ORIGINAL INVESTIGATION

EDAR, LYPLAL1, PRDM16, PAX3, DKK1, TNFSF12, CACNA2D3, and *SUPT3H* gene variants influence facial morphology in a Eurasian population

Yi Li[1] · Wenting Zhao[2] · Dan Li[3] · Xianming Tao[1] · Ziyi Xiong[1] · Jing Liu[2] · Wei Zhang[2] · Anquan Ji[2] · Kun Tang[3] · Fan Liu[1,4] · Caixia Li[2]

Abstract
In human society, the facial surface is visible and recognizable based on the facial shape variation which represents a set of highly polygenic and correlated complex traits. Understanding the genetic basis underlying facial shape traits has important implications in population genetics, developmental biology, and forensic science. A number of single nucleotide polymorphisms (SNPs) are associated with human facial shape variation, mostly in European populations. To bridge the gap between European and Asian populations in term of the genetic basis of facial shape variation, we examined the effect of these SNPs in a European–Asian admixed Eurasian population which included a total of 612 individuals. The coordinates of 17 facial landmarks were derived from high resolution 3dMD facial images, and 136 Euclidean distances between all pairs of landmarks were quantitatively derived. DNA samples were genotyped using the Illumina Infinium Global Screening Array and imputed using the 1000 Genomes reference panel. Genetic association between 125 previously reported facial shape-associated SNPs and 136 facial shape phenotypes was tested using linear regression. As a result, a total of eight SNPs from different loci demonstrated significant association with one or more facial shape traits after adjusting for multiple testing (significance threshold $p < 1.28 \times 10^{-3}$), together explaining up to 6.47% of sex-, age-, and BMI-adjusted facial phenotype variance. These included *EDAR* rs3827760, *LYPLAL1* rs5781117, *PRDM16* rs4648379, *PAX3* rs7559271, *DKK1* rs1194708, *TNFSF12* rs80067372, *CACNA2D3* rs56063440, and *SUPT3H* rs227833. Notably, the *EDAR* rs3827760 and *LYPLAL1* rs5781117 SNPs displayed significant association with eight and seven facial phenotypes, respectively ($2.39 \times 10^{-5} < p < 1.28 \times 10^{-3}$). The majority of these SNPs showed a distinct allele frequency between European and East Asian reference panels from the 1000 Genomes Project. These results showed the details of above eight genes influence facial shape variation in a Eurasian population.

Introduction

Facial morphology represents the most recognizable feature in humans with a strong genetic component. Several family based studies have estimated the heritability of certain facial shape features up to 0.73 (Alkhudhairi and Alkofide 2010),

Yi Li and Wenting Zhao contributed equally to this work.

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✉ Fan Liu
liufan@big.ac.cn

✉ Caixia Li
licaixia@tsinghua.org.cn

Extended author information available on the last page of the article

but an understanding of the genetic basis of normal variation in human facial morphology remains limited.

To date, ten genome-wide association studies (GWASs) have been performed to examine the associations between DNA variants and normal facial variation. These studies reported a total of 125 SNPs at 103 distinct genomic loci with genome-wide significant association to a number of different facial features (Adhikari et al. 2016; Cha et al. 2018; Claes et al. 2018; Cole et al. 2017; Crouch et al. 2018; Lee et al. 2017a; Liu et al. 2012; Paternoster et al. 2012; Pickrell et al. 2016b; Shaffer et al. 2016). These GWASs used a variety of phenotyping approaches, ranging from questionnaires on anthropological features to the analysis of 2D images and/or 3D head MRI or facial surface data. With the exception of a few, most of the identified loci are non-overlapping between the independent GWASs. These findings are largely consistent with a highly polygenic model and suggest

a high degree of population heterogeneity underlying human facial variation. Because most of the previous GWASs of facial variation were conducted on European populations, whether these findings are generalizable in Asian populations remains unclear. Here, we investigated the potential effects of the 125 facial variation-associated SNPs on facial morphology in a European–Asian admixed population.

