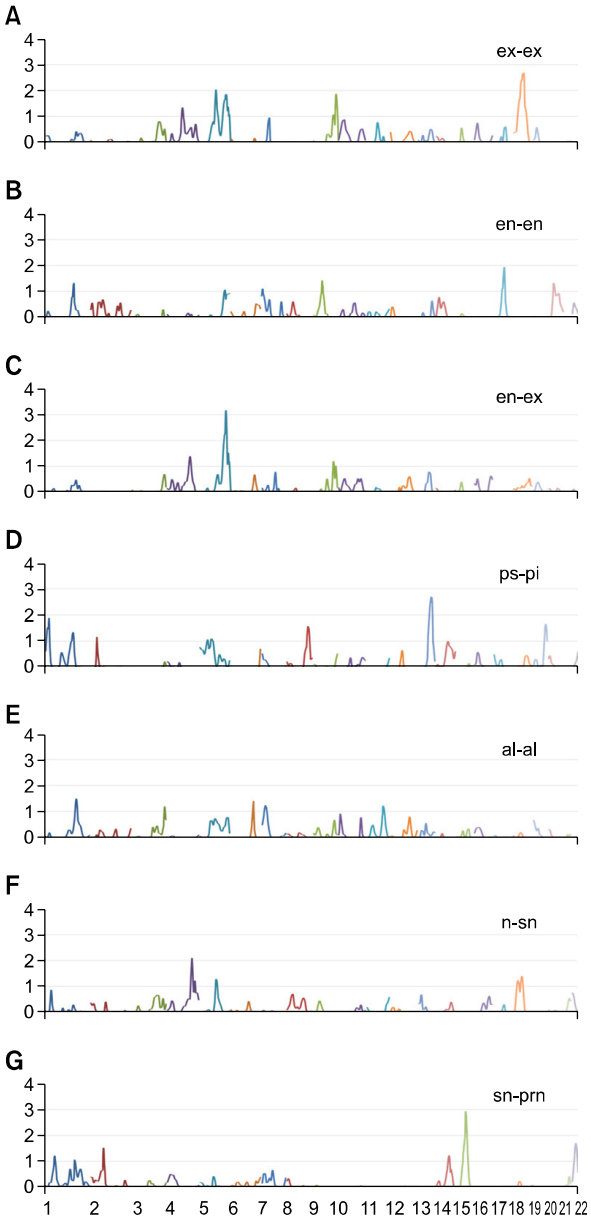

Figure 1. Result of the multipoint linkage analysis of seven ocular and nasal traits. (A) ex-ex, (B) en-en, (C) en-ex, (D) ps-pi, (E) al-al, (F) n-sn, and (G) sn-prn. All traits were adjusted for significant covariates identified among age, sex, age*sex, age2, age2*sex, height, weight and BMI. The x-axis represents 22 autosomes (sequentially), and the y-axis depicts empirically adjusted LOD scores for all graphs.

Discussion

Several studies have reported on the sizes of ocular and nasal traits in particular populations (Yuen and Hiranaka, 1989; Miyajima *et al*., 1996; Hwang *et al*., 2002), yet many ethnic groups, including Mongolians, have received little research attention. Residents in genetically isolated areas have been considered ideal resources for genetic study because of the relatively high homogeneity of their environment and genetic background.

We have also reported genetic evidence and candidate loci for heart rate, QT interval and intraocular pressure in inhabitants of rural areas of Mongolia (Gombojav *et al*., 2008; Im *et al*., 2009; Lee *et al*., 2010). Here, we performed a large-scale investigation of the ocular and nasal anthropometric traits in a Mongolian population, and obtained precise and reliable measurements. Our results may serve as a valuable tool for extending comparative analyses of different populations.

After correcting for significant covariates, we found that the heritability of eye-related traits ranged from 0.48 to 0.90, whereas the heritability of nose-related traits ranged from 0.50 to 0.74 (Table 3). This suggests a major genetic contribution to ocular and nasal sizes. Raposo-do-Amaral and colleagues (Raposo-do-Amaral *et al*., 1989) have reported that the heritability of binocular width, intercanthal width, and length of the eye fissure are 0.34, 0.39 and 0.51, respectively. The heritability of height and breadth of the nose have been reported to be 0.42 and 0.50, respectively (Arya *et al*., 2002). Similarly, another group (Ermakov *et al*., 2005) has reported that the heritability of nose height is 0.42. Our data showed similar or slightly higher heritability values relative to previously reported ranges.