Materials and methods

Samples

This study was approved by the Ethics Committee of the Institute of Forensic Science of China, and all individuals provided written informed consent. The participants were all volunteers. The consent was discussed in their native language and the signature was in their native language. We sampled a total of 612 unrelated Eurasian individuals living in Tumxuk City in Xinjiang Uyghur Autonomous Region, China. All individuals met the following conditions: (1) their parents and grandparents were both of Uyghur origin; (2) they had not received hormone therapy; (3) they had no thyroid disease, pituitary disease, or tumors; and (4) they had no medical conditions affecting growth and development, such as dwarfism, gigantism, and acromegaly. The 3D facial surface data were ascertained using an Artec Spider scanner in combination with Artec Studio Professional v10 software, and all volunteers were requested to maintain the same sitting position and neutral expression.

Phenotyping

The x–y–z coordinates of 17 facial landmarks were derived from the 3D face images based on an automated pipeline developed in-house by fine-tuning a previously detailed protocol (Guo et al. 2013). The method starts with preliminary nose tip localization and pose normalization, followed by localization of the six most salient landmarks using principal component analysis (PCA) and heuristic localization of 10 additional landmarks. Trained experts reviewed all landmarks from the automated pipeline by comparing the landmark positions with example images pre-landmarked according to the definition of the landmarks (Table S1) using the FaceAnalysis software (Guo et al. 2013). Obviously inaccurately positioned landmarks were corrected using the 3dMD patient software (www.3dmd.com). After generalized procrustes analysis (GPA), a total of 136 Euclidean distances between all pairs of the 17 landmarks were quantitatively derived. Outliers with values greater than three standard deviations were removed. Z-transformed phenotypes were used in the subsequent analyses.

DNA genotyping, quality control, and imputation

Venous whole blood samples were collected in EDTA-Vacutainer tubes and stored at − 20 °C until processed. DNA samples were genotyped on an Illumina Infinium Global Screening Array 650 K. SNPs with minor-allele frequency < 1%, call-rate < 97%, Hardy–Weinberg p values < 0.0001, and samples missing > 3% of genotypes were excluded. One sample with excess of heterozygosity ($F < 0.084$) was excluded. Two samples were identified as second-degree relatives in identity by descent (IBD) estimation, and one was removed. Genotype imputation was performed to capture information on unobserved SNPs and sporadically missing genotypes among the genotyped SNPs, using all haplotypes from the 1000 Genomes Project Phase 3 reference panel (Genomes Project et al. 2012). Pre-phasing was performed in SHAPEIT2 (Delaneau et al. 2013), and imputation was performed using IMPUTE2 (Howie et al. 2011; Howie et al. 2009). Imputed SNPs with INFO scores < 0.8 were excluded. The imputed dataset contained genotypes for 5,289,934 SNPs. We ascertained a list of 125 SNPs that have been associated with facial morphology in previous facial morphology GWASs (Adhikari et al. 2016; Cha et al. 2018; Claes et al. 2018; Cole et al. 2016; Crouch et al. 2018; Lee et al. 2017b; Liu et al. 2012; Paternoster et al. 2012; Pickrell et al. 2016a; Shaffer et al. 2016). Out of the 125 SNPs, 10 were genotyped, 47 were imputed and passed quality control, and 68 were excluded by quality control.

Statistical analyses

Linear regressions were iteratively conducted to test genetic association between the facial shape-associated SNPs and the facial phenotypes under an additive genetic model, while adjusting for sex, age, BMI, and the first three genomic principal components from the –pca function in PLINK V1.9 (Purcell et al. 2007). We conducted a genomic PCA analysis to detect the presence of potential population substructures, using three population samples, i.e., 612 Uyghurs (UYG) from the current study, 504 East Asians (EAS) and 503 Central Europeans (EUR) from the 1000 Genomes Project (Genomes Project et al. 2012), and an overlapping set of 5,085,557 SNPs. The relative contribution was derived for the top 20 PCs. An unsupervised K-means clustering analysis was used to cluster the three population samples into three clusters based on the top-contributing genomic PCs (Hartigan and Wong 1979). We used the distance matrix that was derived from the phenotypes correlation matrix to perform hierarchical clustering analysis with the –dist and –hclust function in R V3.3.2 and obtained four phenotype clusters.

To adjust for the multiple testing of multiple phenotypes, we conducted a Bonferroni correction to the effective number of independent variables, which was estimated using the Matrix Spectral Decomposition (matSpD) method (Li and Ji 2005). The fraction of trait variance explained by the SNPs was estimated using multiple regressions, where the face residuals were considered as the phenotype, i.e.: the effects of sex, age, and BMI were regressed out prior to the analysis. The distribution of allele frequencies in the 2504 subjects of the 1000 Genomes Project was visualized using Mapviewer software version 7.

Results

This study included 590 males and 22 females, ranging from 16 to 59 years of age (mean age was 34.9 years, Table S2), of admixed European-Asian ancestry. We focused on 17 anatomical landmarks (Fig. 1), and the 136 Euclidian distances (Figure S1, Table S2) between all of these landmarks. Age had a significant effect on 80.1% of all 136 face phenotypes ($1.06 \times 10^{-17} < p < 0.05$, Table S3), and sex had a significant effect on 83.8% of the face phenotypes ($4.88 \times 10^{-15} < p < 0.05$, Table S3). The effect of BMI was significant on 80.1% of the face phenotypes ($1.38 \times 10^{-114} < p < 0.05$, Table S3) and most significantly associated with ObiR-ObiL, which is equal to the width of face, as expected.

We selected a total of 125 SNPs at 103 distinct loci that associated with facial features in previous GWASs (Table S4) (Adhikari et al. 2016; Cha et al. 2018; Claes et al. 2018; Cole et al. 2016; Crouch et al. 2018; Lee et al. 2017b; Liu et al. 2012; Paternoster et al. 2012; Pickrell et al. 2016a; Shaffer et al. 2016) and tested their association with 136 facial phenotypes in 612 individuals.

We derived 20 PCs from a genomic principal component analysis using the combined dataset including 503 EUR, 504 EAS, and 612 Eurasian individuals. The 1st PC alone accounted for the majority (59.74%) of the total genomic variance explained by all 20 PCs (Figure S2A). K-means clustering of the top 2 PCs clearly differentiated the three populations into separate clusters (Figure S2B). No indications of population sub-structures were detected within the Uyghur individuals. The significance threshold was derived as $p < 1.28 \times 10^{-3}$ using Bonferroni correction, and the effective number of independent variables was estimated as 39 using the matSpD method. The association testing identified eight SNPs displaying significant association with facial phenotypes after adjusting for multiple testing (Table 1). Of these eight SNPs, three were genotyped and five were imputed (Table S4). These included *EDAR* rs3827760 (min $p = 2.39 \times 10^{-5}$), *LYPLAL1* rs5781117 (min $p = 1.43 \times 10^{-4}$), *PRDM16* rs4648379 ($p = 8.55 \times 10^{-4}$), *PAX3* rs7559271 ($p = 7.88 \times 10^{-4}$), *DKK1* rs1194708 ($p = 1.77 \times 10^{-3}$), *TNFSF12* rs80067372 ($p = 5.90 \times 10^{-4}$), *CACNA2D3* rs56063440 ($p = 5.29 \times 10^{-4}$), and *SUPT3H* rs227833 ($p = 9.89 \times 10^{-4}$). All eight SNPs together explained up to 6.47% of the sex-, age-, BMI-, and first three genetic PC-adjusted facial phenotype variance (top explained phenotypes: Entocanthion-Otobasion Inferius, Table S5, Fig. 2a). Sex-stratified analysis did not reveal any sex-specific association (Table S6), and more significant association was observed in males than in females, likely explained by the larger sample size of males.

The strongest association signal was observed for *EDAR* rs3827760, which showed significant association with eight facial phenotypes (Fig. 2b). The derived G allele demonstrated significant length-increasing effects on eight facial phenotypes belonging to two distinct

Fig. 1 Positions and definitions of the 17 landmarks. 17 anatomical landmarks were located in 3D facial surfaces, and the left picture clearly shows their positions mapped onto the 2D frontal picture. The definitions of the 17 landmarks are stated in the right table
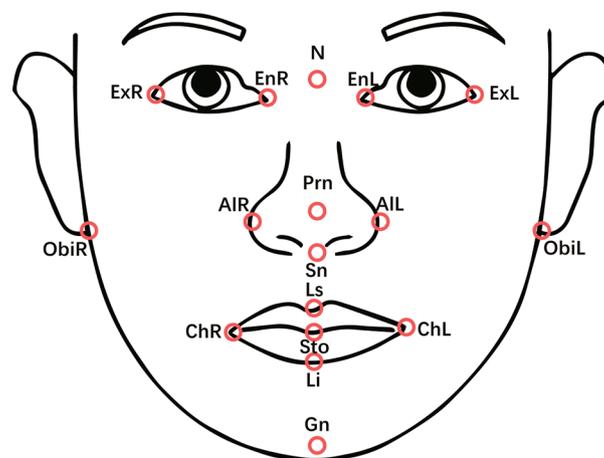
Abbreviation	Name
ExR	Right Ectocanthion
EnR	Right Entocanthion
N	Nasion
EnL	Left Entocanthion
ExL	Left Ectocanthion
ObiR	Right Otobasion Inferius
AlR	Right Alare
Prn	Pronasale
AlL	Left Alare
ObiL	Left Otobasion Inferius
Sn	Subnasale
ChR	Right Cheilion
Ls	Labrale Superius
Sto	Stomion
Li	Labrale Inferius
ChL	Left Cheilion
Gn	Gnathion