We were able to identify candidate genes that appeared to be related to the determinants of ocular or nasal traits in the regions of linkage peaks. Two genes, *TCOF1* and *MSX2*, known to be related to congenital craniofacial anomalies, are located in a region of 5q34 with evidence of linkage for ex-ex and en-ex (Figure 2 and Table 3). A loss-of-function mutation in *TCOF1* is the cause of Teacher Collins syndrome, which is an autosomal-dominant disorder of craniofacial development (Dixon *et al*., 2007). More than 120 mutations have been identified in *TCOF1*, including splicing mutations, insertions, nonsense mutations and deletions. The features associated with these genetic anomalies include abnormalities of ears and eyes, hypoplasia of mandible and zygomatic complex, and cleft palate (Dixon, 1996). *MSX2* is the culprit gene for Boston-type craniosynostosis and parietal foramina. *Msx2* has been reported to be expressed during early ocular development in the optic vesicle of the mouse embryo (Monaghan *et al*., 1991). According to Wu *et al*. (2003), overexpression of *Msx2* in transgenic mice results in optic nerve aplasia and microphthalmia. Our results, taken together with the findings from these groups, suggest *TCOF1* and *MSX2* as candidate

Table 2. Mean and SD (mm) for the ocular and nasal distances of the adults (≥ 18) by sex.

List	Total (*n* = 636)		Male (*n* = 249)		Female (387)	
	Mean	SD	Mean	SD	Mean	SD
Biocular width (ex-ex)	8.57	0.52	8.76	0.52	8.45*	0.49
Intercanthal width (en-en)	3.57	0.32	3.61	0.35	3.54*	0.29
Length of the eye fissure (en-ex)	2.52	0.26	2.59	0.28	2.47*	0.24
Height of the eye fissure (ps-pi)	0.90	0.16	0.91	0.16	0.89*	0.15
Width of the nose (al-al)	3.77	0.39	4.00	0.37	3.62*	0.32
Height of the nose (n-sn)	4.71	0.48	5.01	0.48	4.52*	0.38
Nasal protrusion (sn-prn)	1.77	0.22	1.87	0.22	1.70*	0.19

*Significant difference by sex $P < 0.05$.

genes for determining ocular morphology.

SMAD2, found on chromosome 18, is another potential candidate gene for ex-ex. According to Nomura & Li (1998), some embryos from *Smad2* heterozygous knockout mice exhibit severe gastrulation defects that result in the lack of mandibles or eyes.

A linkage peak on chromosome 13 for ps-pi includes the *ZIC2* gene. A heterozygous mutation in *ZIC2* is reported to be associated with holoprosencephaly (Brown *et al*., 1998). Because holoprosencephaly comprises a spectrum of anomalies in the brain and face, including eyes, nose and upper lip, *ZIC2* may also play a role in determining ocular and nasal morphology.

This study has several key features. First, it catalogs reliable average values of ocular and nasal sizes for adults of an Asian population of Mongolian origin. Second, it is the first genome-wide linkage study on eyes- and nose-related anthropometric traits in humans. Lastly, it targets a general population with large extended families rather than patients with facial abnormalities, and thus could provide statistical strength for discovering QTL for normal variation (Borecki and Province, 2008; Fuller *et al*., 2008). We believe that our study and further validation studies will provide new insights into the genetic basis of human anthropometric traits.

Methods

Study subjects and baseline measurements

This study was approved by the Institutional Review Committee of Seoul National University (H-0307-105-002). All participants provided written consent for the collection of information and publication of results. A total of 1,324 individuals from Selenge province, Mongolia, were selected for this study as part of the GENDISCAN (GENe DIScovery for Complex traits in Asians of Northeast) project. A total of 142 pedigrees were included; the number of pedigree members ranged from 3 to 210, and the mean pedigree size was 10.22. For each individual, age, sex and hereditary information were collected, and height (cm) and weight (kg) were recorded. BMI was calculated according to the formula, BMI (kg/m^2) = body weight/(body height)^2,

Table 3. Results of heritability estimation and multipoint linkage analysis for eyes and nose traits.