Table 1 SNPs associated with facial features in 612 Eurasian individuals

Locus	Gene	SNP	Previous results						Current study				
			EA/OA	EAF (EUR)	EAF (EAS)	EAF (AFR)	Phenotype	Ref (PMID)	Phenotype	Beta	SE	p value	EAF (UYG)
1p36.32	*PRDM16*	rs4648379	T/C	0.31	0.55	0.40	AlrL-Prn	23028347	Sn-ChR	0.18	0.05	8.55E−04	0.39
1q41	*LYPLAL1*	rs5781117	T/TG	0.34	0.18	0.52	Nose size	27182965	AlR-ObiL	−0.16	0.04	1.43E−04	0.35
2q12.3	*EDAR*	rs3827760	G/A	0.01	0.87	0.00	Chin protrusion	27193062	ExL-ObiL	0.21	0.05	2.39E−05	0.35
2q36.1	*PAX3*	rs7559271	A/G	0.60	0.39	0.45	Nasion position	22341974; 27193062	EnL-AlR	0.18	0.05	7.88E−04	0.44
3p14.3	*CACNA2D3*	rs56063440	C/G	0.28	0.01	0.25	Nose size	27182965	ObiR-ObiL	0.22	0.06	5.29E−04	0.08
6p21.1	*SUPT3H*	rs227833	C/G	0.28	0.27	0.14	Nose area	29459680	EnR-ObiL	0.14	0.04	9.89E−04	0.31
10q21.1	*DKK1*	rs1194708	A/G	0.73	0.14	0.14	Chin_dimple	27182965	AlR-AlL	0.17	0.05	1.17E−03	0.49
17p13.1	*TNFSF12*	rs80067372	A/G	0.27	0.00	0.01	Chin_dimple	27182965	ExR-Sn	0.30	0.09	5.90E−04	0.11

EA/OA effect allele/other allele, *EAF* effect allele frequency, *Phenotype* the most significant phenotype, *Beta* standardized beta corresponding to the effect allele

clusters, including the eye-otobasion distances (ExR-ObiR, EnR-ObiR, EnL-ObiL, ExL-ObiL, and N-ObiR, $2.39 \times 10^{-5} < p < 9.54 \times 10^{-4}$) and the distances between nosewing and center of mouth (AlR-Sto, AlL-Sto, and AlR-Li, $2.05 \times 10^{-4} < p < 1.24 \times 10^{-3}$, Figure S3). This allele was highly polymorphic in Eurasians ($f_{UYG} = 0.35$) and East Asians ($f_{EAS} = 0.87$), but nearly non-polymorphic in Europeans ($f_{EUR} = 0.01$) and Africans ($f_{AFR} = 0.01$) (Figure S4A). Rs3827760 is known as an East-Asian specific variant and has been repeatedly reported to be subjective under positive selection in East Asians (Grossman et al. 2013; Sabeti et al. 2007). Rs3827760 alone explained 2.86% of sex-, age-, BMI-, and the first three genetic PC-adjusted ExL-ObiL variance. The second significant signal belonged to *LYPLAL1* rs5781117. Its ancestral T allele displayed significant length-decreasing effects on seven facial distances between otobasion and other landmarks (AlR-ObiL, AlL-ObiR, EnL-ObiL, N-ObiL, AlL-ObiL, EnR-ObiR, and ExL-ObiR, $1.43 \times 10^{-4} < p < 1.13 \times 10^{-3}$). These facial phenotypes belong to the one facial phenotype cluster that (Figure S3) was also characterized by the distances between the otobasion inferius and other facial landmarks ($1.43 \times 10^{-4} < p < 1.13 \times 10^{-3}$, Fig. 2c). This allele is polymorphic in Africans ($f_{AFR} = 0.52$) and Europeans ($f_{EUR} = 0.34$) and minor in East Asians ($f_{EAS} = 0.18$) (Figure S4B). Rs59156997 explained 2.36% of sex-, age-, BMI-, and the first three genetic PC-adjusted AlR-ObiL variance. The other six SNPs were significantly associated with only one facial phenotype (Table 1, Table S7). The effect alleles of these six SNPs also showed substantial frequency differences between European and East Asian populations, as illustrated using samples from the 1000 Genomes Project (Figure S4). *DKK1* rs1194708 especially demonstrated a reversed allele frequency distribution between East Asians and Europeans.

Discussion

In an admixed Eurasian population, we identified eight SNPs (*EDAR* rs3827760, *LYPLAL1* rs5781117, *PRDM16* rs4648379, *PAX3* rs7559271, *DKK1* rs1194708, *TNFSF12* rs80067372, *CACNA2D3* rs56063440, and *SUPT3H* rs227833) that were significantly associated with facial features. Together, they explained a considerable proportion of facial variation. *EDAR* and *LYPLAL1* gene variants demonstrated large effects on facial morphology in the Eurasian population, and these effects are likely further pronounced in other East Asian populations. These findings bridged the gap between European and Asian populations in terms of the genetic basis of facial shape variation.

All of the eight face associated SNPs showed significant allele frequency differences between different continental

Fig. 2 The genetic effects on facial morphology in 612 Eurasian individuals. **a** Face map depicting the percentage of facial phenotype variance (R^2) explained by eight facial shape associated SNPs: including *EDAR* rs3827760, *LYPLAL1* rs5781117, *PRDM16* rs4648379, *PAX3* rs7559271, *DKK1* rs1194708, *TNFSF12* rs80067372, *CACNA2D3* rs56063440, and *SUPT3H* rs227833. **b** Face map denoting the significance ($-\log_{10}P$) level for the associations between *EDAR* rs3827760 and facial phenotypes, as well as the direction of the genetic effect. **c** Face map denoting the significance ($-\log_{10}P$) level for the associations between *LYPLAL1* rs5781117 and facial phenotypes, as well as the direction of the genetic effect

groups and four of them (rs4648379, rs3827760, rs7559271 and rs1194708) showed an inversed allele frequency between Europeans and East Asians, emphasizing population heterogeneity as a key feature underlying the genetic architecture of human facial variation. Recent population genetic studies on human nose morphology have demonstrated that climate changes have significantly contributed to the evolution of the human face (Wroe et al. 2018; Zaidi et al. 2017). The observation of the large allele frequency differences in our study is in line with the previous findings and supports the hypothesis that climatic adaptation and natural selection have shaped the human face during the history of evolution.