Trait	h^2	LOD score	Cytogenetic location	Nearest marker	Empirical *P* value	Covariates
ex-ex	0.72	2.7	18q12.2	D18S1102	0.0006	age, sex, age*sex, age^2, H, W, B
		2.0	5q15	D5S644	0.0015	
		1.9	9q34.2	D9S164	0.0017	
		1.9	5q34	D5S422	0.0018	
en-en	0.67	1.9	17q22	D17S787	0.0017	age, age^2, H, W, B
en-ex	0.90	3.2	5q34	D5S422	< 0.0001	sex, age*sex, age^2, H, W, B
ps-pi	0.48	2.7	13q33.3	D13S173	0.0002	age, age*sex
		1.9	1p36.22	D1S2667	0.0020	
al-al	0.74					age, sex, age*sex, age^2, age^2*sex, H, W, B
n-sn	0.50	2.1	4q32.1	D4S1629	0.0011	age, sex, age*sex, age^2, age^2*sex, H
sn-prn	0.60	2.9	15q22.31	D15S153	0.0002	age, sex, age*sex, H

H, height; W, weight; B, BMI.

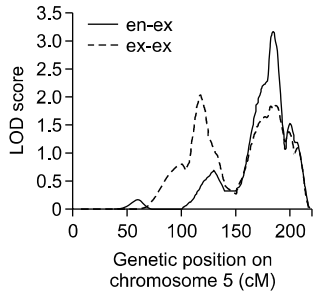

Figure 2. Result of the multipoint linkage analysis of en-ex and ex-ex on chromosome 5. The x-axis is genetic position (cM) and the y-axis is empirically adjusted LOD scores.

where body weight is in kilograms and body height is in meters.

Measurement of facial landmarks

This study targeted only healthy individuals; those with any facial anomalies were excluded. Frontal and lateral photographs of each subject were taken by a single trained photographer with a digital camera using a standardized protocol. The distance between the participant and the camera was 3 m, and subjects held a ruler while pictures were taken to control for distance artifacts. After careful review, 1,220 photographs with defined ocular and nasal landmarks were selected for analysis. Based on a previous reference (Farkas, 1994), 13 landmarks on the eyes and nose area were selected (Supplemental Data Figure S1 and Table S1). Measurements of these landmarks were performed using Image J software (available as freeware from http://rsbweb. nih.gov/ij/).

After all 13 landmarks were marked on photographs, they are saved on Image J software as 2D coordinates. Two landmarks were selected, and then the length of the straight line that connected them was calculated and saved. Using this method, we measured seven parameters that well represented the characteristics of eyes and nose. Three trained raters participated in the measurements. En-ex and ps-pi were measured on both right and left side, and the average values were used. The nasal trait n-sn was obtained from frontal photographs.

Intra- and inter- observer precisions were tested for all seven measurements on 30 subjects. Two widely used precision estimates were calculated: TEM and rTEM (Weinberg *et al*., 2005). For intraobserver precision estimates of seven measurements, TEM ranged from 0.08 to 0.30, and rTEM ranged from 1.58 to 5.68. Interobserver precision estimates, calculated by TEM and rTEM, were 0.07-0.65 and 1.37-7.06, respectively.

DNA extraction and genotyping

Leukocyte DNA was extracted from buffy coat specimens of each subjects according to the protocol described by the manufacturer (Gentra DNA isolation kit). The resulting genomic DNA was subsequently genotyped for 349 short tandem repeat (STR) microsatellite markers on 22 autosomes with a spacing average of 10 cM intervals (ABI co., LMS v2.5 HD10). A total of 1,080 subjects were successfully genotyped; 1,014 subjects with both genotypic and phenotypic (photograph) information were included in the statistical and genetic analysis.

Statistical analysis

Mean and standard deviation (SD) for the study population as a whole and for each sex separately were calculated using SAS version 9.1 (SAS Institute, Cary, NC). To prevent against growth effects, individuals under age 18 were not included in calculations of mean or SD. Narrow sense heritability (h2) estimations and multipoint linkage analyses were conducted using the SOLAR package (Almasy and Blangero, 1998) with a variance-component algorithm. For multipoint linkage analysis using the SOLAR package, multipoint identity by descent (MIBD) matrices were estimated with the LOKI package (Heath, 1997) via Markov Chain Monte Carlo (MCMC) methods for 22 autosomes. Multipoint LOD scores were calculated only for 22 autosomes, not for sex chromosomes. To eliminate type I error and validate the robustness of our results, we performed a permutation test of 10,000 replicates using the "lodadj" command implemented in SOLAR (Blangero *et al*., 2000, 2001). Empirically adjusted LOD score and empirical *P*-values were presented in the results.

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Supplemental data

Supplemental Data include a figure and a table, and can be found with this article online at http://e-emm.or.kr/article/article_files/SP-42-12-01.pdf.

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