The most significant finding was *EDAR* rs3827760. *EDAR* encodes a cell-surface receptor important for the development of ectodermal tissues, including skin. rs3827760 is a missense variant (*V370A*) that affects protein activity (Bryk et al. 2008; Mou et al. 2008), and the derived G allele is associated with several ectodermal-derived traits such as chin protrusion (Adhikari et al. 2016), increased hair straightness (Tan et al. 2013) and thickness (Fujimoto et al. 2008a; Fujimoto et al. 2008b), teeth single and double incisors shoveling (Kimura et al. 2009; Park et al. 2012), increased earlobe attachment, decreased earlobe size, decreased ear protrusion, and decreased ear helix rolling (Adhikari et al. 2015; Shaffer et al. 2017). Previous population genetics studies repeatedly suggested that *EDAR* has undergone strong positive selection in East Asia populations (Adhikari et al. 2016; Grossman et al. 2010; Kamberov et al. 2013; Sabeti et al. 2007). In our Eurasian sample, the *EDAR* rs3827760 G allele was significantly associated with increases in eight facial landmark distances and showed a pronounced effect on eye-otobasion distances. This finding is consistent with an Asian-specific and pleiotropic effect of rs3827760. A previous facial shape GWAS in Latin Americans reports that rs3827760 explains 1.32% of chin protrusion variance (Adhikari et al. 2016). In this study of Eurasians, we did not quantify chin protrusion, but rs3827760 explained a considerably larger proportion (2.86%) of the phenotypic variance for a different facial phenotype, i.e., the eye-otobasion distance. Because the G allele is nearly absent (~ 0.01) in Europeans and Africans (~ 0.01), highly frequent in our Eurasian study population (~ 0.35), and abundant in East Asians (~ 0.87), we expect the effect of
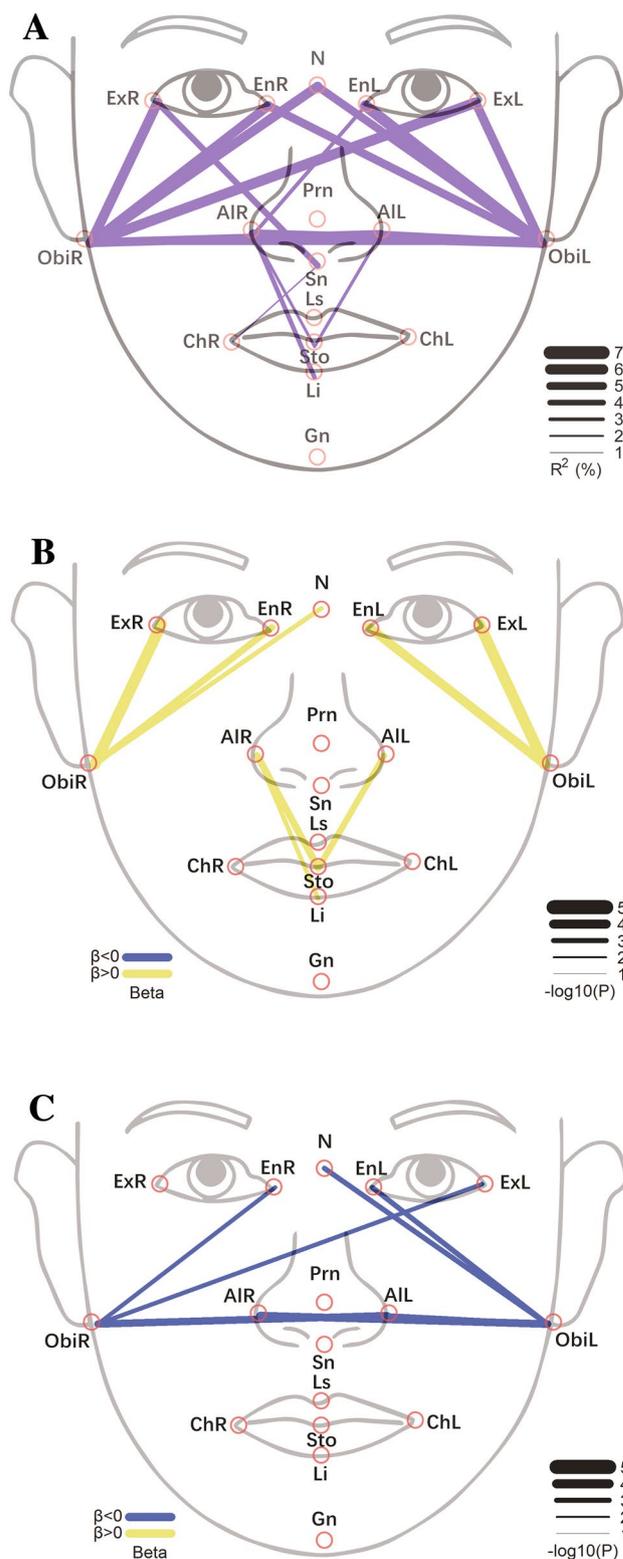
EDAR on facial variation is even more pronounced in East Asian populations.

Rs5781117 is close to the *LYPLAL1* (Lysophospholipase Like 1) gene, which is a protein coding gene. Gene

ontology (GO) (Gene Ontology 2015) annotations related to this gene include hydrolase activity and lysophospholipase activity. The ancestral T allele of rs5781117 has been previously associated with an increase in nose size (Pickrell et al. 2016a). Gene variants in this region are also associated with the waist-hip ratio (Heid et al. 2010), obesity (Lv et al. 2017; Nettleton et al. 2015), and adiposity and fat distribution in different populations (Hotta et al. 2013; Lindgren et al. 2009; Liu et al. 2014; Wang et al. 2016). This may suggested that *LYPLAL1* slightly affects facial phenotypes by impacting fat distribution. Although we did not ascertain the nose size ordinal phenotype in the current study, the *LYPLAL1* rs5781117 SNP was significantly associated with a good number of facial phenotypes, with a pronounced effect on distances between the otobasion inferius and several other facial landmarks (including two nose landmarks) and explained a considerable proportion of the phenotypic variance (up to 2.36% for AlR-ObiL). rs59156997 is highly polymorphic in all continental groups, suggesting a rather universal effect on a variety of facial traits.

The other six SNPs (*PRDM16* rs4648379, *PAX3* rs7559271, *DKK1* rs1194708, *TNFSF12* rs80067372, *CACNA2D3* rs56063440, and *SUPT3H* rs227833) were each only significantly associated with one facial trait. Two previous GWASs report that the ancestral A allele of *PAX3* rs7559271 has a significant effect on a decreased nasion to mid-endocanthion point distance (Adhikari et al. 2016; Paternoster et al. 2012) in European and Latin American populations. The other two variants including *CACNA2D3* rs56063440 and *SUPT3H* rs227833 are associated with the nose (nose size and nose area) (Claes et al. 2018; Pickrell et al. 2016a). The *PRDM16* variant rs4648379 is reported to be associated with a decreased pronasale to left alare distance (Liu et al. 2012). Both the *DKK1* variant rs1194708 and *TNFSF12* variant rs80067372 are associated with chin dimples (Pickrell et al. 2016a). In our study of Eurasians, although the genetic association survived multiple testing correction, the associated traits did not exactly match the previous GWAS findings. Here, the effect of *PAX3* rs7559271 was on the distance between the left entocanthion and right alare, the effect of *PRDM16* rs4648379 was on the distance between the subnasale to right cheilion, the effect of *DKK1* rs1194708 was on the width of the nosewing, the effect of *TNFSF12* rs80067372 was on the subnasale to right ectocanthion, the effect of *CACNA2D3* rs56063440 was on the right otobasion inferius to left otobasion inferius, and the effect of *SUPT3H* rs227833 was on the right entocanthion to left otobasion inferius. This may be explained by genetic effects on multiple facial traits, and further validations of these effects in East Asian populations are warranted. In addition, we note that the small sample size of females is a limit of the current study. Excluding these female samples showed little

effect on the detected associations and did not change our conclusions. Although the sex-stratified analysis did not reveal any sex-specific association, and previous GWASs did not report any sex-specific effects of the highlighted SNPs, the effects of these SNPs in Eurasian females warrant further investigations in future studies.

A clustering analysis of the 136 facial phenotypes resulted in four clusters. These clusters followed certain anthropological patterns. The 1st two clusters of the facial phenotypes were in line with the horizontal and vertical facial variations, respectively. The 3rd cluster mainly contained the facial phenotypes involving the otobasion landmark. The 4th cluster mainly involve the phenotypes explaining the variation in the lower part of the face. It is reasonable to speculate that phenotypes in the same cluster may share more or stronger genetic factors than those in different clusters, and genetic factors involved in early stages of facial development may affect more facial phenotype across different clusters. For example, the missense variant rs3827760 of *EDAR*, which showed significant association with multiple facial phenotypes belonging to two different phenotype clusters, plays an important role in the early embryonic ectoderm development of mice (Kamberov et al. 2013).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest regarding this work.

Data Availability Statement The dataset analyzed during the current study is restricted due to participant confidentially. Restrictions apply to the availability of these data, which were used under license for the current study, and so are not entirely publicly available. However, the variation data reported in this paper have been deposited in the Genome Variation Map (Song et al. 2018) in the BIG Data Center (Members BIGDC 2018), Beijing Institute of Genomics (BIG), Chinese Academy of Sciences, under accession number GVM000031 and can be publicly accessed at http://bigd.big.ac.cn/gvm/getProjectDetail?project=GVM000031.

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Affiliations

Yi Li[1] · Wenting Zhao[2] · Dan Li[3] · Xianming Tao[1] · Ziyi Xiong[1] · Jing Liu[2] · Wei Zhang[2] · Anquan Ji[2] · Kun Tang[3] · Fan Liu[1,4] · Caixia Li[2]

[1]   CAS Key Laboratory of Genomic and Precision Medicine, Beijing Institute of Genomics, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Beijing, China

[2]   Key Laboratory of Forensic Genetics, National Engineering Laboratory for Forensic Science, Institute of Forensic Science, Beijing, China

[3]   CAS-MPG Partner Institute and Key Laboratory for Computational Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China

[4]   Department of Genetic Identification, Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands