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WYDAWNICTWO UNIWERSYTETU ŁÓDZKIEGO
Łódź 2024

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Identification of the genetic determinants of shovel-shaped incisors and Carabelli's cusp

Fatma Nur Erbil[1], *David Andrew Merriwether*[2]

[1] Department of Anthropology, Burdur Mehmet Akif Ersoy University, Burdur, Turkey
[2] Department of Anthropology, Binghamton University, Binghamton, New York, United States

Abstract: Shovel-shaped incisors (SSI) and Carabelli's cusp (CC) are noteworthy human dental non-metric traits which presence and degree of expression have been reported to cluster within distinct populations. Recent advances in developmental biology suggest that SSI and CC are likely under polygenic developmental control; therefore, genetic variation in multiple genes is likely to contribute to differential SSI and CC expression. The exact genetic mechanisms underlying variation in SSI and CC development, however, remain mostly unknown. This study aims to identify whether variation in the basal DNA sequences of six candidate genes, *NKX2-3*, *SOSTDC1*, *BMP4*, *FGF3*, *FGF4*, and *WNT10A*, has any impact on SSI and/or CC expression. Study methods involve collection of saliva samples and dental data from 36 participants. The Arizona State University Dental Anthropology System (ASUDAS) has been used to score SSI and CC expression. Next-generation sequencing (NGS) methods were utilized to sequence the entire gene region of the candidate genes. Spearman's correlation test was used to score the relationship between the genotype and degree of trait expression of participants. Fifteen SNPs/INDELs belonging to *SOSTDC1*, *FGF3*, *FGF4* and *WNT10A* were significantly associated with SSI and/or CC expression. No SNPs/INDELs were detected in the genes *BMP4* and *NKX2-3* that significantly contributes to observed phenotypes. *FGF3*, *FGF4*, *SOSTDC1* and *WNT10A* were possibly involved in the formation of shoveling and Carabelli's cusp. However, because of the small sample size, more studies are needed to confirm their role and rule out any potential role of *NKX2-3* and *BMP4* in the production of SSI and CC.

Key words: dental nonmetric traits, Next Generation Sequencing, long-range PCR, variant identification, genotype-phenotype

Original article
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Introduction

Teeth develop through a complex and multidimensional process called *odontogenesis*, which involves several evolutionarily conservative elements interacting during embryonic and postnatal development. Genetic, epigenetic, and environmental factors are the main factors that can alter the final dental morphology (Brook et al. 2014). Therefore, the normal dental variation we observe within a population is the result of polygenic and environmental influences working in concert. Due to the multifactorial nature of tooth development, identification of the causal biological mechanisms that result in dental characteristics is rather challenging (Scott et al. 2018).

Nonmetric dental traits are inheritable features of teeth that exhibit patterned geographic variation due to the strong genetic component involved during their development (Scott et al. 2018). Previous work posited that the nonmetric dental traits are selectively neutral and thus do not easily adapt to the changing environmental conditions (Irish et al. 2020). Therefore, anthropologists have used nonmetric dental traits as proxies for genetic relatedness within and between human populations (Hanihara 2008; Scott et al. 2018). Currently, over 40 dental variants have been described by the ASUDAS (Arizona State University Dental Anthropology System) (Turner et al. 1991; Scott and Irish 2017). Among these variants, shovel-shaped incisors (SSI) and Carabelli's cusp (CC), which are the focus of this study, are the two dental features that have drawn the greatest attention from anthropologists (Fig. 1) (Carayon et al. 2019). SSI is prevalent, with the occurrence nearing 100%, in some North and East Asian, as well as Native American groups (Hlusko et al. 2018; Scott et al. 2018). On the other hand, populations with a predominance of European ancestry frequently exhibit CC (Scott and Irish 2017). SSI and CC have a well-established global distribution (Hrdlička 1920; Scott 1980; Tsai et al. 1996; Scott et al. 2018).

During development, reciprocal interactions between chemical signals within and around the cells of a developing tooth determine the final dental phenotype (Hughes and Townsend 2013). Two tissue layers involved in tooth development, the dental epithelium and the underlying mesenchyme, play intricate roles in gene activation and silencing which results in the development of the dental nonmetric characteristics (Jernvall and Thesleff 2000; Thesleff 2006; Jussila and Thesleff 2012; Scott et al. 2018). Currently, over 300 genes have been identified that are involved in the process of *odontogenesis* (Thesleff 2006). Still, the precise genetic pathways influencing the development of distinct nonmetric dental features are not fully understood. Further research is needed to identify genes involved in the formation of dental nonmetric traits.

This study aims to provide an initial investigative framework for understanding the genetic and genomic regulatory mechanisms that induce the production of two anthropologically and forensically relevant discrete dental traits: shovel-shaped incisors and Carabelli's cusp. We employed the candidate gene approach, which required the selection of the pre-specified genes of interest that were previously demonstrated to be involved in tooth development (Tabor et al. 2002). This study aims to determine whether the polymorphisms in *NKX2-3*,

FGF3, *FGF4*, *WNT10A*, *BMP4*, and *SOSTDC1* contributes to SSI and CC expression observed in an individual in order to better understand the genetic basis of geographic differences in tooth morphology.

Material and Methods

Dental data collection

The original objective of this project was to obtain dental impressions from the participants. However, due to the COVID-19 restrictions, we had to transition to a remote dental photo collection method instead of physical dental impressions. Individuals who showed interest in volunteering in the study received an informed consent form along with instructions for how to effectively and safely take dental photos. Participants were requested to take detailed photographs of their upper and lower teeth using adequate lighting to ensure clear visibility of the incisors and molars, which exhibit the two dental traits of interest in this study. Participants then emailed the photos to the first author of this study (i.e., FNE) to determine their eligibility to participate in the study. We also used the photos to score the dental traits of interest.

After the COVID-19 restrictions were lifted, in addition to dental pictures, we took negative impressions of upper and lower teeth from seventeen participants in order to make dental casts. Impressions were taken using vinyl polysiloxane (VPS), an alginate substitute dental impression material. The Arizona State University Dental Anthropology System (ASUDAS) plaques were used to score the dental traits (Figure 1). Only the incisors and molars on the left side of the dental arch was scored.

Saliva sample collection

Saliva was collected using a mouthwash collection protocol. The participants rinsed their mouths for 30 seconds with 10 ml of mouthwash before spitting into a collecting tube. DNA was extracted using the QIAamp DNA Mini Kit following the manufacturer's instructions (Qiagen, Germany).

Primer Design for Long-range Polymerase Chain Reaction (PCR)

The National Center for Biotechnology Information (NCBI)'s Primer-BLAST tool was utilized to design long-range PCR primers with high specificity (Ye et al. 2012). The entire gene region of *NKX2-3*, *FGF3*, *FGF4*, *BMP4*, and *SOSTDC1*, including the intronic and exonic regions, were targeted in the primer design. *WNT10A* was separated into three smaller sections due to its length, and separate primer sets were designed for each section. However, only the last section of *WNT10A* was included in this study due to the unreliable amplification issues encountered for the first two sections. The primer sequences, genomic positions, melting temperatures (Tm) of the primer pairs, and amplicon lengths are displayed in Table 1.

PCR Optimization

The GeneAmp® PCR System 9700 (Applied Biosystems, Foster City, CA) was utilized to perform the PCRs. TaKaRa LA (Long and Accurate) Taq polymerase enzyme (Takara Bio Inc.) and reagents were used to amplify each gene area in 50 μl volumes. The entire gene area for *NKX2-3*, *FGF3*, *FGF4*, *BMP4*, and *SOSTDC1* was amplified using a two-step PCR method, which combines the annealing and extension stages. *WNT10A* was amplified utilizing the touch-down (TD) PCR

method due to the specificity problems that we encountered. The PCR cycle conditions applied for each target region are displayed in Table 2. The 0.4% agarose gel electrophoresis was used to confirm the success of the PCR amplifications.

Table 1. Primer sequences, genomic locations, melting temperatures (T_m) °C, and length of amplicons

Gene name	Genomic location (GRCh38/hg38)	Sequence (5′ → 3′)	T_m °C (Melting Temperature)	Length of amplicon (bp)
FGF3	chr11:69809200-69820343	Forward: CCAAGTGCCAGGAGAGGTTAGTACACTGC	68.22	11144
		Reverse: GGGACAGAGGACCAGGAAGCAAGAGAAA	67.64	
FGF4	chr11:69770778-69776854	Forward: TACAGTGCGGGAATGGCGTGAATTAGC	67.46	6077
		Reverse: AGACAACACAGCAAGTGAGGGATGGGT	67.87	
BMP4	chr14:53949462-53959648	Forward: CATCCCAGTGTTTCTCCAAGGCATGTGT	67.17	10187
		Reverse: GGGCAGGACCAGGAAGTCTGCATTTCATC	68.95	
NKX2-3	chr10:99532030-99537060	Forward: TTTGCCTCATTCAACCCTAGCAACAACCA	67.10	5031
		Reverse: CTCCGCAAGTGACAAGGAGCCGCATA	68.86	
SOSTDC1	chr7:16458386-16465969	Forward: TCTCACACCGAGCATCCTAAGTCACCTC	67.23	7584
		Reverse: GCGTCGGCTCACAGACAAGTGATGAAGT	68.79	
WNT10A	chr2:218886144-218894785	Forward: TGTACCCAGAGAGGTGAGCTGGTGCAA	69.04	8642
		Reverse: CACAAGAGGCCCAGGAAGAATGTGCCC	69.30	
			Total amplicon length	48,665

Table 2. PCR cycling conditions

Target name	Cycle temperatures and times	Cycle Number	Cycle name
FGF3	94 °C 1 min	1×	Initial denaturation
	98 °C 10 sec + 68 °C 10 min	33×	Amplification
	72 °C 10 min	1×	Final elongation
WNT10A	94 °C 1 min	1×	Initial denaturation
	98 °C 20 sec + 73 °C 5 min 40 sec	5×	Amplification
	98 °C 20 sec + 71 °C 5 min 40 sec	5×	Amplification
	98 °C 20 sec + 69 °C 5 min 40 sec	25×	Amplification
	72 °C 10 min	1×	Final elongation

Target name	Cycle temperatures and times	Cycle Number	Cycle name
NKX2-3 and *FGF4*	94 °C 1 min	1×	Initial denaturation
	98 °C 10 sec + 69 °C 4 min 33 sec	30×	Amplification
	72 °C 10 min	1×	Final elongation
BMP4 and *FGF3*	94 °C 1 min	1×	Initial denaturation
	98 °C 10 sec + 68 °C 9 min	30×	Amplification
	72 °C 10 min	1×	Final elongation

PCR Product Purification, DNA Quantification, and Amplicon Pooling

Following the manufacturer's instructions, amplicons were purified using the Agencourt AMPure XP PCR Purification systems (Beckman Coulter, Pasadena, CA). The purified PCR product was quantified using Qubit® 2.0 Fluorometer (Life Technologies, Carlsbad, CA, USA) and the Qubit® dsDNA HS Assay Kit. Before pooling, each amplicon (i.e., purified PCR product) from the 36 individuals was diluted to 1 ng/μl. 5 μl of each amplicon from a single participant was pooled and used as the starting material for library preparation.

Library Preparation and Next-generation DNA Sequencing

Using the Nextera XT DNA library preparation kit (Illumina, Inc.), libraries were constructed using 1 ng of the pooled amplicons of each participant and indexed separately using IDT Illumina DNA/RNA UD indexes (Illumina, Inc.). The tagmentation, amplification, clean-up, library quality check, normalization, and library pooling stages are the primary steps of the Nextera XT DNA library preparation workflow. The libraries were finally pooled at a final concentration of 2nM. PhiX was also included as a sequencing control in the pool at a concentration of 12.5 pM.

2nM of the pooled libraries were further subject to denaturation and dilution to a loading concentration of 10 pM for sequencing. Libraries were sequenced in Dr. D. Andrew Merriwether's Molecular Anthropology Lab at Binghamton University. We used an Illumina MiSeq next-generation sequencer and MiSeq Reagent Kit v2 with a 2×149-cycle paired-end run configuration (Illumina, Inc.). The reason for choosing a 2×149 read length configuration rather than the commonly used 2×151 read length is that we used IDT for Illumina UD indexes, which are 10 bp long, as opposed to the Nextera XT indexes, which are 8 bp long.

Data analysis

Bioinformatics pipeline for NGS data

The raw NGS output data was analyzed using the variant calling pipeline that utilizes various programs/tools including GATK, BWA, Picard, and Samtools (McKenna et al. 2010; DePristo et al. 2011; Van der Auwera et al. 2013; Poplin et al. 2018; Van der Auwera and O'Connor 2020). The variant calling pipeline uses a FASTQ file as a starting material which contains raw sequencing data with quality scores assigned to each base call (Cock et al. 2010). As the final output, the pipeline generates a VCF (Variant Call Format) file that contains the variants that were detected in the sample. The non-variable sections of the genome, which comprise most of the human genome, are not included in the VCF file. Each step of the bioinformatics data analysis is provided in the Supplementary Materials. A linkage

disequilibrium analysis was conducted using LDlink software to distinguish between the causative variants and those in linkage disequilibrium (LD) (Machiela and Chanock 2015).

Spearman's Rank Analysis

Spearman's rank correlation coefficient (rho) was performed to estimate the relationship between a detected genetic variant on dental trait expression. In Spearman's rank correlation tests, two ordered or ranked variables were correlated by their strength as well as their direction (Hauke and Kossowski 2011). We ranked the genotypes based on the number of copies of the alternate (A) and reference (R) alleles: 0: homozygotes for the reference allele (RR); 1: heterozygotes (RA); and 2: homozygotes for the alternate allele (AA) (Kimura et al. 2015). The other variable (i.e., level of dental trait expression) was already designed in the ranked format in the ASUDAS (Fig. 1) (Turner et al. 1991). In other words, degrees of expression of a dental trait were classified on an ordinal scale starting with the lowest grade and ending with the highest grade.

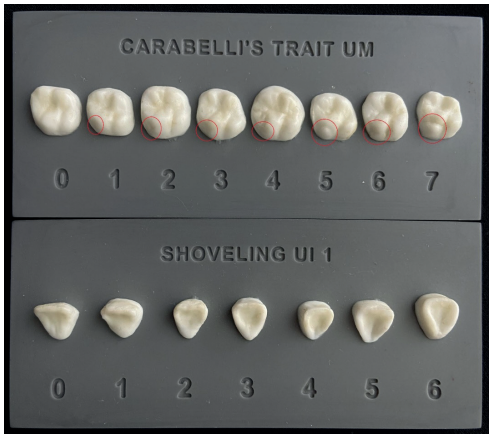

Fig. 1. ASUDAS plaques illustrating the range of Carabelli's cusp and shoveling expression. UM – Upper molar, UI 1 – Upper lateral incisor

Results

Dental Traits

Table 3 displays the prevalence of Carabelli's trait and shoveling for each grade among the study participants. Three individuals exhibited grade 3, and four grade 4 Carabelli's cusp expression. A total of 13 participants displayed the cusp form of Carabelli's feature, which is grades 5 and above. Out of 36 participants, 16 displayed no Carabelli's cups expression. On the other hand, most study participants demonstrated a weak expression of shoveling (i.e., grades 1 and 2) in UI1L and UI2L. In UI2L, one person demonstrated grade 3 shoveling, while another demonstrated grade 5. 21 and 19 individuals showed no shoveling in UI1L and UI2L, respectively.

Table 3. Distribution of trait grades observed in the study participants. UM1L – upper left first molar, UI1L – upper left central incisor, UI2L – upper left lateral incisor

Trait	Grade								
	0	1	2	3	4	5	6	7	Total
Carabelli's cusp (UM1L)	16	0	0	3	4	7	1	5	36
Shoveling (UI1L)	21	6	9	0	0	0	0	0	36
Shoveling (UI2L)	19	7	8	1	0	1	0	0	36

Statistical analysis

The variant calling pipeline identified 277 variants out of 48,665 bp DNA sequence that was amplified and sequenced in this study (see Tab. 1 for the amplicon lengths). The remaining 48,388 bp were excluded from the further statistical analysis since they did not exhibit any variable areas.

Among 277 variations, the Spearman's rank correlation test showed moderate significant correlation between fifteen loci in four genes (*WNT10A*, *SOSTDC1*, *FGF4*, and *FGF3*) and the two dental phenotype (i.e., shoveling and Carabelli's cusp) (Tab. 4). Significant negative and positive correlation was found between the dental features and two loci in *WNT10A*, seven loci in *SOSTDC1*, one locus in *FGF4*, and five loci in *FGF3*. The positions of the variations that were significantly linked with the dental features are shown in Figure 2. *BMP4* and *NKX2-3* were excluded from the statistical analysis since the variant calling method did not identify any variation in these genes.

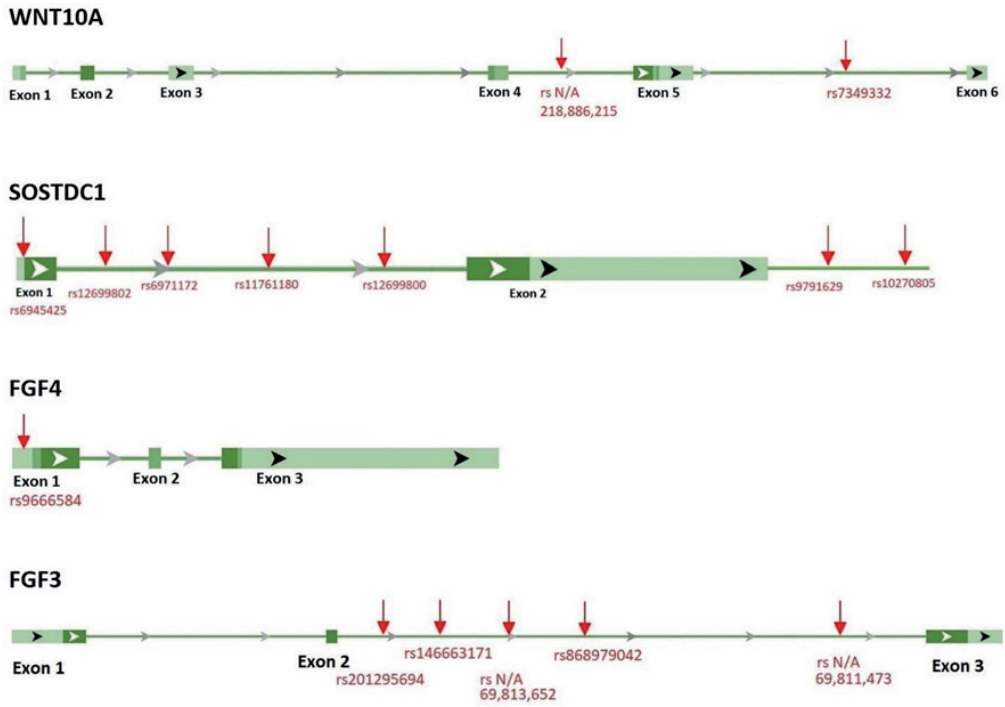

Fig. 2. Locations of the detected variants (Red arrows). Dark green bars indicate coding exons, and the light green bars indicate non-coding untranslated regions (UTRs). Horizontal lines that connect exons show the introns. White and black arrows indicate the direction of transcription from 5′ to 3′. Grey arrows in the introns indicate the direction of splicing. Green bars and connecting lines showing exon and intron regions were taken from the National Center for Biotechnology Information's website (https://www.ncbi.nlm.nih.gov/)

The majority of the variations found in this study—11—were intron variants, as shown in Table 5. Two of the observed variants were 5 prime UTR variants, and two are downstream gene variants. Three of the fifteen mutations were INDELs, whereas the other twelve are SNPs.

Three of the found variants were INDELs, located at the following positions:

chr2:218886215, chr11:69811473, and chr11:69813652. The reference and alternate alleles found by the variant calling pipeline in this study did not match the reference and alternate alleles in the NCBI's dbSNP database (https://www.ncbi.nlm.nih.gov/snp/). In addition, no rs ID was assigned to the variant at chr11:69813652 by the variant calling pipeline. Therefore, the genomic positions (i.e., chr2: 218886215, chr11: 69811473, and chr11: 69813652) were used throughout the text instead of the rs numbers to avoid any confusion.

Table 4. Spearman's rank correlation coefficients (rho), p values and dental traits that are associated with each locus. Asterisks (*) indicate correlations significant at 0.01 level. The rest of the correlations are significant at the 0.05 level. chr – chromosome, UI1L – Upper left first (central) incisor, UI2L – Upper left second (lateral) incisor, UM1L – Upper left first molar, N/A – rs numbers not available

Chromosome Position	SNP/INDEL ID	Gene	Rho	Sig. (2-tailed)	N	Associated trait(s)
chr2:218891661	rs7349332	*WNT10A*	-0.437	0.026	26	Shoveling UI2L
chr2: 218886215	N/A	*WNT10A*	-0.458	0.019	26	Carabelli's cusp UM1L
chr7:16460517	rs10270805	*SOSTDC1*	0.378	0.023	36	Shoveling UI1L
			0.430*	0.009	36	Shoveling UI2L
chr7:16460784	rs9791629	*SOSTDC1*	0.378	0.023	36	Shoveling UI1L
			0.430*	0.009	36	Shoveling UI2L
chr7:16463435	rs12699800	*SOSTDC1*	-0.329	0.050	36	Carabelli's cusp UM1L
chr7:16464081	rs11761180	*SOSTDC1*	-0.329	0.050	36	Carabelli's cusp UM1L
chr7:16464648	rs6971172	*SOSTDC1*	0.340	0.043	36	Shoveling UI1L
			0.388	0.019	36	Shoveling UI2L
			-0.366	0.028	36	Carabelli's cusp UM1L
chr7:16464881	rs12699802	*SOSTDC1*	-0.329	0.050	36	Carabelli's cusp UM1L
chr7:16465716	rs6945425	*SOSTDC1*	0.416	0.012	36	Shoveling UI1L
			0.341	0.042	36	Shoveling UI2L
chr11:69775191	rs9666584	*FGF4*	0.450*	0.006	36	Shoveling UI2L
chr11:69813640	rs868979042	*FGF3*	0.354	0.034	36	Carabelli's cusp UM1L
chr11:69813824	rs146663171	*FGF3*	0.342	0.041	36	Shoveling UI1L
chr11:69813844	rs201295694	*FGF3*	0.437*	0.008	36	Shoveling UI1L
			0.412	0.013	36	Shoveling UI2L
chr11:69811473	N/A	*FGF3*	-0.349	0.037	36	Carabelli's cusp UM1L
chr11:69813652	N/A	*FGF3*	0.405	0.014	36	Carabelli's cusp UM1L

Table 5. Ensemble Variant Effect Predictor (McLaren et al. 2010) results with possible consequences of the variants detected in this study. Asterisks (*) indicate an allele deletion

Genomic Position	Variant ID	Variant type	Reference allele	Alternate allele	Gene	Consequence
chr2:218891661	rs7349332	SNP	C	T	*WNT10A*	intron variant
chr2:218886215	N/A	INDEL	GCA	G	*WNT10A*	intron variant
chr7:16460517	rs10270805	SNP	A	G	*SOSTDC1*	downstream gene variant
chr7:16460784	rs9791629	SNP	C	T	*SOSTDC1*	downstream gene variant
chr7:16463435	rs12699800	SNP	C	T	*SOSTDC1*	intron variant
chr7:16464081	rs11761180	SNP	A	G	*SOSTDC1*	intron variant
chr7:16464648	rs6971172	SNP	G	C	*SOSTDC1*	intron variant
chr7:16464881	rs12699802	SNP	T	C	*SOSTDC1*	intron variant
chr7:16465716	rs6945425	SNP	T	C	*SOSTDC1*	5 prime UTR variant
chr11:69775191	rs9666584	SNP	A	G	*FGF4*	5 prime UTR variant
chr11:69813640	rs868979042	SNP	G	*,A	*FGF3*	intron variant
chr11:69813824	rs146663171	SNP	G	*,A	*FGF3*	intron variant
chr11:69813844	rs201295694	SNP	T	A,*	*FGF3*	intron variant
chr11:69811473	N/A	INDEL	GA	G	*FGF3*	intron variant
chr11:69813652	N/A	INDEL	ATGGAT-GGATG-GGTG-GATGGC	*,A	*FGF3*	intron variant

Linkage Disequilibrium (LD)

The LD heatmaps for the *SOSTDC1*, *FGF3*, and *FGF4* variations are shown in Figures 3 and 4. The LD r^2 and D′ values are provided in tables S1, S2, S3, and S4 in the Supplementary Materials. The degree of the LD between the variants is shown by the color intensity in the Figures 3 and 4. For each pair of variants, the r^2 measurements are displayed in red, while the D′ measurements are displayed in blue. Due to the issues with inconsistent rs numbers, alternate alleles, and reference alleles encountered during data analysis, the variations at chr2:218886215, chr11:69811473, and chr11:69813652 were excluded from the LD analysis.

The r^2 values for the *SOSTDC1* variants show a range of correlations from "strong" to "weak" and "no LD" (Fig. 3). D′ values, on the other hand, exhibit no variation and all show a significant correlation among all *SOSTDC1* variants. Similarly, r^2 values for the *FGF3* and *FGF4* variants all show no correlation between the variants in these genes. D′, on the other hand, indicates strong LD for many variants except for the associations between rs9666584, rs201295694, and rs146663171, which are depicted with a lighter shade of blue (Fig. 4).

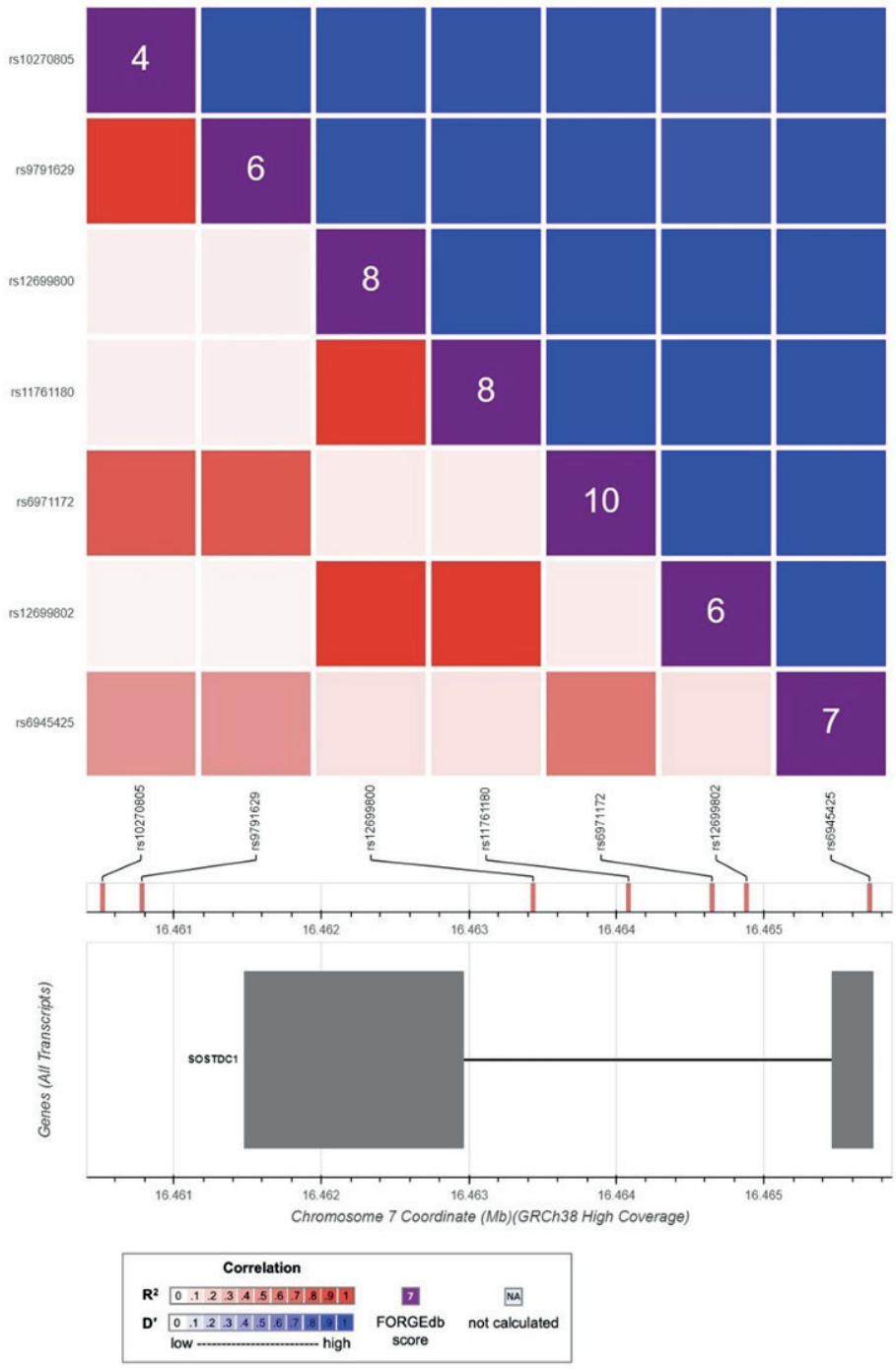

Fig. 3. Linkage disequilibrium heatmap showing correlations between *SOSTDC1* variants

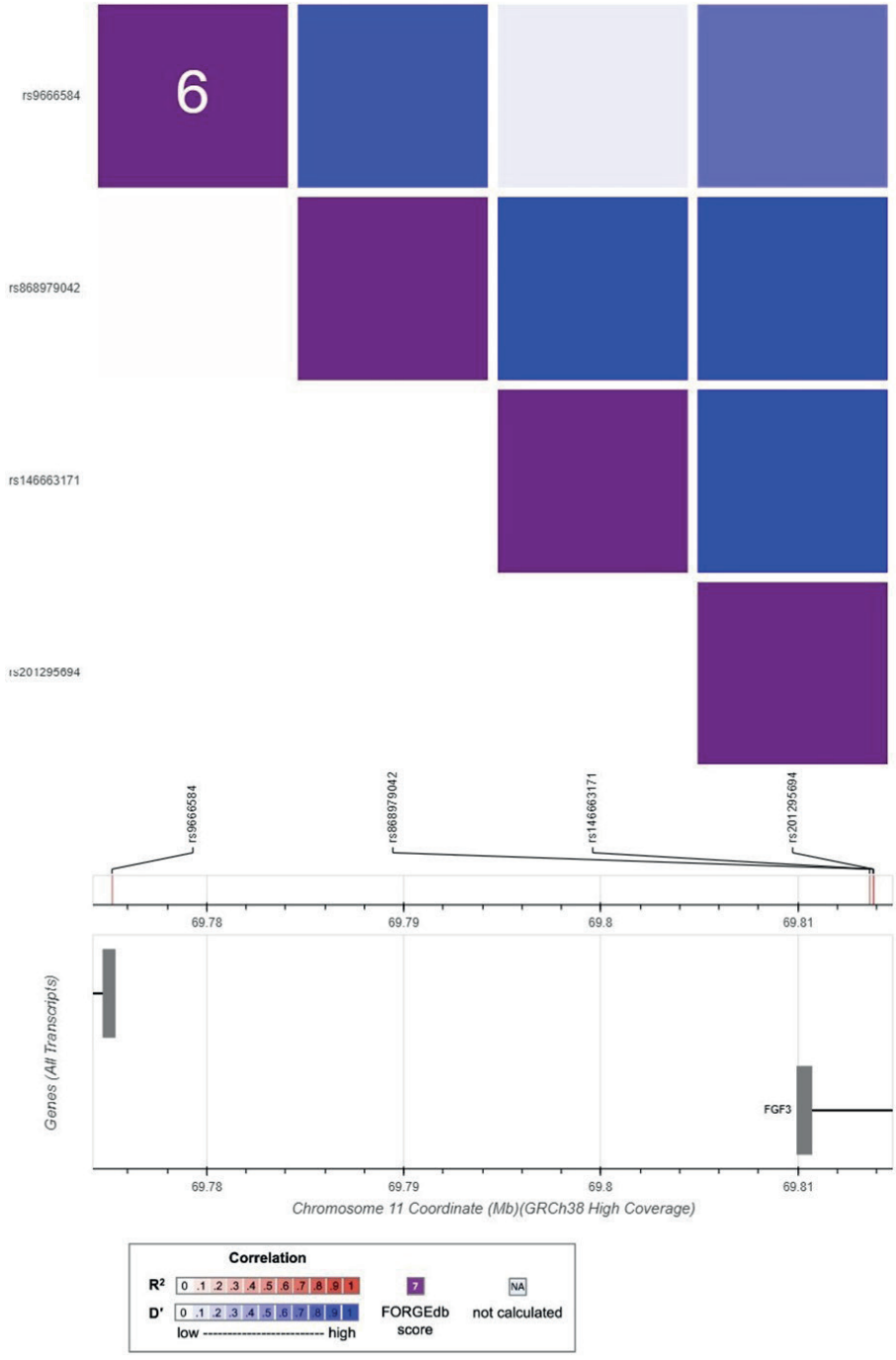

Fig. 4. Linkage disequilibrium heatmap showing correlations between *FGF3* and *FGF4* variants

Discussion

The genetic pathways that are involved in the embryonic development of teeth have been described in detail over the past few decades. Hundreds of genes that ultimately produce teeth have been identified, and the gene network interactions that cascade during embryonic development to produce teeth are well understood (Pillas et al. 2010). However, only few genes that play a significant role in the production of common dental nonmetric variation have been identified so far (Kimura et al. 2009, 2015; Lee et al. 2012). The etiology behind many nonmetric dental traits still remains to be elucidated.

The purpose of this study was to determine whether variation in the basal DNA sequences of six candidate genes, *NKX2-3*, *SOSTDC1*, *BMP4*, *FGF3*, *FGF4*, and *WNT10A*, which have been previously implicated in dental development, has impact on an individual's expression of shovel-shaped incisors (SSI) and/or Carabelli's cusp (CC). The findings reveal that fifteen SNPs/INDELs in *SOSTDC1*, *FGF3*, *FGF4*, and *WNT10A* significantly correlate with shoveling and/or the Carabelli's cusp grades.

Significant Single Nucleotide Polymorphisms (SNPs) and Insertions or Deletions (INDELs)

SSI and CC were negatively correlated with seven variants, including rs7349332 and chr2:218886215 in *WNT10A*; rs12699800, rs11761180, rs6971172, and rs12699802 in *SOSTDC1*; and chr11:69811473 in *FGF3* (Tab. 4). The rho values vary from -0.329 to -0.458 which indicate a moderate negative association. A negative Spearman's rho value means that an individual having an increased number of the alternate allele(s) is correlated with a decreased level of trait expression. Six of the seven negatively correlated variants were associated with CC, and one is associated with SSI (UI2L). This finding is interesting because Carabelli's cusp expression consistently displays negative associations with the alternate alleles in these six loci. In other words, at these loci, the reference allele is more linked to higher grades of Carabelli's cusp expression compared to the alternate allele. Future research, including a bigger sample size and a more geographically diversified group of study participants, is required to confirm these negative correlations.

SSI and CC expression was positively linked to nine variants: rs10270805, rs9791629, rs6971172, rs6945425 in *SOSTDC1*, rs9666584 in *FGF4*, rs868979042, rs146663171, rs201295694, and chr11:69813652 in *FGF3* (Tab. 4). The rho values ranged between 0.340 and 0.450 indicating moderate correlations. A positive Spearman's value suggests that the higher grades of SSI and CC are associated with the number of alternate alleles.

Five SNPs, rs10270805, rs9791629, rs6971172, rs6945425, and rs201295694, were positively correlated with shoveling in both the central (UI1L) and lateral (UI2L) incisors (Tab. 4). These results are not unexpected given the previous research that showed that shoveling expression in central and lateral incisors is significantly correlated with each other (Hasegawa et al. 2009). In other words, if the upper central incisors in an individual exhibits shoveling, there is a high likelihood that the lateral incisors will also have some degree of shoveling expression. These observations can

be explained by the fact that the same genetic factors affect both the central and lateral incisors (Hasegawa et al. 2009). The only variant that we found to be associated with both SSI and CC is the SNP rs6971172 in *SOSTDC1*. This particular SNP exhibited a positive correlation with SSI and a negative correlation with CC. This outcome is also not surprising, given that Carabelli's cusp and shoveling are typically thought to have opposite manifestations across Asian-Native American and European populations (Scott et al. 2018). According to Scott et al. (2018), individuals from these regions often exhibit either shoveling or Carabelli's cusp, but not (in most cases) both.

This study found no significant correlations between the *NKX2-3* and *BMP4* variants and the two dental traits of interest. However, it is important to note that this result does not necessarily mean that these genes do not have any specific functions related to the formation of shoveling and Carabelli's cusp. The lack of correlation may be attributed to the limited sample size used in this study. Thus, future research with a larger sample size is necessary to reliably determine the role of these genes in the formation of dental traits.

It is noteworthy that the majority of the variations detected in this study have not been reported before, but are included in the ClinVar database. ClinVar is a publicly available database that archives genetic variations with associated phenotypes or diseases (https://www.ncbi.nlm.nih.gov/clinvar/). The fact that the variants detected in this study have not been reported in scientific publications and yet are included in the ClinVar database may be due to the possibility that these SNPs/INDELs may have been discovered in earlier Genome-Wide Association Studies (GWAS), and their functions are still unknown. One exception to this is SNP rs7349332 in the *WNT10A* gene, which has been previously linked to increased risk of colorectal cancer, hair loss and hair shape (Li et al. 2017). Kimura et al. (2015) discovered a significant correlation between crown size and rs7349332. In addition, Eriksson and colleagues (2010) reported an association between the alternate allele of this particular SNP and hair curl. In our study, this SNP was negatively associated with shoveling (UI2L) indicating that the increased number of alternate alleles at this locus is associated with decreased grade of shoveling expression in UI2L.

Location and consequence of variants

Introns make up the majority of the variants found in this study (Tab. 5). Figure 2 shows the visual representation of the locations of the discovered variants. Introns refer to non-coding sections of DNA, which do not provide instructions for the production of amino acids. Introns are often regarded as functionless DNA "junk" because they are removed during transcription and not involved in protein synthesis (Parenteau and Abou Elela 2019:923). Recently, crucial roles that introns play during gene expression have been recognized (Jo and Choi 2015). Immediately after transcription, introns are removed from the pre-mRNA transcript through a process known as splicing. Subsequently, the exons are joined together to form a mature mRNA, which will eventually result in the production of the protein. The process of splicing does not always follow the same pattern. Although it is a tightly controlled molecular mechanism, splicing errors and the alternative splicing events frequently occur which results in the alternative forms of a protein

from the same mRNA template. Alternative splicing is a widespread phenomenon, occurring in about 95% of multi-exon genes in humans (Jo and Choi 2015).

Contrary to the common belief, introns are evolutionarily advantageous as they are a major source of novel genes and gene products (Jo and Choi 2015). The process of alternative splicing can potentially generate many isoforms of proteins from a single gene. In addition, research revealed that genes with introns exhibit enhanced levels of gene expression than genes without introns (Shabalina et al. 2010).

The intron variants discovered in this study are unlikely to change the protein's amino acid sequences or functions. Nonetheless, there is a possibility that these variants could modify gene expression through processes such as alternative splicing and gene expression enhancement. This highlights the necessity of performing deep sequencing of the entire gene region, encompassing both intronic and exonic regions, instead of focusing solely on exons. Variation in introns, the 3′ and 5′ untranslated regions (UTRs), and the level of gene expression can all affect the dental phenotypes such as the ones that are investigated in this study.

Linkage Disequilibrium (LD)

The results of the LD analysis suggest that there is significant linkage disequilibrium among multiple variants, which indicates a non-random association (Figures 3 and 4, and Table S1, S2, S3, and S4 in Supplementary Materials). This result suggests that the variants detected in this study may not actually be causing SSI and CC. Instead, they might be potentially linked to an as-of-yet unelucidated variant or variants that are nearby and under selection pressure. If that is the case, this makes SSI and CC "hitchhiking" phenotypes that are inherited together with another phenotype which might be the actual target of natural selection (Park et al. 2012:508). Therefore, the identification of the causal genes is made more difficult by the fact that the variations are in substantial LD. As a result, it is unclear which SNPs or INDELs are actually responsible for SSI and CC. Future research needs to clarify in more detail how these genes interact with other genes and how they affect the expression of Carabelli's cusp and shovel-shaping.

Supplementary materials available on the request.

Conclusion

The current study aimed to shed light on the genetic basis of Carabelli's cusp and shovel-shaped incisors. The degree of expression of the two dental characteristics and fifteen short variations in *FGF3*, *FGF4*, *SOSTDC1*, and *WNT10A* were shown to be significantly correlated. The conclusion may be formed in part because of the small sample size that variations in the genes *FGF3*, *FGF4*, *SOSTDC1*, and *WNT10A* may play a role in the development of shoveling and Carabelli's cusp. More research is required to determine if the genes *NKX2-3* and *BMP4* contribute to the development of shoveling and Carabelli's cusp.

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Conflict of interests

The authors declare no conflict of interests.

Authors' contribution

FNE – conception and design of the study, funding acquisition, data collection, performing the lab work and data analysis, manuscript writing; DAM – conception and design of the study, funding acquisition, reviewing and editing, critical revision of the article. All authors have read and agreed to the published version of the manuscript.

Informed consent

The study protocol used in this project was approved by the Binghamton University Institutional Review Board (IRB). All participants volunteered in this study provided an informed consent form which was approved by the IRB at Binghamton University (STUDY00002536). Please visit https://www.binghamton.edu/research/division-offices/research-compliance/human-subjects/about.html#Contact%20Information for more information about the Binghamton University IRB office.

This article is based on Fatma Nur Erbil's Ph.D. dissertation titled "GENETIC DETERMINANTS OF SHOVEL-SHAPED INCISORS AND CARABELLLI'S CUSP". Please visit https://www.proquest.com/docview/2694486327?pq-origsite=gscholar&fromopenview=true&sourcetype=Dissertations%20&%20Theses for a copy of the dissertation.

Corresponding author

Fatma Nur Erbil, Burdur Mehmet Akif Ersoy Universitesi Istiklal Yerleskesi Fen Edebiyat Fakultesi Antropoloji Bolumu, 15000 Burdur, Turkey, e-mail: fnerbil@mehmetakif.edu.tr, phone number: +905441034520

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Translation practices in cross-cultural social research and guidelines for the most popular approach: back-translation

Marta Kowal

IDN Being Human Lab – Institute of Psychology, University of Wrocław, Wrocław, Poland

Abstract: In recent years, there has been a notable increase in the number of cross-cultural research, marking a positive shift from the predominantly WEIRD (Western, Educated, Industrialized, Rich, and Democratic) scientific focus. Most people are not WEIRD, and thus, such a trend is widely appraised. However, cross-cultural research bears many risks, one of which is a language barrier. Conducting studies in various populations that communicate in different languages results in the need to translate the study materials. A proper translation is essential for ensuring the validity and reliability of the data. This study aims to discuss translational practices in cross-cultural research, based on the analysis of studies published between 2017 and 2021 in two respected in cross-cultural social research journals (i.e., Cross-Cultural Research and Journal of Cross-Cultural Psychology). The results revealed that one fifth of the analyzed studies lacked crucial information regarding translation procedures. Among the studies that did report on translation methods, back-translation was the most popular approach, with nearly half of the studies utilizing this technique. The recommendations for cross-cultural researchers are outlined, with an emphasis on the sufficient description of the samples, including their nationality and used language. In addition, guidelines for the back-translation are reiterated: 1) forward and 2) back translation, 3) versions' comparison, 4) pilot study, and 5) revision of the final version.

Key words: forward-back translation, brislin, research methods, linguistic recommendations.

Original article
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Introduction

The analyses from the first decade of the 21st century revealed a significant bias in research, with the majority of studies being conducted in WEIRD (Western, Educated, Industrialized, Rich, and Democratic) countries (Henrich et al. 2010; Arnett 2016). However, the situation is slowly taking a turn (Rad et al. 2018; Pollet and Saxton 2019), with more voices raising the importance of going 'beyond WEIRD' (see a special issue with this title in the *Evolution and Human Behavior*). The number of studies conducted in non-WEIRD countries published in high-impact journals is on the rise (Pollet and Saxton 2019), and so does the number of cross-cultural studies that simultaneously span many countries (Coles et al. 2022). Although science still mainly relies on data from WEIRD participants, changing this might be beneficial in manifold ways.

First, examining data from studies conducted on non-WEIRD participants expands the understanding of human nature and the impact of culture and environment on psychological, cognitive, behavioral, and physiological phenomena (Henrich 2008). This is especially important, given that many discoveries did not hold as universal truths when participants from non-WEIRD countries were examined, such as people's strive for fair economic offers (Henrich et al. 2010), pupils' dilatation under water (Gislén et al. 2006) or proneness to perceptual illusions (Phillips 2019).

Second, broadening the focus of research beyond WEIRD countries also addresses issues of geographical bias and promotes inclusivity in academia. Most research centers are in the USA and Europe (Skopec et al. 2020; Thalmayer et al. 2021; Klein et al. 2022). Most of the annual awards go to scientists from US institutions (ASP 2020). Most of the funding devoted to science remains in WEIRD countries (Morgan and Zahl 2021). This geographical bias (Kowal et al. 2022) sets the entry threshold for being included in the scientific mainstream higher for scholars from non-WEIRD countries, making it sometimes challenging (or impossible) to surpass (Tindle 2021).

To ensure the advancement of science, studies need to be conducted worldwide. However, certain requirements must be met, especially in social and behavioral sciences. Many, if not most, research conducted within the fields of anthropology, psychology, international marketing research, quality of life research, etc. involve human participants and utilize all sorts of questionnaires (Tyupa 2023). Thus, ensuring participants' comprehension of the study and measures' reliability is crucial (Choi et al. 2012). However, sometimes scientists focus on the tools' reliability at the expense of the study's comprehension. Many scales are validated in English, and thus, using these scales with established validity in all investigated societies might be tempting.

While the increasing number of individuals learning and speaking English as a second or additional language (Salomone 2022) may seem to justify using only English scales, this approach is unfavorable for several reasons. English proficiency is often associated with higher education levels, potentially leading to sampling biases (for a review on the impact of English proficiency in non-English speaking countries, see Li et al. 2022). Moreover, language

can also impact cognition, behaviors, emotions, and morality, leading to substantial differences in responses when participants use a non-native language (Roberts and Felser 2011; Pavlenko 2012; Chen 2013; Coughlin and Tremblay 2013; Hadjichristidis et al. 2017; 2019).

Overall, reaching participants from non-WEIRD countries is essential for a comprehensive understanding of human nature, and thus, cross-cultural studies are needed. However, studying populations that speak different languages should be approached with caution. A preferable approach would be to translate the scales into local languages, aiding ease of survey comprehension by participants from different societies. Importantly, for the scale's translation to serve its scientific purposes, is must be equivalent to the source scale (Hulin 1987; Spector et al. 2015). The translated scale should measure the psychological phenomenon for which it was created in the same manner as the source scale. In other words, individuals with the same level of underlying construct should present a similar pattern of responses regardless of the linguistic version of the scale. This can be easily assessed with, for instance, statistical tests of equivalence of invariance (Milfont and Fischer 2010). So far, researchers have used various approaches to translate their surveys into local languages, including, but not limited to, back-translation, long translation, and ad hoc translation.

Back-translation has a long tradition in cross-cultural research. It has been already discussed in cross-cultural research in the 1960s by Werner and Campbell (1969), Fink (1963), and Sinaiko (1963). However, it was not until Brislin that back translation, also called forward-back translation, gained widespread recognition, making Brislin (1970; 1983) its father. Brislin, in his seminal works, described five steps of back-translation. First, translating from the source language into the local language. Second, back translating from the local language to the source language. Third, comparing the original and back-translated versions into the source language and adjusting for any resulting differences. Fourth, conducting a pilot study with a semi-final version on representatives of the future research. Fourth, reviewing the final version. Ideally, two different bilinguals carry out the two first steps, with the second (back-translating into the source language) being blind to the original source version. Forward-back translation has been widely used in many studies (e.g., Lieberoth et al. 2021; Kowal et al. 2024; Sorokowski et al. 2023). Although some argue that such a method, focused on comparing the two versions (source and translated), provides rather limited or even misleading insight into the quality of the translation (Survey Research Center 2016), it is often described as a recommended translational method in research (Brislin 1970; 1983; van de Vijver and Leung 2011; Moshontz et al. 2018; Klotz et al. 2023).

Building on back-translation, a more nuanced method for cross-cultural translation was introduced as a gold standard, namely, long-translation. It has been also known as TRAPD, from Translation, Review, Adjudication, Pretesting, and Documentation (Pennell et al. 2017; Curtarelli and Van Houten 2018). It strives for perfection in translation's output. Researchers interested in translating according to long translation

guidelines should meticulously plan the whole process and take a holistic approach, keeping in mind both the study's design, its goals, and the translation. First, several individuals are asked to produce parallel translations of the source text. Then, other individuals review the translations (preferably with the original translators). Then, an adjudicator decides which versions of the translations are to be further processed. When the initial version of the translation is ready, it is further pretested on a pilot sample to detect any potential issues. After the last revision and re-adjudication, the final version of the survey is ready. If the researcher has time and resources, long translation might seem the best choice, even better than back-translation. It involves several quality checks and often produces a translation tailored to a given cultural context (Survey Research Center 2016). However, a long translation is rather time and resource consuming. Furthermore, one needs to bear in mind that following long translation guidelines does not guarantee that the translation's output would be flawless (Vujcich et al. 2021).

In contrast to back- and long translations, ad hoc translation relies entirely upon a single bilingual person who translates a text into another language or, alternatively, a local bilingual person who serves as an ad hoc interpreter. Although such individuals obviously know two languages and are rather highly motivated to perform their translating task well, their resultant translations are prone to exhibit a level of quality deemed suboptimal (Hagan et al. 2013). In addition to usually insufficient or even a lack of training, which is useful in attesting proficiency in translating (Vandevoorde et al. 2019), the solitary nature of translation by a single person poses a heightened susceptibility to potential errors. Conversely, when two translators are engaged, the risk of such errors is substantially lower, given that any mistakes can be more readily identified by the other translator (Cha et al. 2007).

When it comes to the prevalence of different translational methods, prior analyses revealed that back-translation might be the most popular approach in Academia (Maneesriwongul and Dixon 2004; Douglas and Craig 2007; Klotz et al. 2023). For instance, Maneesriwongul and Dixon (2004) analyzed studies within international nursing research (published up to 2002) and showed that as much as 80% of research devoted to instrument translation utilized back-translation. Douglas and Craig (2007) analyzed studies published in the Journal of International Marketing between 1993 and 2005, and found that 76% of them reported using back-translation procedure. Klotz et al. (2023) analyzed works in organizational research, published in the Journal of Applied Psychology between 1997 and 2021 and found that among the studies which reported on the translation procedure, 91.3% utilized principles of back-translation.

However, no other study would investigate the prevalence of different translating methods in cross-cultural social realms. The present work aims to address this gap in knowledge and probe the most recent state of art in translational practices within cross-cultural social research by analyzing studies published between 2017 and 2021 in two respected journals in the cross-cultural domain, namely Cross-Cultural Research

and Journal of Cross-Cultural Psychology. The second aim is to delineate and reiterate the recommendations for one of the most widely recognized, classic, and arguably one of the best methods – back-translation (Brislin 1970; 1983; Maneesriwongul and Dixon 2004; van de Vijver and Leung 2011; Moshontz et al. 2018).

Material and methods

Search strategy

Two target journals respected in the cross-cultural research were chosen, namely, Cross-Cultural Research and Journal of Cross-Cultural Psychology. Next, 5-year period was chosen, as this time window allows to extensively probe the studied topic. The most recent years for which full versions of works were easily accessible were then selected, that is, 2017 and 2021. The analyzed studies were identified through the publishers' official websites, which listed all published works, divided by year, volume, and issue.

Eligible studies

Out of 431 studies published in the Cross-Cultural Research (n = 100) and Journal of Cross-Cultural Psychology (n = 331) between 2017 and 2021, 374 (~87%) were empirical studies, 55 (~13%) were theoretical works, including reviews, analyses of other data (such as historical or anthropological evidence) and meta-analyses, and 2 (~0.5%) were retracted. Within the empirical studies (n = 374), two types were distinguished: re-analyses of secondary data (N = 106, 28%) and original studies (N = 268, 72%). Many studies utilized the same datasets, such as the World Values Surveys. To avoid duplication of results, only original studies were further analyzed (N = 268).

Synthesis of results

Out of 268 original studies, 113 (~38%) were conducted in English[1], 18 (6%) did not require translation as they involved tasks unrelated to language (e.g., behavioral tasks), 22 (~7%) did not specify the language used but authors' affiliation suggested non-English speaking participants, and 147 (49%) employed translations.

Excluding the ones that did not need translations and used (presumably) English scales (N = 131), of the remaining (N = 192), 26 (13.5%) relied solely on previously linguistically validated measures[2], 7 (3.6%) incorporated sort of long-translation procedure, 89 (46.4%) used back-translation, 30 (16%) used simple translation (including forward translation or a live translation by an interpreter), and 40 (20.8%) did not provide explicit information regarding the translation process (see Fig. 1). For detailed list of all studies, see Table S1 in the Supplementary Material. Suplementary materials are available after request.

1 This determination was based on explicit information provided in the respective studies, and in cases where such information was lacking, recourse was made to the authors' affiliations and the ethical approvals granted by Institutional Review Boards (IRBs).

2 It is important to note that studies were categorized as using 'previously validated measures' if they exclusively employed such scales in given languages. If a study used both previously linguistically validated measures and not yet translated scales, a study fell under other types (i.e., not under the 'previously validated measures').

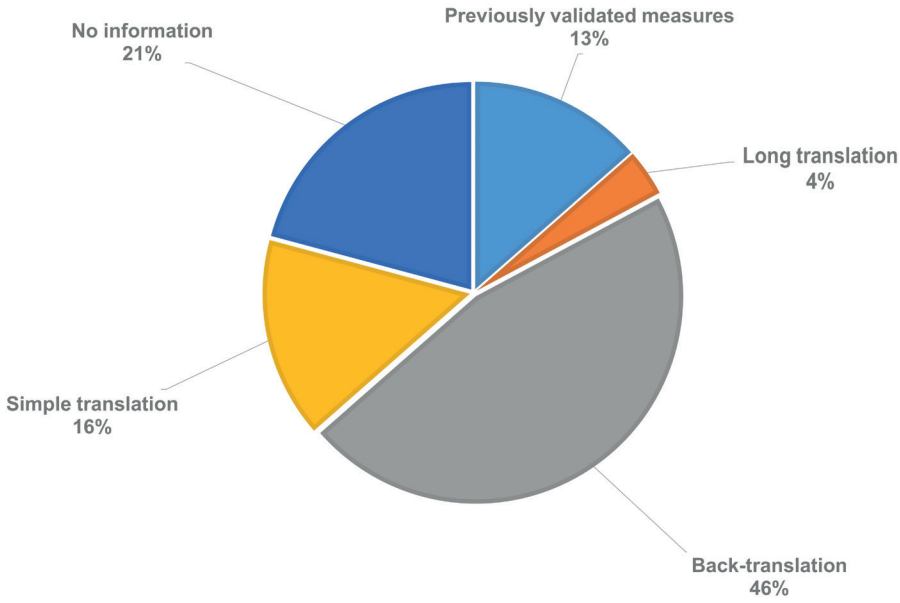

Fig. 1 The analysis of translating practices in original studies that involved using non-English language (N = 134)

Discussion of results

The analysis of studies published in the journals devoted to cross-cultural research (i.e., Cross-Cultural Research and Journal of Cross-Cultural Psychology) over a five-year period (between 2017 and 2021) reveals several important findings regarding the translation practices in cross-cultural research. More than half of the original studies (51.3%) were conducted in societies using other than English language, indicating that social and behavioral science is embracing the human diversity by exploring experiences of individuals from various cultures. On the other hand, many analyzed studies did not include information about the studied sample, including nationality and the language used. That was especially the case for studies conducted in, presumably, the American population, as could be inferred from the author's affiliation, IRB's ethical approval, used scales or the lack of information on their translations, suggesting that the original English scales were utilized. Insufficient description of the samples has serious implications for the replicability and generalizability of research findings. It is unacceptable, for instance, not to provide information on the number of recruited participants or their age. However, just as it is essential to provide comprehensive information about the sample size and age distribution, equally essential is the disclosure of participants' nationality and the language used (Valdez et al. 2021). Otherwise, any replicating attempts might be doomed to failure (Flake et al. 2022).

Furthermore, it is crucial to note that a significant number of studies (almost a quarter) did not provide detailed information about the translation pro-

cess for the scales used – neither whether it was conducted nor how the translation process looked like. Inadequate description of the translation process raises questions of whether the scales have been appropriately translated and whether the translated scales measure the same latent constructs that did the original and validated scales (Klotz et al. 2023). The absence of such information limits other researchers' ability to draw informed conclusions about the quality of the translated scales. In extreme cases, poor translation might lead to dubious results (Flake et al. 2022).

Another significant concern arises from the finding that approximately one fifth of the original studies relied solely on simple translation methods. While it is possible for a linguistically talented individual to produce high-quality translations suitable for a specific language, study purpose, and cultural context, it is essential to recognize that errors can still occur. After all, to be human is to err (Croskerry 2010). Thus, it is more advisable if more rigorous translating techniques are employed to ensure that the given study fully leverages its potential to explore the studied phenomena. It would be a huge waste if the study's results were questionable just because of the linguistic issues of the used scales. This could lead to disastrous consequences of not only wasted resources, such as time and funding, but also to, for instance, implementing ineffective social programs (Ennett et al. 1994; Petrosino et al. 2000).

Moreover, the current analysis provides evidence that back-translation is the most popular translational approach in studies published in the Cross-Cultural Research and Journal of Cross-Cultural Psychology, and, most likely, in cross-cultural research in general. Almost half of the original studies adhered to the guidelines laid by Brislin (1970; 1983). Although some scholars advocated for using even more advanced than back-translation techniques (Pennell et al. 2017; Curtarelli and Van Houten 2018), weighing gains and losses, back-translation might be a good enough approach. For the sake of resources at hand, researchers might prefer to invest in producing a translation that is sufficient and tailored to research goals. Notably, the back-translation method consists of five steps and comes with several quality checks, thus, any errors and ambiguity should be easily spotted and corrected (Brislin 1970; 1983).

However, it is worth noting that the description of the back-translation method in the analyzed studies typically included only four steps (forward translation, back-translation, comparison, and revision), omitting the step of piloting the semi-final version of the survey in the target population. This omission poses a potential risk that could be easily mitigated. Administering the semi-final version to individuals outside of academia might provide valuable insights into how future participants perceive the survey, which could allow for necessary adjustments. It is worth acknowledging that each profession uses its jargon, holds common knowledge, and relies on understanding basic concepts that might not be universally understood (Hudson 1978). It is easy to miss seemingly obvious things that can be yet ambiguous for others. Take, for example, 'acting-out.' Very few psychologists (if any) would not know the meaning of acting-out (Weiner et al. 2012). However, an average person without a psychological background might struggle to fully grasp this phrase (Bernard 2014).

Furthermore, some phrases cannot be translated directly into other languages. Take, for example, 'romantic relationship'. A question about one's romantic relationship should not stir the pot among English-speaking participants. However, a direct translation into other languages, say Polish, might be problematic. A team of researchers involved in one of the cross-cultural projects of Psychological Science Accelerator translated 'romantic relationship' literally. Only piloting the survey on a population outside of Academia made the researchers realize this term led to participants' confusion. In Polish, instead of saying 'I'm in a romantic relationship with X', one would say 'I'm in a relationship with X.' The additional adjective 'romantic' seemed unnatural and unclear for the Poles. They were unsure whether the intention behind the question was to ask if the given relationship involved numerous sexual encounters or was particularly romantic, including giving and receiving flowers, whispering sweet words, and staring into each other's eyes – the things that are closely related to initial phases of a romantic relationship (Sternberg 1986). Probably because the Polish researchers were accustomed to seeing the 'romantic relationship' in English publications, no red flags rose. Only the outside academia check allowed to spot and fix this nuisance.

Recommendations

In light of these findings, several recommendations of back-translation approach should be reiterated. First, all studies, not just cross-cultural ones, should provide sufficient information about the studied sample, including nationality and the language used (Klotz et al. 2023). By explicitly stating this information, researchers demonstrate scientific maturity, respect for the diversity of humankind, and the recognition that not all principles derived from WEIRD populations might universally apply (Henrich et al. 2010).

Second, all studies that translated the survey or even its part should provide comprehensive information on the translation process. It is not enough to state that, for instance, 'scales were back-translated from English to *[language]*'. The bare minimum are details of each step taken and the individuals involved. Helpful might be answering the following questions: Who was involved in the translation process? How many individuals? What was their background and qualifications (e.g., academics, bilingual students, professional interpreters)? What did the translation exactly look like? Was it first forward-translated, then back-translated, then reviewed, then piloted? Were any of the above steps omitted? How many individuals (if any) were recruited to pilot the semi-final version? Did all translators involved in the translation agree on the final version? These seemingly simple questions offer a potential Reader a better understanding of the translation process and informed judgement on the quality of resulting translations (Klotz et al. 2023). Furthermore, providing all necessary information promotes scientific transparency, facilitates informed judgment on translation quality, and aligns with principles of open research practices (Aguinis et al. 2018; Christensen et al. 2019). These guidelines are presented in Figure 2.

However, even a detailed description of how a translation was done does not mean much if the result is a poor-quality translation. Thus, third, cross-cultural researchers should strive to employ rigorous translation approaches to ensure the highest possible quality of trans-

lations. Considering that most of the studies are non-funded (Kokol 2019) and long, extensive, expert paid translations might be unattainable, researchers might instead opt for a good enough translational method that serves its purpose, such as back-translation. Importantly, there are several steps of back-translation, which aid in ensuring the resulting output is of good quality. These include 1) forward-translating the survey into the target language by a first bilingual(s), 2) back-translating the survey into the original language by a second bilingual(s), 3) comparing the original and back-translated into the original language versions and sorting out the reasons for the discrepancies, 4) piloting the semi-final version of the translation on the representatives of the target population, and 5) revising the final version of the translation. All the recommendations are presented in Figure 2. Last, but not least, after conducting a cross-cultural study in societies speaking different languages, regardless of the employed translation method, one should always assess whether different linguistic versions of the survey reflect the same underlying constructs. This can be achieved by relying on statistical tests of equivalence of invariance (Milfont and Fischer 2010).

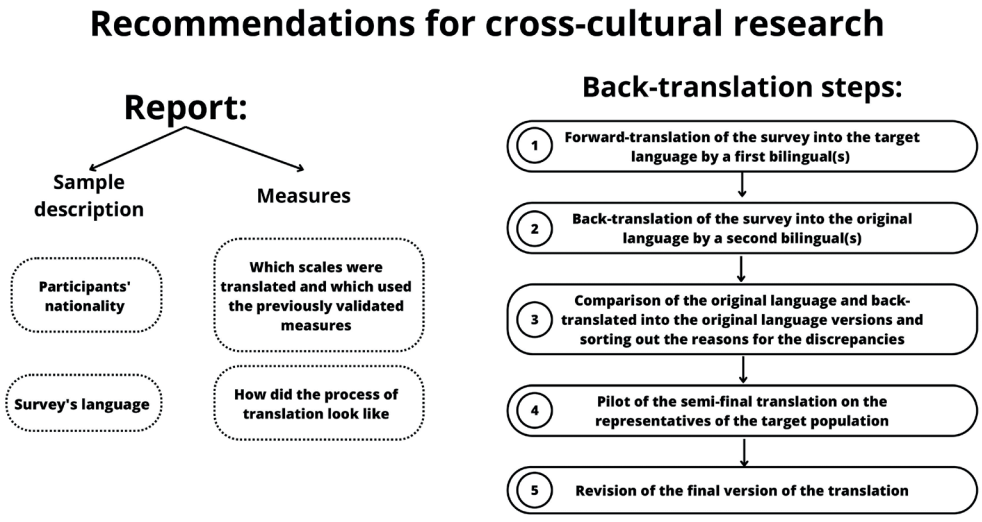

Fig. 2 Recommendations for cross-cultural research

Limitations

While the present study provides valuable insights into the translation techniques in cross-cultural research, it is important to note several limitations. First, the overview of different translation techniques is not exhaustive. Second, the present analysis is limited to studies published between 2017 and 2021 in two cross-culturally oriented journals. Therefore, it is essential to consider that practices and approaches may differ across other journals or time periods. Third, there is no

firm evidence that the back-translation approach, although seemingly the most widely recognized and utilized, ensures the best quality of resulting translation (Schaffer and Riordan 2003; Epstein et al. 2015). Future studies should explore and directly compare the results of various translation methods. This was, however, not possible herein, as there was no case of two same scales that were translated into the same language but using different methods.

Conclusions

Researchers have a moral responsibility to adhere to the best research practices. That includes transparency in the sample description and, if applicable, the translation process (Valdez et al. 2021). Reiterating this is especially important, considering that the current analysis reveals that not enough studies report how they handled the scales' translation. The present work also reviews various translating approaches and their prevalence in cross-cultural research. In light of the findings, with all its limitations, the back-translation approach seems like an appropriate choice when conducting a cross-cultural study on populations that speak different languages. By implementing these recommendations universally, more accurate comparisons across different cultures and languages could be achieved.

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Conflict of interests

The author declares no conflict of interest.

Data availability statement

The data that support the findings of this study are contained in the Supplementary Material and available on the request.

Corresponding author

Marta Kowal, IDN Being Human Lab – Institute of Psychology, University of Wrocław, Dawida 1, 50-529 Wrocław, Poland, telephone/fax: 71 367 20 01, e-mail: marta7kowal@gmail.com

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Investigation of hand index, digit finger ratio (2D:4D), and grip strength among court sports

Md. Hamidur Rahman[1,2], *J.P. Sharma*[3]

[1] Department of Physical Education and Sports Sciences, University of Delhi, New Delhi, India
[2] Department of Physical Education and Sports Science, Jashore University of Science and Technology, Jashore, Bangladesh
[3] Indira Gandhi Institute of Physical Education and Sports Sciences, University of Delhi, New Delhi, India

Abstract: Hand index, finger ratio, and grip strength are potential indicators of proficiency in court sports. The aim of this study is to explore hand dimensions, fingers length ratio, and grip strength in court sports players, a domain in which such characteristics can significantly influence performance. Measurements, such as hand length (HL), hand breadth (HB), hand index (HI), palm length (PL), hand span (HS), index finger length (2D), ring finger length (4D), 2D to 4D ratio (2D:4D), low digit ratio (LDR), and high digit ratio (HDR) were studied in the field of hand anthropometry, along with a handgrip strength (HGS) test. Data were obtained from 135 male court sports players, including basketball, handball, and volleyball, with 45 players from each discipline. Descriptive statistics, one-way ANOVA, and an independent t-test were used to compare variables, with statistical significance set at $p < 0.05$. The ANOVA results indicated that there were no significant differences in hand variables, namely HL, HB, PL, HS, 2D, 4D, 2D:4D, LDR, HDR, and HGS, except for the HI variable. Post-hoc test results showed HI differences in basketball versus handball and volleyball. Compared to standard HI, their ranges show that all-court sports often fall into the Dolichocheri type, characterized by long fingers and a narrow, small palm. A low digit ratio may have some effect on HI in basketball and volleyball. However, it does not appear to have a significant effect on HGS across the study. In summary, the results of our study show that court athletes are similar in hand characteristics, 2D:4D, and grip strength for the nature of the game.

Key words: hand anthropometry, hand index, digit ratio (2D:4D), grip strength, court sports.

Original article
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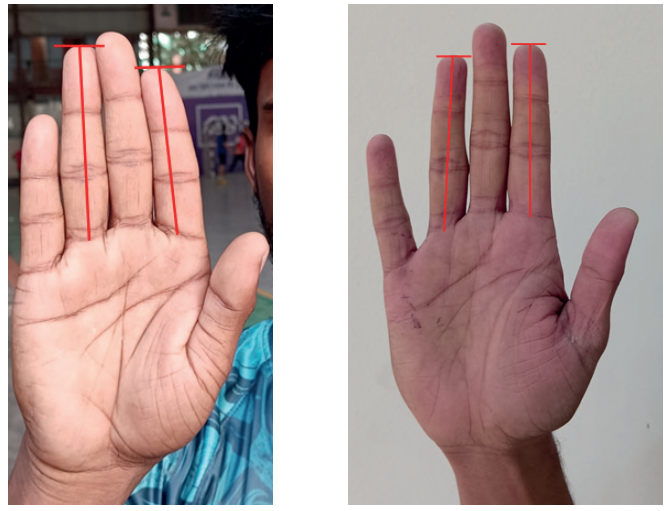
Introduction

Physical characteristics and athletic performance are crucial in court sports, such as basketball, handball, and volleyball, where skillful ball control requires having adequate hand size and grip strength (Rahman and Sharma 2023). In these sports, attributes such as hand length (HL), hand breadth (HB), hand span (HS), finger length, and handgrip strength (HGS) are vital for activities, such as shooting and dribbling in basketball, gripping and catching in handball, and spiking and blocking in volleyball. The elongated fingers of the hand, with extra skin, enhance the efficiency and comfort of gripping objects, such as a ball, by minimizing the need to spread the fingers (Nag et al. 2003). Furthermore, Visnapuu and Jürimäe (2007) suggested that individuals with broad, flat hands and longer fingers might possess a stronger grip. The hand span is used to determine the highest possible handgrip strength values (Ruiz et al. 2006), which helps to grip the ball in hand. In court players, there is a strong link between handgrip strength and general hand anthropometric measures (Apostolidis and Emmanouil 2015; Zapartidis et al. 2016; Kurtoğlu and Çiftçi 2023). The arm is composed of three segments: the upper arm, forearm, and hand (Forro et al. 2023). Hand anthropometry, which involves measuring hand size and finger lengths, especially index and ring finger length, has been correlated with athletic performance in various sports (Manning and Taylor 2001) and the ability to grip and the span of the hand were effective indicators of performance in volleyball players (Faraji et al. 2014). For instance, larger hands can enhance abilities in handling, passing, catching, and serving the ball, thereby greatly influencing individual skills and team strategies in sports where hand usage is key (Blackwell et al. 1999; Barut et al. 2008). In addition, analyzing hand dimensions can provide important insights into an individual's height, gender, and age (Aboul-Hagag et al. 2011).

In a variety of clinical settings, HGS is commonly evaluated as a gauge of general fitness and upper-limb strength (Nicolay and Walker 2005; Schlüssel et al. 2008). The simplest and most reliable measure of a person's muscular strength level is their HGS (Lee 2021; Nara et al. 2022), and it can serve as a tool for monitoring cognitive status (Kobus et al. 2021). Hand strength is extremely important in sports that require throwing, catching, and striking, making it a critical factor in the performance of court game athletes. Playing with the ball in court sports requires significant isometric hand grip strength to effectively execute their skills (Wiliński et al. 2022; Reza et al. 2023). The length of the hand has been demonstrated to exert a notable impact on hand strength and play a significant role as a reflective parameter of hand function (Hepping et al. 2015; Wichelhaus et al. 2018). Fallahi and Jadidian (2011) indicated that grip sports, such as handball, basketball, volleyball and baseball are associated with grip strength and anthropometric characteristics of their hands, indicating its potential utility in identifying sports talent. HGS and the 2D:4D ratio are negatively correlated (Zhao et al. 2012; Shen et al. 2016; Lu et al. 2017; Kociuba et al. 2019), whereas HGS shows a positive association with hand dimensions (Mahmoud et al. 2020). Therefore, in relation to hand dimensions including finger length, grip strength, with larger hands and fingers contribute to increased hand stiffness.

The 2D:4D ratio, a tentative biological marker, refers to the proportion between the lengths of the index finger (2D) and the ring finger (4D) on the same hand (Kim and Kim 2016; Fusar-Poli et al. 2021). The digit ratio, or the ratio of the lengths of different fingers, especially the 2D and 4D, is hypothesized to indicate prenatal testosterone (PT) levels, potentially influencing physical and athletic prowess (Manning 2002). Testosterone, a steroid hormone, is decisive for developing and maintaining masculine traits in the human body and is influenced by exposure in the mother's womb (Mazur and Booth 1998; Islam and Kundu 2019). Masculine characteristics might correlate with a lower ratio of the index to ring digits (2D:4D) (Islam and Kundu 2020a). The growth of the ring finger is significantly influenced by the level of PT hormone in the fetus. Higher testosterone production results in a longer ring finger, leading to a low digit ratio (LDR) (Tomkinson and Dyer 2017). A low 2D:4D ratio is associated with high PT levels and low prenatal estrogen (PE) hormone levels. Conversely, a high 2D:4D ratio indicates lower PT and higher PE levels, leading to a high digit ratio (HDR) (Manning and Fink 2018). Previous research has indicated that individuals with low 2D:4D ratios tend to exhibit superior athletic and physical performance (Kozieł et al. 2024). The 2D:4D ratio, along with other physical and physiological assessments, can play a key role in identifying young sports talent (Islam 2021). In humans, the right-hand 2D:4D is more responsive to prenatal sex hormones than the left (Manning et al. 1998), with the right-hand ratio correlating more strongly with testosterone levels and sperm count. In addition, mean digit ratios remain fairly consistent throughout one's life (Manning et al. 1998; Manning 2002). Typically, the 4D on a masculine hand (LDR) is about 1 cm longer than the 2D, while in a feminine hand (HDR), the 2D tends to be 1 cm longer than the 4D (Fig. 1.).



(A) (B)

Fig. 1. (A). Masculine hand (LDR), (B). Feminine hand (HDR)

Basketball, handball, and volleyball involve handling a ball on a court, and excelling in these games requires players to use their hands and strength to control the ball. Hand dimensions, including lengths, breadth, span, digit lengths, digit ratio, and grip strength can significantly influence players' performance. A player's hand measurements, digit finger ratios, and hand grip strength might be all considerable factors in player selection for team sports involving ball games, in addition to their level of physical fitness. In addition, lower digit-to-finger ratios are linked to more masculine hands and can be indicators of athletic success. Therefore, researchers have looked at these areas in court sports, particularly basketball, handball, and volleyball, to investigate whether there were differences in hand variables, finger length ratios, and grip strength.

Material and methods

Participants

This study involved a random selection of 135 male court game athletes, split evenly among three sports: basketball, handball, and volleyball, including 45 players in each discipline. The athletes who did not have any hand abnormalities or injuries were selected for the study. The athletes, aged 17 to 24, who had competed at least at the inter-university level in their respective sports, were selected from ten universities located around Bangladesh.

Table 1 shows that basketball players were significantly taller (177.78 cm) and heavier (71.84 kg) compared to volleyball players (174.26 cm, 68.03 kg) and handball players (170.44 cm, 66.41 kg). In addition, compared to handball players, volleyball players were much taller. Despite these differences, their BMIs were quite similar, usually falling within the 22–23 range.

Instruments

Anthropometric measurements of hand and digit length were taken using the Digital Vernier Caliper (Mitutoyo Corporation, Japan), and HGS was measured with the Hand Grip Dynamometer (JAMAR, USA). HI was calculated by multiplying the HL by hundred, divided by the HB, and the 2D:4D ratio was the length of 2D divided by 4D.

Procedures

This study's hand measurements and grip strength data were limited to the right hand only. For hand measurements, all study participants were instructed to place their right hands flat on the table, palms up with fingers extended, except for HB, where the palm downward, fingers together, and thumb stretched out. All measurements of the right hand were taken using a Digital Vernier Caliper. Furthermore, a Hand Grip Dynamometer was used to assess HGS.

Table 1. General anthropometric characteristic of the subjects (mean±SD)

Groups	N	Age (yrs)	Height (cm)	Weight (kg)	BMI (kg/m^2)
Basketball	45	22.04±1.21	177.78±6.75	71.84±6.75	22.72±1.65
Handball	45	21.69±1.68	170.44±6.37	66.41±7.87	22.82±1.92
Volleyball	45	21.82±1.85	174.26±7.08	68.03±8.66	22.38±2.35
Sig. level		0.57	0.00	0.00	0.56

Measurements of hand dimensions

HL was gauged from the Mid-stylion (a wrist point) to the Dactylion (middle finger's tip); ensuring fingers were extended but not overstretched, to determine the hand's length from wrist to middle fingertip. HB involved measuring from the second metacarpal's outermost point (index finger base) to the fifth metacarpal's innermost point (little finger base). Palm length (PL) measurement extended from the wrist's farthest central crease to the middle finger's base crease. HS referred to the span between the tips of the thumb and little finger when the hand is perfectly stretched. The 2D and 4D lengths were taken from the basal crease to the fingertip along the medial line of a fully extended hand. All measurements of the hand were recorded using a digital caliper, with the results noted in millimeters (mm).

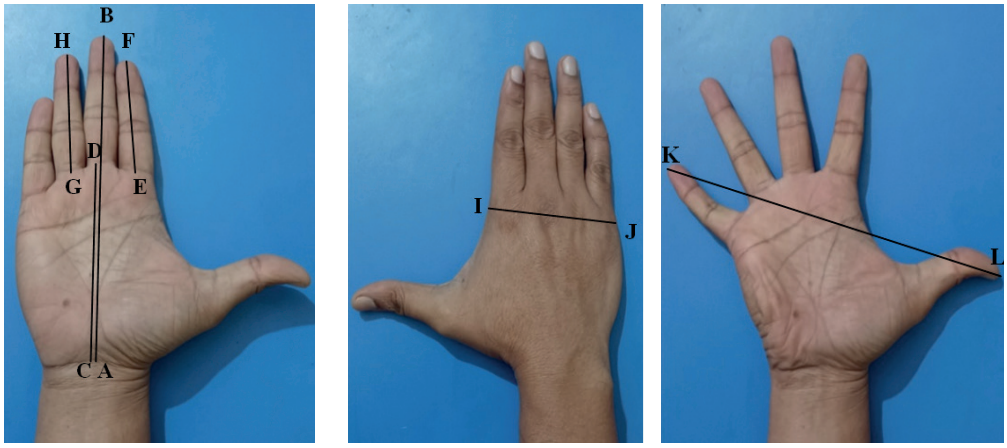


Fig. 2. Hand measuring landmarks: HL (A-B), PL (C-D), 2D (E-F), 4D (G-H), HB (I-J), and HS (K-L)

Hand Index (HI)

The HI was determined by dividing the HB by the HL and then multiplying the resulting score by hundred. The HI scores were compared using the standard HI and five distinct categories: Hyperdolichocheir, Dolichocheir, Mesocheir, Brachycheir, and Hyperbrachycheir, as defined by Martin and Saller (1957). In this study, the mean HI values of 42.50 for basketball, 43.59 for handball, and 43.50 for volleyball players, often fell into the Dolichocheri type. This type is characterized by long fingers and a narrow, small palm.

2D:4D, LDR, and HDR

To calculate the 2D:4D ratio, the length of 2D is divided by 4D. All court players (N=135) were categorized into LDR and HDR groups based on their 2D:4D ratios, using the quartile deviation method. Those with a digit ratio of 0.951 and below (25% and below) were categorized into the LDR group, while those with 0.987 and above (75% and above) were categorized into the HDR group. Analysis of the quartile deviation revealed distinct groups among basketball, handball, and volleyball players. In basketball (N=24), 9 players were in the LDR

and 15 in the HDR group. In handball (N=21), there were 12 LDR and 9 HDR players. Finally, in volleyball (N=26), the distribution was 14 LDR and 12 HDR players.

HGS

The handgrip strength of each subject was assessed using the JAMAR hydraulic hand dynamometer. While taking the measurements study participants sat upright and gripped the dynamometer in a comfortable sitting position while keeping their shoulder and elbow at 0° and 90°, respectively. The maximum HGS was automatically recorded in kilograms (kg) by a peak-hold needle. The average score from the three attempts was used as the final score.

Statistical analysis

Descriptive statistics, an independent t-test, and a one-way ANOVA were employed to compare variables used in this study. Levene's test showed equal variances, indicating a normal distribution of data. All statistical procedures were conducted using the IBM's SPSS version 22 for Windows (George and Mallery 2019). Results were considered significant at the $p<0.05$ level (two-sided).

Results

Table 2 indicates that there were no significant differences between the hand variables, namely HL ($F = 1.38$, $p = 0.26$); HB ($F = 0.36$, $p = 0.70$); PL ($F = 0.07$, $p = 0.93$); HS ($F = 0.17$, $p = 0.85$); 2D ($F = 0.94$, $p = 0.39$); 4D ($F = 0.51$, $p = 0.60$); 2D:4D ($F = 0.89$, $p = 0.42$; LDR ($F = 0.65$, $p = 0.53$); HDR ($F = 0.53$, $p = 0.59$); and HGS ($F = 0.50$, $p = 0.61$). However, a significant difference was noted among the groups for the variable HI ($F = 3.31$, $p = 0.047$). The result shows that there were no significant differences in various hand measurements and handgrip strength among the groups, except for the HI variable, where a significant difference was found.

Table 2. Comparison of hand dimensions, finger length ratios, and grip strength among court sports athletes

Variables	Groups	N	Mean	Std. Deviation	F-value	p level
HL (mm)	Basketball	45	193.29	8.76	1.38	n.s.
	Handball	45	190.38	10.28		
	Volleyball	45	190.10	11.12		
HB (mm)	Basketball	45	82.08	4.81	0.36	n.s.
	Handball	45	82.93	5.20		
	Volleyball	45	82.54	4.21		
HI (mm)	Basketball	45	42.50	2.37	3.13	<0.05
	Handball	45	43.59	2.14		
	Volleyball	45	43.50	2.38		
PL (mm)	Basketball	45	109.80	5.06	0.07	n.s.
	Handball	45	109.62	6.21		
	Volleyball	45	109.35	6.31		
HS (mm)	Basketball	45	215.81	11.28	0.17	n.s.
	Handball	45	214.67	12.92		
	Volleyball	45	216.06	12.23		

Variables	Groups	N	Mean	Std. Deviation	F-value	p level
2D (mm)	Basketball	45	75.45	4.08	0.94	n.s.
	Handball	45	74.26	4.59		
	Volleyball	45	74.33	5.14		
4D (mm)	Basketball	45	77.50	4.22	0.51	n.s.
	Handball	45	76.88	5.04		
	Volleyball	45	76.50	5.02		
2D:4D	Basketball	45	0.974	0.02	0.89	n.s.
	Handball	45	0.967	0.03		
	Volleyball	45	0.972	0.03		
LDR	Basketball	09	0.940	0.02	0.65	n.s.
	Handball	12	0.934	0.02		
	Volleyball	14	0.940	0.01		
HDR	Basketball	15	1.000	0.01	0.53	n.s.
	Handball	09	1.003	0.01		
	Volleyball	12	1.006	0.02		
HGS (kg)	Basketball	45	48.40	8.12	0.50	n.s.
	Handball	45	49.42	7.22		
	Volleyball	45	47.89	6.74		

The LSD post-hoc test (Fig. 3) showed that there was a statistically significant difference in the HI between basketball and handball and between basketball and volleyball; however, no significant difference was found between handball and volleyball.

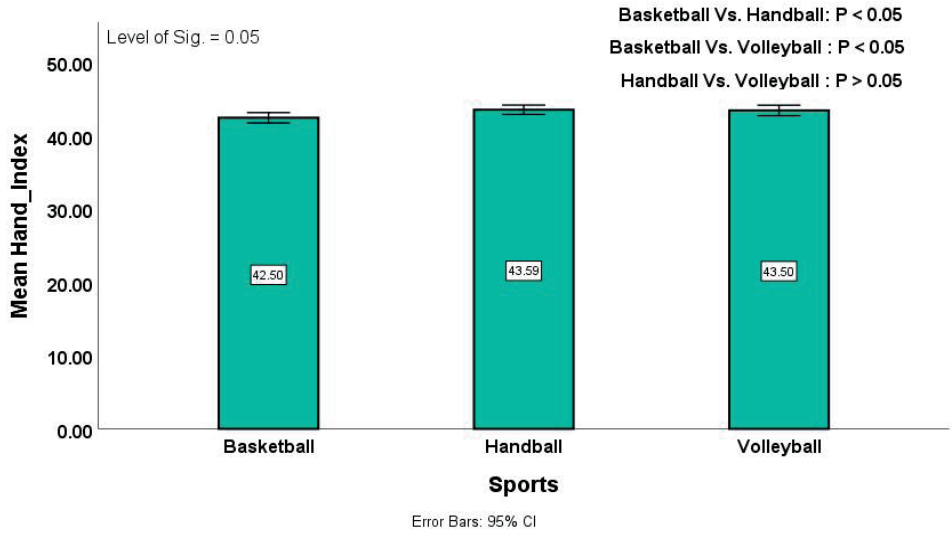


Fig. 3. The difference in the mean value of HI between the three groups

Table 3. HI and HGS between the LDR and HDR (2D:4D)

Groups	Variables	Digit Ratio	N	Mean	Std. Dev.	t	df	p (2-tailed)
Basketball	HI	LDR	9	43.37	1.57	2.36	22	<0.05
		HDR	15	41.45	2.41			
	HGS	LDR	9	49.74	6.96	0.16	22	n.s.
		HDR	15	49.11	11.90			
Handball	HI	LDR	12	43.47	2.12	0.09	19	n.s.
		HDR	9	43.55	1.60			
	HGS	LDR	12	50.47	5.12	1.51	16	n.s.
		HDR	9	46.70	6.01			
Volleyball	HI	LDR	14	44.29	3.25	2.10	22	<0.05
		HDR	12	42.09	2.03			
	HGS	LDR	14	48.26	3.67	0.07	19	n.s.
		HDR	12	48.39	5.37			

Discussion

The findings in Table 2 suggest that there was not a notable variation in hand measurements and handgrip strength across the groups, except for the HI variable, which exhibited a significant difference. Our study involved court sports players using a cross-sectional design. Findings indicated no notable variations in the width, length, and palm length of the right hand, as well as grip strength. However, significant statistical differences were observed in the hand index values among male basketball, volleyball, and handball athletes (Barut 2008). Basketball players had greater values in right hand length and span compared to volleyball players; however, no significant differences were observed between the two groups (Gaurav et al. 2015). Athletes from different sports, including handball, basketball, and football, exhibit similar levels of hand grip strength (Karakoç et al. 2015). The grip strength of ball game athletes was found to be almost identical (Rahman and Sharma 2023). The grip strength of the dominant hand in males exhibited a tendency to be influenced by hand shape, although the impact was not statistically significant (Bardo et al. 2021). 2D:4D ratios in right hands were compared among non-athletes, volleyball, and soccer players, showing no significant differences (Tomaszewska and Lubońska 2022). Koziel et al. (2016), reported significant differences in mean 2D:4D values among the three distinct male sporting groups on the right hand. The study identified a significant difference in the right 2D:4D ratio between the three groups tested (Kociuba et al. 2022). The present study HI shows that basketball players exhibit differences between handball and volleyball players. In addition, the mean values of court players often fall within the Dolichocheri type, characterized by long fingers and a narrow, short palm. A cross-sectional study of 100 university students, aged 17–26, found that the most common hand index was like that (Sarkodie et al. 2023). The average index for the right hand was 42.83 mm (Cha-

nana and Bandapalle 2022), 43.08 mm (Dey and Kapoor 2017), showing that the hand morphology of male individuals is predominantly categorized as Dolichocheir type (Chia and Anyanwu 2020).

Table 3 revealed significant differences in HI between basketball and volleyball players, while for HGS, no significant differences were found between low and high digit ratios across sports, with the 2D:4D ratio (Table 2) nearly identical in basketball (0.974), handball (0.967), and volleyball (0.972). Ball players with a lower digit ratio have better anthropometric measurements of body composition compared to those exhibiting a higher digit ratio, although the difference is not significant (Islam 2020). Participants in team sports such as soccer (0.965), volleyball (0.969), basketball (0.972), and handball (0.978) generally had higher digit ratios, with the 2D:4D being nearly the same (Malik and Singh 2014). Among ball players, the right-hand 2D:4D ratio showed no significant difference between opposition and cooperative ball players (Ramos et al. 2022). The digit ratio of 108 participants was classified into high (0.973 and above, top 25%, n=28) and low (0.942 and below, bottom 25%, n=28) groups based on quartile deviation (Islam and Kundu 2020b). A low digit ratio is associated with improved endurance and handgrip strength (Ranson et al. 2015; Koziel et al. 2017).

In summary, anthropometric hand measurements, including size, shape, and length, play a crucial role in the strength and precision of hand movements, thereby significantly influencing performance in court games. Because basketball, handball, and volleyball games involve handling a ball, hand anthropometry and grip strength are paramount. Consequently, no notable differences in hand length, digit length, or grip strength were observed among players in the three court games in the present study. This finding aligns with the results reported by numerous previous researchers.

The limitation of the study is that hand measurements and grip strength data were only taken from the right hand. However, expanding the variety of court sports and increasing the sample size both contribute to achieving more accurate results and improved precision by including more measurements. Further research is needed to determine the extent to which these variables relate to performance.

Conclusions

In summary, all court sports athletes were found to exhibit similar hand dimensions, 2D:4D, and HGS, except for the HI. According to HI, basketball players differ between handball and volleyball, and all HI's were characterized by long fingers and a narrow, short palm. The 4D was significantly higher than the 2D, and the LDR exhibited higher HI values in basketball and volleyball. Regarding HGS, no significant differences were found between low and high digit ratios across sports. Court athletes were similar in hand features and grip strength for the nature of play.

Acknowledgment

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Conflicts of interests

The authors declare no conflicts of interest.

Authors' contribution

MHR – conceived the idea of the study, collected and analyzed the data, prepared the tables and figures, drafted the manuscript, and revised and finalized the manuscript. JPS – planned and supervised the research, set the goals, provided substantive supervision, and finalized the manuscript.

Corresponding author

Md. Hamidur Rahman, Department of Physical Education and Sports Science, Jashore University of Science and Technology, Jashore-7408, Bangladesh, e-mail: hamid.pess.just@gmail.com

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Forensic facial identification – reconstruction of facial geometry and shape from dental dimensions

Nandini Chitara, *Kewal Krishan*

Department of Anthropology, Panjab University, Chandigarh, India

Abstract: Human identification has always remained as a main task of forensic anthropology and forensic science for various purposes. The purpose of human identification may vary from legal identity to disaster victim identification, from criminal identity to unidentified deceased identification. The condition, such as putrefaction, charring and mutilation of corpse always become an obstacle during the process of identification. Due to surviving nature of teeth, they may serve as evidence for identification in highly decomposed conditions. Therefore, a cross-sectional study was conducted on 207 participants (93 males and 114 females) in the age range of 21 to 45 years with the aim of two-dimensional facial reconstruction. Dental casts, anthropometric facial measurements and facial photographs were obtained from the participants. Dental measurements were taken on the cast in the laboratory. Statistical analysis revealed a weak but statistically significant correlation between the dental and facial parameters. The geometrical faces and the shapes were reconstructed based on the dental dimensions. The reconstructed facial geometry and shapes were very similar to the true facial geometry and facial shapes of the individual. By improving identification of disaster victims and unidentified deceased, the results of the study can have considerable implications in forensic and medico-legal case-works.

Key words: facial morphology, facial reconstruction, facial dimensions, dental dimensions, forensic identification, disaster victim identification.

Original article
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Introduction

Teeth, which are the hardest part of human body, serve as a crucial identifier for commingled, decomposed, mutilated, charred, skeletonized and putrefied corpses in various disasters and medico-legal scenario (Mohammed et al. 2019; Krishan et al. 2015). Besides being a crucial identifier, according to the INTERPOL teeth are reliable and scientifically grounded evidence used as primary identifier in disaster victim identification (Interpol 2018). The significance of individualistic features e.g., dental restorative work, dental jewelry, metal wiring, metal amalgamation, decorative work, morphological traits (such as peg shaping of incisors, shoveling in incisors, Carabellis's cusp, occlusion type, groove pattern of molars, hyperdontia, hypodontia, taurodontism etc.), shape and size variations, teeth wearing and dental anomalies has been well established in the literature and in forensic case-work (Madi et al. 2013; Jodalli et al. 2016; Anu et al. 2018; Chitara et al. 2023; Hinchliffe 2011). Similarly, teeth and jaw measurements (e.g., maxillary incisor-incisor distance, inter canine distance, combined width of central incisors, inter- molar distance, inter- premolar distance, dental arch height and so on) have been reported to be individual, sex and population specific (Omar et al. 2018; Filipovic et al. 2016; Banerjee et al. 2016). The importance of morphometric dental traits is related to their value in anthropological, medical and forensic studies (Singh and Bhasin 1968; Jain et al. 2021; Chunhabundit et al. 2013; Jayakrishnan et al. 2021). The association of morphometric dental traits with specific ancestries and ethnic groups was reported by Matis and Zwemer (1971) in Western United States population, Tinoco et al. (2016) in Southeast Brazilian population, Filipovic et al. (2016) in Siberian population and Omar et al. (2018) in Saudi population. These studies may help in allocating a specific population group to unidentified deceased and narrow down the investigation process.

In the past, researchers have strengthened the significance of morphometric dental traits by exploring links and associations between various dimensions of teeth and face (Chunhabundit et al. 2023; Kini and Angadi 2012; Mishra et al. 2016; Alshamri et al. 2023). Similarly, anthropological and forensic studies have explored an ethnic association of various facial measurements and face forms (shape and structure), which helps in finding the similarities and differences in various endogamous populations (Lu and Jain 2004; Jahanshahi 2012; Voegeli et al. 2021). Thus, predicting facial dimensions from teeth dimensions can also aid in identifying the ancestry of unknown deceased.

Moreover, facial and dental correlation can be effectively utilized in facial reconstruction. However, there is a lack of literature addressing facial reconstruction using morphometric dental traits. To address this research gap, the present research aimed to determine a relationship between facial dimensions and dental dimensions. The study also aimed to geometrically approximating the facial shapes and geometry from the predicted facial values using various dental dimensions.

Material and Methods

Research Area and Population

The present cross-sectional study was conducted in Karnal region of the Haryana state in North India. The research population comprised of 207 healthy participants (93 males and 114 females) aged between 21 and 45 years from Haryana state of North India. An informed written consent

was taken from all study participants after explaining to them the nature and the purpose of the study. The present study is a part of Ph.D. research conducted in the Department of Anthropology, Panjab University, Chandigarh, India. The ethical approval for the study was obtained from the Panjab University Institutional Ethical Committee (vide approval number: PUIEC 230602-I-114, dated 9th June 2023).

Data Collection

Inclusion and exclusion criterion

Only study participants with no dental attrition, no oral diseases, no accidental missing teeth were included in the study. Any study participants with a history of restorative and orthodontic dental treatment were excluded from the study.

Preparing a dental cast

Having obtained general demographic information of study participants, such as name, age, sex and address, dental casts were prepared by obtaining the impression of the teeth in Neoalgin alginate impression material (i.e., mixing the alginate material with distilled water to make a slurry which is then immediately applied to impression tray and dental impressions were obtained) with the help of impression tray. Afterwards, the obtained dental impression was poured with dental stone (Kalabhai Kalstone plaster class III) by mixing the dental stone and distilled water (i.e., making a slurry). The prepared casts were than taken out from the trey after drying at room temperature (37°C).

Obtaining dental measurements

Standardized dental measurements (Zorba et al. 2011; Moreno-Gómez 2013) were recorded from the prepared dental casts with the help of sliding caliper. The dental measurements included in the study are shown in Figure 1 and described in Table 1.

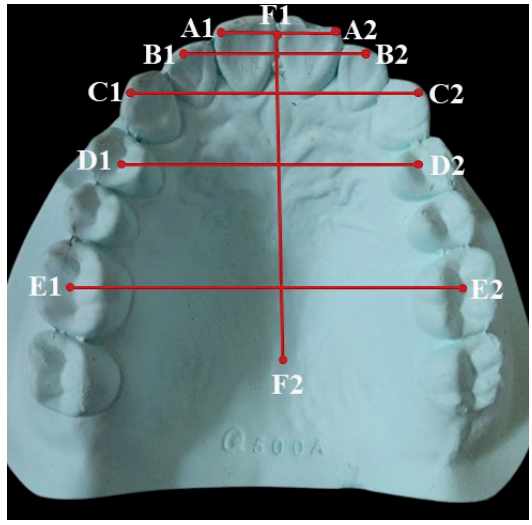

Fig. 1. Dental dimensions included in the study. Distance between A1-A2 = combined width of central incisors, B1-B2 = incisor to incisor distance, C1-C2 = inter canine distance, D1-D2 = inter premolar distance, E1-E2 = inter molar distance, F1-F2 = dental arch height

Table 1. Description of facial and dental anthropometric measurements included in the present study

FACIAL MEASUREMENTS (Taken directly on the participant's face following Hall et al. 1989)			
Sr. No.	Anthropometric Measurement	Description of the measurement	Instrument used
1	Facial height (FH)	Straight distance from nasion to gnathion in the mid-saggital plane.	Sliding Caliper
2	Physiognomic facial length (PFL)	Straight distance from trichion to gnathion in the mid-saggital plane.	Sliding Caliper
3	Maximum head width or Maximum biparietal diameter (MHW)	Distance between right eurion to left eurion.	Spreading Caliper
4	Minimum frontal breadth (MFB)	Distance between frontotemporalia to frontotemporalia	Spreading Caliper
5	Upper facial height or Nasal length (UFH)	Distance from nasion to subnasion in the mid-saggital plane.	Sliding Caliper
6	Lower facial height or Total jaw height (LFH)	Distance from subnasion to gnathion in the mid-saggital plane.	Sliding Caliper
7	Facial width or Bizygomatic distance (FW)	Distance from right zygion to left zygion.	Spreading Caliper
8	Inner Canthal distance (ICD)	Distance from right inner canthi to left inner canthi	Sliding Caliper
9	Outer Canthal distance (OCD)	Distance from right outer canthi to left outer canthi	Sliding Caliper
10	Nasal width or Interalar distance (NW)	Distance from right alare to left alare.	Sliding Caliper
11	Mouth width or Intercommissural distance (MW)	Distance between right cheilion and left cheilion	Sliding Caliper
12	Bigonial distance or Mandible width (BD)	Distance between right gonion to left gonion	Spreading Caliper
DENTAL MEASUREMENTS (Taken on the dental cast following Zorba et. al. 2011, Moreno-Gómez, 2013)			
Sr. No.	Anthropometric Measurement	Description of the measurement	Instrument used
1	Incisor-Incisor distance (IID) (maxillary)	It is the distance between upper right and upper left lateral incisors. The distance is measured from centre point of lateral incisors.	Sliding Caliper
2	Inter Canine distance (*ICD) (maxillary)	It is the distance between the cusp tip of upper right and upper left canines.	Sliding Caliper
3	Combined Width of Central Incisors (CWCI) (maxillary)	It is the combined mesio-distal width of maxillary central incisors.	Sliding Caliper
4	Inter-Premolar Distance (IPD) (maxillary)	It is the distance from buccal cusp tip of right first premolar to buccal cusp tip of left first premolar.	Sliding Caliper
5	Inter-Molar Distance (IMD) (maxillary)	It is the distance between buccal groove of right first molar and buccal groove of left first molar.	Sliding Caliper
6	Dental Arch Height (DAH)	It is the distance/height from occlusal plane of first permanent molar to palatal contour.	Sliding Caliper

Obtaining facial measurements and photographs

After letting the participants to sit relaxed on a chair and aligning their head in Frankfurt Horizontal plane, various anthropometric landmarks were identified, and dimensions were measured using sliding and spreading caliper in order to obtain various standardized anthropometric measurements. All anthropometric measurements (with their respective landmarks) included in the study are shown in Figure 2 and described in Table 1. Moreover, mid-range facial photographs of all the study participants were taken from a distance of 1 meter using phone's camera fixed on tripod stand. The photographs of the participants were used for comparison of predicted facial geometry with original facial geometry.

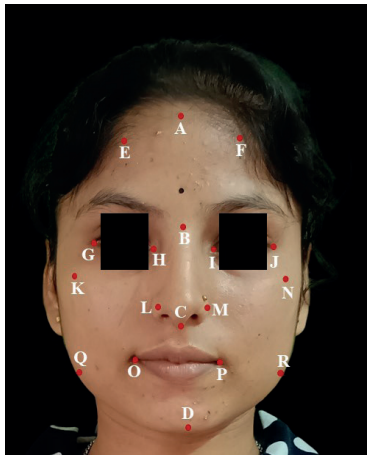

Fig. 2. Anthropometric facial measurements included in the study. Distance between A-D = Physiognomic facial length, B-D = Facial height, B-C = Nasal length, C-D = Total jaw height, E-F = Minimum frontal breadth, G-J = Outer Canthal distance, H-I = Inner Canthal distance, K-N = Bizygomatic distance, L-M = Inter alar distance, O-P = Inter commissural distance, Q-R = Bigonial distance

Statistical and manual analysis

After entering the data into a computer program MS-Excel, statistical analyses were carried out using the IBM SPSS (Statistical Product and Service Solution) software version 20.0. The following statistical tests were applied to the data in four steps for the fulfillment of objectives of the study:

Step 1: First step involved is the normality assessment of the data, which was carried out by graphical assessment methods (normal Q-Q plots, P-P plots, boxplots), descriptive statistics (mean=mode=median) as well as by confirmatory statistics (Shapiro-Wilk's test). These tests showed that out of 12 variables 4 variables are normally distributed whereas eight variables are non-normally distributed.

Step 2: In the next step, existence of any correlation between the variables was investigated by applying the parametric test, i.e., Karl Pearson's correlation coefficient test for normally distributed parameters and non-parametric test, i.e., Spearman's rank correlation coefficient test for non-normally distributed parameters.

Step 3: In the third step, multiple linear regression models were formulated by step-wise regression method. The stepping criteria for the models were selected as the f-probability between the range of 0.05 to 0.1 (other measurements were excluded). Stepwise regression excludes the insignificantly correlated variables in the model formation and incorporates only those independent variables that significantly explain the dependent variable. This overcomes the issue of overfitting of model and enhances the accuracy and the reliability of the regressions used to fit the models.

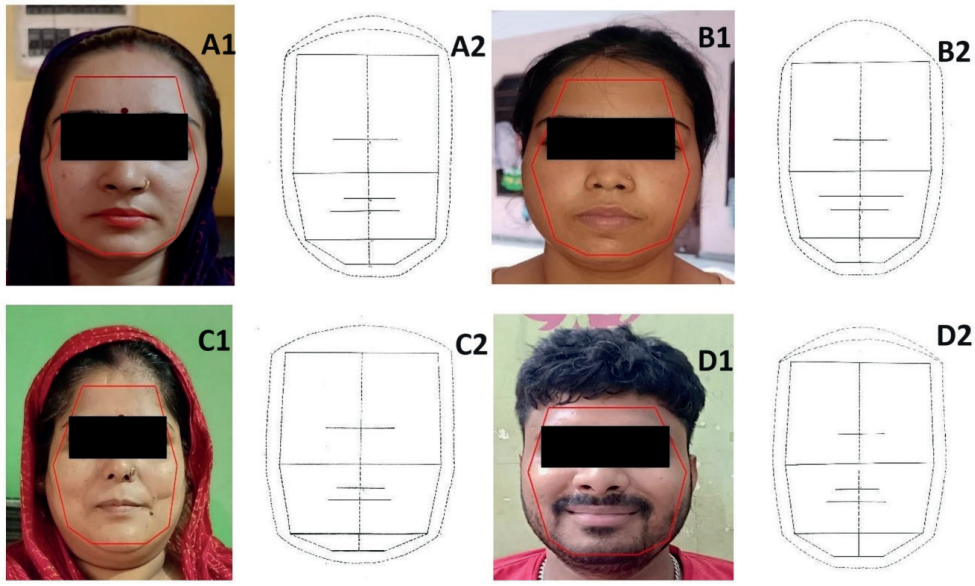

Fig. 3. Predicted facial geometry in comparison with true facial geometry of the study participant. A1, B1, C1 and D1 are the true geometry of the study participant (after identifying the anthropological landmarks on the photograph, tracing is drawn in red). A2, B2, C2 and D2 show facial geometry reconstructed from regression models

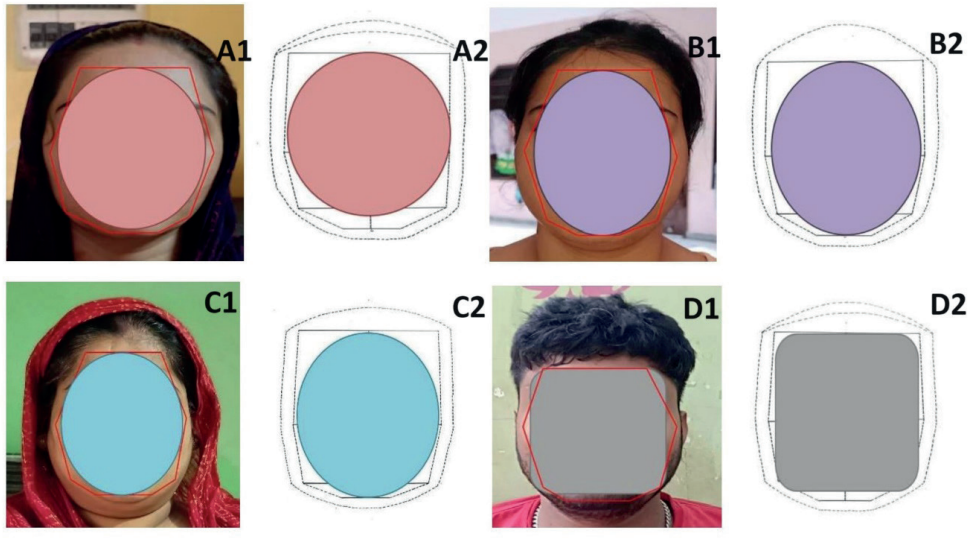

Fig. 4. Predicted facial shape in comparison to the true facial shape of the participant. A1, B1, C1 and D1 show the true facial shapes of the participant (shapes are drawn in color). A2, B2, C2 and D2 show the predicted facial shapes of the participant. Participant A shows an oval face; B and C show a circular face; D shows a squarish facial form

Step 4: Last step in the statistical analysis is the prediction of facial dimensions from the dental dimensions by using regression models. This step provides the outputs of predicted facial dimensions.

Afterwards, facial geometry was drawn manually using a pencil and paper by utilizing the predicted facial dimensions. For bilateral symmetry of the face, the A4 size white bond paper was marked into equal halves (longitudinally and horizontally). The predicted facial measurements of each participant were plotted on the sheet by dividing the measurements into two equal halves and plotted by following the bilateral symmetry. The predicted longitudinal and vertical dimensions of face were plotted on the sheet and joined together to form a facial geometry. For accuracy test the predicted facial geometry and shape was compared manually with original facial geometry and shape (via photographs) (Fig. 3 and 4).

Results

The Shapiro-Wilk's (95% confidence level) test showed that the physiognomic facial height, outer canthal distance, bigonial distance and inter commissural distance were normally distributed whereas all other parameters, i.e., facial height, maximum head width, minimum frontal breadth, nasal length, bizygomatic distance, total jaw height, inner canthal distance, and interalar distance were non-normally distributed parameters. Table 2 shows the descriptive statistics and Shapiro-Wilk's test results for normality check.

Further, Table 3 shows the Karl Pearson's correlation coefficient (for normally distributed variables) and Spearman's correlation coefficient (for non-normally distributed variables) for assessing the relationship between the facial dimensions and dental measurements. Facial measurements exhibited statistically significant but weak correlation with the dental measurements (Tab. 3). The highest correlation was observed between facial height and IMD (Tab. 3), outer canthal distance and IID (Tab. 3), facial width and IMD (Tab. 3). However, very weak correlation was observed between maximum head width and *ICD, CWCI, IPD, IMD; upper facial height and CWCI; inner canthal distance and CWCI and IPD; lower facial height and *ICD. Beside this, DAH showed insignificant correlation with all the facial measurements except inner canthal distance and nasal width (Tab. 3).

Table 2. Confirmatory normality test (Shapiro-Wilk test) with descriptive statistics of the data

Anthropometric Measurement	Sample size (N)	Minimum (cms.)	Maximum (cms.)	Mean (cms.)	Standard Deviation (cms.)	Shapiro-Wilk Test	*p*-value
FH	207	9.00	12.50	10.38	0.68	0.984	0.020
PFL	207	13.90	18.80	16.44	0.93	0.995	0.684
MHW	207	11.70	15.40	13.59	0.63	0.983	0.012
MFB	207	9.70	13.20	11.33	0.68	0.980	0.004
UFH	207	3.90	5.70	7.74	0.37	0.979	0.004
LFH	207	4.40	6.60	5.47	0.47	0.984	0.018
FW	207	10.00	14.00	12.03	0.77	0.987	0.047

Table 2. cont.

Anthropometric Measurement	Sample size (N)	Minimum (cms.)	Maximum (cms.)	Mean (cms.)	Standard Deviation (cms.)	Shapiro-Wilk Test	*p*-value
ICD	207	2.10	3.60	2.71	0.30	0.974	0.001
OCD	207	7.30	10.30	8.87	0.54	0.989	0.111
NW	207	2.70	4.20	3.38	0.31	0.977	0.002
MW	207	3.60	6.10	4.83	0.50	0.988	0.093
BD	207	7.90	12.90	10.35	0.97	0.991	0.193
IID	207	2.60	3.50	3.01	0.19	0.965	<0.001
*ICD	207	2.80	3.61	3.61	0.28	0.979	0.003
CWCI	207	1.30	2.40	1.86	0.18	0.943	<0.001
IPD	207	3.10	4.20	3.65	0.23	0.973	0.001
IMD	207	4.00	5.50	4.82	0.29	0.976	0.002
DAH	207	3.30	5.10	4.15	0.40	0.979	0.003

FH= Facial height, PFL= Physiognomic facial length, MHW= Maximum head width, MFB= Minimum frontal breadth, UFH= Upper facial height, LFH= Lower facial height, FW= Facial width, ICD= Inner Canthal distance, OCD= Outer Canthal distance, NW= Nasal width, MW= Mouth width, BD= Bigonial distance, IID= Incisor-Incisor distance, *ICD= Inter Canine distance, CWCI= Combined Width of Central Incisors, IPD= Inter-Premolar Distance, IMD= Inter-Molar Distance, DAH= Dental Arch Height

Table 3. Description of correlation coefficients of facial dimensions with dental dimensions

Karl Pearson's Correlation Coefficient (for normally distributed variables)						
Anthropometric measurement	IID	*ICD	CWCI	IPD	IMD	DAH
PFL	0.281**	0.179**	0.183**	0.176**	0.284**	0.101
OCD	0.367**	0.240**	0.194**	0.199**	0.180**	0.089
MW	0.283**	0.201**	0.251**	0.289**	0.208**	0.115
BD	0.207**	0.183**	0.156*	0.195*	0.277**	-0.015
Spearman's Rank Correlation Coefficient (for not normally distributed variables)						
Anthropometric measurement	IID	*ICD	CWCI	IPD	IMD	DAH
FH	0.208**	0.134*	0.223**	0.281**	0.369**	0.058
MHW	0.191**	0.077	0.075	0.130	0.105	-0.012
MFB	0.274**	0.116	0.257**	0.184**	0.245**	0.081
UFH	0.167*	0.174*	0.065	0.166*	0.205**	0.026
FW	0.293**	0.201**	0.197**	0.263**	0.352**	0.011
LFH	0.241**	0.81	0.298**	0.215**	0.274**	0.075

Anthropometric measurement	IID	*ICD	CWCI	IPD	IMD	DAH
ICD	0.150*	0.229**	0.045	-0.009	0.158*	0.182*
NW	0.288**	0.267**	0.152*	0.201**	0.263**	0.143*

*$p<0.05$, **$p<0.01$; FH= Facial height, PFL= Physiognomic facial length, MHW= Maximum head width, MFB= Minimum frontal breadth, UFH= Upper facial height, LFH= Lower facial height, FW= Facial width, ICD= Inner Canthal distance, OCD= Outer Canthal distance, NW= Nasal width, MW= Mouth width, BD= Bigonial distance, IID= Incisor-Incisor distance, *ICD= Inter Canine distance, CWCI= Combined Width of Central Incisors, IPD= Inter-Premolar Distance, IMD= Inter-Molar Distance, DAH= Dental Arch Height

Regarding correlation coefficients, multiple linear regression models were formulated (95% confidence level) for the prediction of facial dimensions (Tab. 4). The stepping criteria includes the probability of F-to-enter = 0.50, F-to-remove = 0.1. Because of stepwise method of regression formulation, two models (for each parameter) were generated for physiognomic facial height, minimum frontal breadth, total jaw height, bizygomatic distance, inner canthal distance, inter alar distance and inter commissural distance. In contrast, one model for each parameter was formulated for facial height, maximum head width, nasal length, outer canthal distance, and bigonial distance. For assessing the significance of the models' various other parameters were also calculated, i.e., coefficient of determination (R^2), adjusted coefficient of determination or goodness-of-fit (Adj. R^2), standard error of estimation (SEE) significance level of model (*p*-value) (Tab. 4).

Table 4. Regression models formulated (step-wise method) for prediction of facial dimensions

Anthropometric measurement	Regression model	R^2	Adjusted R^2	SEE	*p*-value
Facial height	FH = 6.323+ 0.841 x IMD**	0.131	0.127	0.638	<0.001
Physiognomic facial length	PFL = 12.080+0.905 x IMD**	0.081	0.076	0.899	<0.001
	PFL = 10.196+0.666 x IMD**+ 1.007 x IID**	0.117	0.108	0.883	0.003
Maximum head width	MHW = 11.568+0.672 x IID**	0.041	0.026	0.622	0.004
Minimum frontal breadth	MFB = 8.375+0.981 x IID**	0.073	0.069	0.664	<0.001
	MFB = 7.146+0.759 x IID**+0.394 x IMD**	0.098	0.089	0.657	0.004
Upper facial height	UFH = 3.686+0.219 x IMD**	0.029	0.024	0.372	0.014
Lower facial height	LFH = 4.141+0.717 x CWCI**	0.076	0.071	0.462	<0.001
	LFH = 2.882+0.552 x CWCI**+0.324 x IMD**	0.111	0.103	0.454	0.003

Table 4. cont.

Anthropometric measurement	Regression model	R^2	Adjusted R^2	SEE	*p*-value
Facial width	FW = 7.202+1.001 x IMD**	0.146	0.141	0.713	<0.001
	FW = 5.801+0.823 x IM**+0.749 x IID**	0.175	0.167	0.703	<0.001
Inner canthal distance	ICD = 1.711+0.279 x *ICD**	0.071	0.066	0.291	<0.001
	ICD = 2.187+0.362 x *ICD**- 0.213 x IPD**	0.093	0.084	0.289	<0.001
Outer canthal distance	OCD = 5.692+1.056 x IID**	0.134	0.130	0.511	<0.001
Nasal width	NW = 2.036+0.447 x IID**	0.071	0.067	0.307	<0.001
	NW = 1.409+0.334 x IID**+0.201 x IMD**	0.101	0.092	0.303	0.006
Mouth width	MW = 2.567+0.753 x IID**	0.080	0.075	0.487	<0.001
	MW = 2.269+0.576 x 0.448 x CWCI**	0.102	0.093	0.483	0.003
Bigonial distance	BD = 5.924+0.918 x IMD**	0.077	0.072	0.93700	<0.001

*$p<0.05$, **$p<0.01$, FH= Facial height, PFL= Physiognomic facial length, MHW= Maximum head width, MFB= Minimum frontal breadth, UFH= Upper facial height, LFH= Lower facial height, FW= Facial width, ICD= Inner Canthal distance, OCD= Outer Canthal distance, NW= Nasal width, MW= Mouth width, BD= Bigonial distance, IID= Incisor-Incisor distance, *ICD= Inter Canine distance, CWCI= Combined Width of Central Incisors, IPD= Inter-Premolar Distance, IMD= Inter-Molar Distance, DAH= Dental Arch Height

Further, for evaluating the accuracy and reliability of the models, the mean absolute error (MAE) was assessed for each predicted variable. The formula for calculating the MAE is as follows:

$$MAE = \frac{\Sigma_1^N \text{ Absolute error (AE)}}{\text{Sample size (N)}}$$

Where, absolute error (AE) = Predicted value – True value, sample size (N)= 207

Table 5 depicts the MAE for variables included in the present study. The minimum MAE (-0.0004) was observed for lower facial height whereas the maximum MAE (2.367) was found for upper facial height (Tab. 5). Moreover, for physiognomic facial height both the models have equal MAE (-0.0002). Model 1 was found to be better for minimum frontal breadth, lower facial height, inter alar distance and inter commissural distance model because of lower MAE. However, model 2 was observed to be better for bizygomatic distance and inner canthal distance.

All the predicted facial measurements for each participant were drawn manually with pencil and scale on a standard A4 size white executive bond paper for the reconstruction of facial geometry. The estimation of facial shape was carried out in Microsoft Paint computer program. Figure 3 and 4 show the comparison of facial geometry and facial shape of the participants with the predicted facial geometry and shape. Within the limit of the present study, the predicted facial geometry and shapes were not significantly

different from the true facial geometry and shapes. The manual and visual evaluation of predicted and true facial form and geometry was carried out to determine the reliability. It was observed that predicted facial shapes and geometry significantly resembles the true facial shape (Fig. 3 and 4).

Table 5. Absolute error (AE) and mean absolute error (MAE) for predicted variables

Anthropometric measurement	Absolute error (AE) (Predicted value-true value)		Mean absolute error (MAE) (AE/Sample size)	
	Model 1	Model 2	Model 1	Model 2
FH	0.4041	----	0.0019	----
MHW	-0.0272	----	-0.0001	----
MFB	-0.0386	0.587	-0.00018	0.0028
UFH	0.0049	----	2.367	----
FW	0.8	0.1419	0.0038	0.0006
LFH	-0.0963	-0.5424	-0.0004	-0.0026
ICD	0.1016	-0.2963	0.00049	-0.0014
NW	-0.2412	0.2317	-0.0011	0.0011
PFL	-0.0545	-0.0566	-0.0002	-0.0002
OCD	0.2104	----	0.0010	----
MW	0.0422	0.3622	0.0002	0.0017
BD	0.0704	----	-0.0002	----

Sample size (N) = 207, FH= Facial height, PFL= Physiognomic facial length, MHW= Maximum head width, MFB= Minimum frontal breadth, UFH= Upper facial height, LFH= Lower facial height, FW= Facial width, ICD= Inner Canthal distance, OCD= Outer Canthal distance, NW= Nasal width, MW= Mouth width, BD= Bigonial distance

Discussion

The main aim of forensic facial reconstruction is the prediction of the outline, outlook, and appearance of the face of an unknown individual or skull for the purpose of identification. Reconstruction of the face of the individual is an important aspect in case of highly decomposed dead bodies, mutilated and skeletal remains where the face of the dead is beyond recognition. In these cases, anthropologists, odontologists and the forensic scientists opine regarding the identification of the deceased basing on certain preliminary investigations. In the recent past, the scientists have reported facial reconstruction techniques based upon the soft tissue thickness and modeling clay (Bajnoczky and Kiralyfalvi 1995) two- and three-dimensional computerized methods to reconstruction the face (Damas et al. 2020), cranio-facial superimposition technique (Damas et al. 2020; Ubelaker et al. 1992). All these methods either require a complete skull, life-time photograph or sometimes CCTV footage of the deceased. However, this study presents a novel technique for reconstruction of the geometry and shape of the face using dental dimensions. In many mass disaster cases and other forensic caseworks, only jaw and teeth are available as evidence and the

present study technique may be utilized so that a clue regarding the facial shapes may help as corroborative evidence along with other techniques of facial reconstruction.

The present study used dental dimensions for the reconstruction of the geometry and facial shape of the individual and compared the outcome with the actual shape and the geometry of the face. Alshamri et al. (2023) also examined the relationship between dimensions of maxillary anterior teeth and face in 150 participants of 18–30 years age range. The study found the significant correlations between inter canthal distance and central incisors, and face width with canine dimensions. Similarly, a highly significant correlation was observed between inner canthal distance and upper canine width in a study conducted by Alaghbari et al. (2023) for the prosthetic dental reconstruction. Kini and Angadi (2013) also carried out a study of correlation between facial dimensions and teeth dimensions on dental cast and smile photograph both for denture aesthetic work. The study revealed that the distance between the tips of the canine (accessed from photograph) is significantly related to inter commissural distance while distance between the tips of the canine (accessed from dental cast) is associates with interpupillary distance.

The outcome of the correlation between studied facial and dental dimensions used in the present study was compared to other analogous studies with similar objective conducted for various purposes (Tab. 6).

Table 6. Comparison of present study with other similar studies with respect to the correlation of the facial and dental dimensions

Researcher	Research population and (sample size)	Facial dimensions included	Dental dimensions included	Significant correlation found with dental dimensions	Significant correlation not found with dental dimensions
Özdemir and Köseoglu, 2019	Turkish population (N=210)	ICW, ICD, OCD, IPD, IAD,	Combined mesiodistal width of upper central incisors/2	ICW, IAD, ICD, OCD	IPD
Neda and Garib, 2016	Kurdish population (N=65)	IPD, ICD, IAD	CIW, WAT	IPD	IAD, ICD
Parciak et al. 2017	Asian, African, white (N=360)	BW, IAD, ICD, ICW, IPD	WAT, IW, CW,	ICW	IPD, BW, IAD, ICD
Alshamri et al. 2023	Yemini population (N=150)	ICD, IPD, IAD, ICW, BZW	WAT, CIW, LIW	IPD, ICD, BZW	IAD, ICW
Gomes et al. 2006	Brazilian population (N=81)	ICD, IPD, IAD, ICW, Eye width	WAT, MCD	ICD, IPD, IAD, ICW, Eye width	----

Researcher	Research population and (sample size)	Facial dimensions included	Dental dimensions included	Significant correlation found with dental dimensions	Significant correlation not found with dental dimensions
Chunhabundit et al. 2023	Thai population (N=125)	IPD, ICD, IAD, ICW, BZW, FL, LT	MCD, RIW, LIW, RIH, LIH	IPD. ICD, IAD, ICW, BZW, FL, LT	----
Present study	North-Indian population (N=207)	FH, MHW, MFB, UFH, FW, LFH, ICD, NW, PFL, OCD, MW, BD	IID, *ICD, CWCI, IPD, IMD, DAH	MHW, MFB, UFH, LFH, ICD, NW, PFL, OCD, MW, BD	FH, FW, DAH

IPD= inter pupillary distance, ICD= Inner Canthal distance, OCD= outer Canthal distance, IAD= inter alar distance, ICW= inter commissural width, BZW= Bizygomatic width, FL= face length, LT= lip thickness, CIW= central incisors width (combined), LIW= lateral incisors width, WAT= width of anterior teeth (combined width of centrals, laterals, canines), RIW= right central incisor width, LIW= left central incisor width, RIH= right central incisor height, LIH= left central incisor height, IW= incisor width, CW= canine width, MCD= maxillary canine distance

The results of the present study are also comparable the Mishra et al. (2016) study where weak but significant correlation between combined width of anterior teeth and inter pupillary distance, inter-commissural and inter-alar distance was reported. However, the present study included various other dental and facial variables (Tab. 1) which were not included in the study by Mishra et al. (2016). Nevertheless, some of the other parameters included in the present study were included by Chunhabundit et al. (2023) in a study on Thai population for selection of anterior tooth in orthodontic treatment. The study found that IPD, ICD, ICW and BZW are significantly associated with inter canine distance, right central incisor width, right central incisor height, central incisor height, central incisor width, left central incisor width, left central incisor height in both the sexes. However, this study also revealed sex specific correlation. For instance, lip thickness and Intermedial canthal width were related to dental dimension in women only and face length and lateral canthi to lower border of face distance were related to dental parameters in men only (Chunhabundit et al. 2023).

As far as the prediction of face shape and geometry is concerned, some other researchers explored the association between tooth form and face form for dental prosthetic work and tried to predict the tooth shape from face shape and vice-versa. Koralakunte and Budihal (2012) examined the relation between shape/form of upper right central incisor and face shape/form in 200 (18–29 years) Indian participants. Statistically, they found >50% correlation by visual method and 31.5% correlation by William's method in the two parameters of their study. Contrasting results were obtained by Mehndiratta et al. (2019) that evaluated the association of face shape and maxillary central incisors in 200 Indian study participants (aged between 18 and 30 years). Non-significant correlation was observed between face shape and tooth shape. Similarly, Wolfart et al.

(2004) also reported that there was no association between face and tooth form.

The results of the present study on facial prediction models and the facial geometry and shape approximation can be used in forensic facial reconstruction in medicolegal cases and disaster victim identification. Soft tissue thickness plays an indispensable role in facial reconstruction (Moritsugudi et al. 2022). Anthropological and forensic literature has shown that the soft tissue thickness (STT) exhibits variations with respect to ancestry and sex (Moritsugudi et al. 2022). Therefore, the present study should be extended in the future with appropriate STT (population specific) for more reliable results.

Limitations and future recommendations

The findings of the present study significantly contribute the forensic and anthropological literature. However, there are some limitations of this study. The present study was based on dental and facial dimensions of Jingar population which is an endogamous group. Therefore, due to anthropological variations in populations the results of the present study are applicable only to the analysed population. Therefore, the authors recommend that similar studies should be conducted on other population groups. The results of the present study are also limited due to the lack of soft tissue thickness (STT) data. The ancestry and sex-based polymorphism in STT concludes that the STT of one population cannot be applied to another population. Moreover, the literature lacks the standardized STT for the study population. The present study did not consider sexual dimorphism while reconstructing the face. Therefore, future studies should include sex variation in facial dimensions and STT, which may lead to more reliable results. Furthermore, the limited sample size of the study also poses a check on the reliability of the results.

Conclusion

The present study was conducted with the aim of estimating the facial geometry and facial shape from the dental measurements. The study observed a weak but significant correlation between the facial and dental dimensions of the variables. Two-dimensional reconstruction of the face (visual and manual examination) in terms of facial geometry and shape was successfully achieved in the present study. The designed facial geometry and shape may be used as a corroborative support in forensic examinations and personal identification along with other methods of forensic facial reconstruction.

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Ethical approval

The present study is a part of Ph.D. research work in Department of Anthropology, Panjab University, Chandigarh, India. The

ethical approval of the study was obtained from the Panjab University Institutional Ethical Committee vide approval number: PUIEC 230602-I-114 dated 09.06.2023. The consent of each participant was also obtained before data collection.

Conflict of interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Authors' contributions

NC – Conceptualization, searching the literature, writing original draft, review and editing, final approval; KK – Writing, review and editing, final approval and supervising the work.

Corresponding author

Kewal Krishan, Department of Anthropology, (UGC Centre of Advanced Study), Panjab University, Sector–14, Chandigarh, India, e-mail: gargkk@yahoo.com; kewalkrishan@pu.ac.in

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A bifid mandibular condyle from a cremation grave from Paprotki Kolonia cemetery, Poland

Adam Budziszewski[1], *Maciej Karczewski*[2]

[1] University of Warsaw, Faculty of Archaeology, Poland
[2] University of Bialystok, Faculty of International Relations, Poland

Abstract: This study investigates the etiology of a bifid mandibular condyle found in a Bogaczewo culture cremation burial from the Paprotki Kolonia site 1. Using macroscopic analysis and CT imaging, we identified a sagittal separation of the mandibular condyle, suggesting a developmental origin. This represents the first known case of a bifid mandibular condyle from an Iron Age cremation context. Analytical potential is limited due to the preservation of only one condyle and the absence of teeth and temporobandibular surface, which do not allow us to assess the impact of this condition to the life quality of the individual.

Key words: cremated human remains, bone malformation, Iron Age, Bogaczewo Culture.

Original article
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Introduction

Multi-headed mandibular condyles are often incidentally detected during radiographic examinations in both adults and children (Artvinil and Kansu 2003; Ertas et al. 2013; Jha et al. 2013). Proposed etiologies for these abnormalities include malformations during early childhood development (Blackwood 1957; Ertas et al. 2013), hindrance in blood supply (Hrdlička 1941), and childhood trauma (Cowan and Ferguson 1997; Daniels and Ali 2005). However, these lesions are often classified as non-specific, lacking a known etiology (Almăşan et al. 2011; Antoniades et al. 2004; Cowan and Ferguson 1997; Dennison et al. 2008; Ertas et al. 2013; Espinosa-Femenia et al. 2006; Moraes Ramos et al. 2006; Szentpétery et al. 1990). The earliest known report of a bifid mandibular condyle (BMC) dates back to the Late Neolithic period (Williams and Polet 2017).

This study introduces the case of BMC obtained from an archaeological cremation burial of Bogaczewo culture. We provide a description of this condition, a differential diagnosis, and considerations regarding its etiology. This report contributes to the understanding of populational occurrence of multi-headed mandibular condyles from archaeological contexts, particularly in the context of cremation burials and the potential diagnosis of this paleopathology in burned human remains.

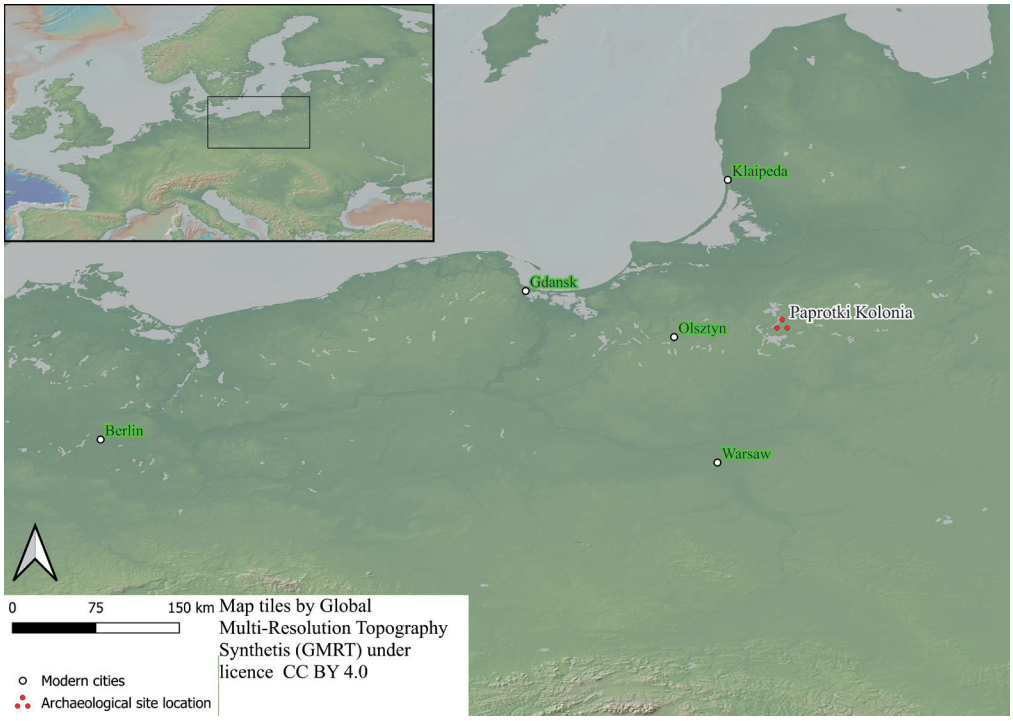

Fig. 1. Geographic location of Paprotki Kolonia site 1. Selected large modern cities marked as the reference

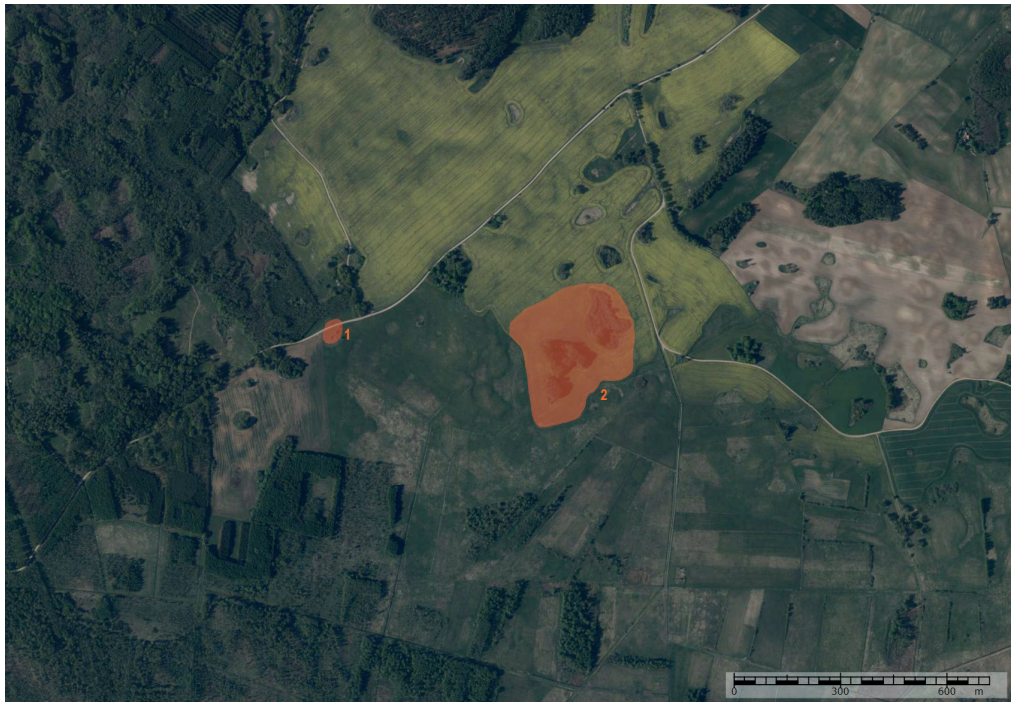

Fig. 2. The present-day landscape of the north shore of the former Lake Wons with the location of relics of the cemetery (1) and associated settlement (2)

Material

The cemetery in the village of Paprotki Kolonia is situated in the Mazurian Lakeland, northeastern Poland (Fig. 1). So far, 539 human graves, 11 offering pits with horse skeletons, and relics of pyres were discovered there. The cemetery is dated from the 1st until the 6th century A.D. All human graves were cremation graves in clay urns or without, usually with the charcoals from the pyre inside the grave pit. Urns exhibited stylistic diversity in terms of form, ornamentation, and metric features. Currently, studies of burials from Bogaczewo culture cemeteries, including Paprotki Kolonia cemetery (French et al. 2024; Karczewski 2011), Łężany (Wiśniewska 2014), and Samławki VII (Budziszewski 2018) reported that while graves with Minimum Number of Individuals (MNI)=1 are the predominant burial form, the occurrence of burials with MNI>1 was confirmed in all bioarchaeologically studied Bogaczewo culture cemeteries. In this category of burials, it is more common for an adult to be buried together with a non-adult. However, graves containing the remains of two or more adults are also known.

However, no clear relationship was found between the MNI and the funerary urn's form, ornamentation or dimensions. Some of the burials with MNI=1 have larger dimensions than urn burials with MNI>1 (Karczewski 2011; Wiśniewska 2014). This cemetery belongs to the so-called Bogaczewo

Culture, an archaeological equivalent for part of the West Balts community in the 1st half of the 1st millennium A.D. Material traces of the funeral rite do not indicate the existence of lasting social differentiation of the community using the cemetery. No graves have been discovered that differed from the others in terms of particularly rich equipment or a different form of burial. Weapon elements discovered in men's graves, such as spearheads, combat knives, shield elements indicate that these were warrior burials. The vertical and horizontal stratigraphy of individual grave clusters indicate that subsequent graves were arranged around the chronologically oldest grave located in the center of grouping. This focal grave usually contained the burned remains of an adult male suggesting a patrilineal structure of the community. The remains of plants and animals discovered in graves were used as elements of the funeral ritual. Such remains were also found in the relics of the settlement whose people used the cemetery (Fig. 2), which proves that it was an agricultural community. Their additional activities included fishing, hunting and gathering. The non-agricultural activities included ferrous and non-ferrous metallurgy, weaving, bone, antler, and amber processing, as well as pottery making.

The grave No. 75 was located in the west part of the cemetery, on the north edge of the large cluster of graves (Fig. 3). It had stratigraphic relations with graves No. 85 and 102. It was a large urn cremation burial with no relics of pyre, excavated during the field season 1992. Insite the urn, between

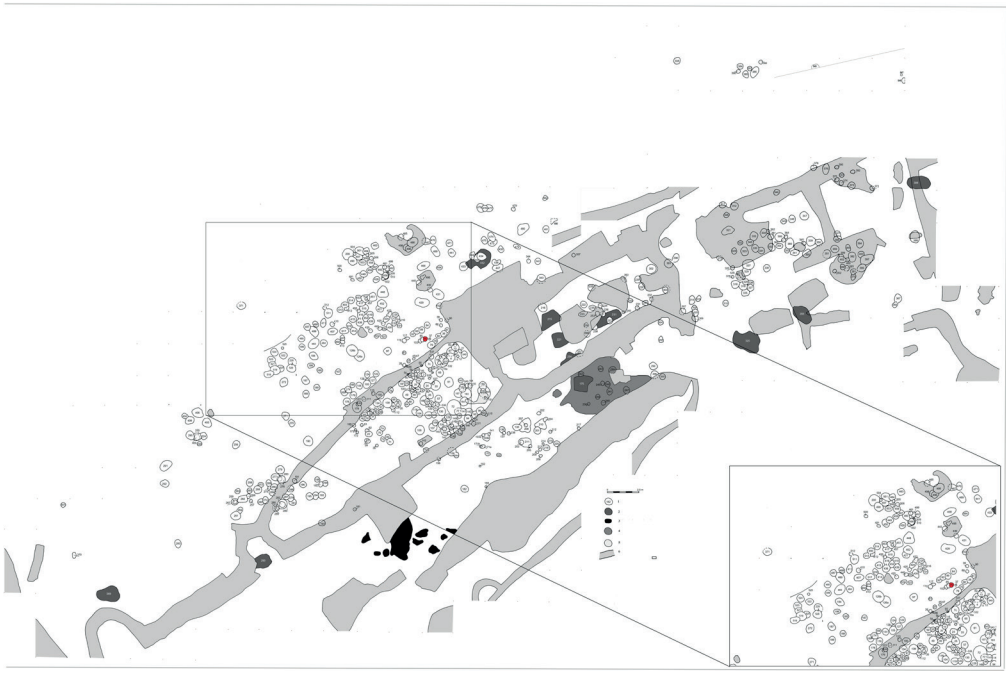

Fig. 3. A fragment of the plan of the western part of the cemetery with the location of grave no. 75 marked by red color. Trenches from World War I marked with gray color

fragments of burnt human bones, an amber bead and a miniature clay vessel were found. All graves – No. 75, 85, and 102 were dated to phases C2-D (ca. 260-450 A.D.).

Methods

The cremation burial was analyzed with the methodological protocol proposed by Jacqueline McKinley (1994) and recently by Elżbieta Jaskulska (2020) with the use of a set of three calibrated sieves. It allowed us to describe and determine the biological profile and cremation burial practices in the case of the single urn burial 75. The sex of individuals was assessed based on the morphology of skull fragments and pelvic morphology (Acsádi and Nemeskéri 1970 cited in Buikstra and Ubelaker 1994; Phenice 1969). Furthermore, the general morphology of preserved bone fragments in terms of robusticity and gracility was taken into account, based on the observation of Jacqueline McKinley (1994:6).

Age-at-death was assessed based on the development of long bones and the axial skeleton (Cunningham et al. 2016), and cranial suture obliteration (Meindl and Lovejoy 1985).

Results

Anthropological analysis

A total of 1837.9 grams of human cremains were deposited in the analyzed urn. The cremains of two adult individuals have been identified in burial 75 based on the presence of two right zygomatic processes of the frontal bone, two right mandibular condyles, and two left frontal processes of the zygomatic bone. Bone fragments also exhibit a visible diversity in size, especially in the case of mandibular condyles. The mediolateral dimension of the first right mandibular condyle (a) is 250 mm, and the second right mandibular condyle (b) is 150 mm. The presence of a male individual (Acsádi and Nemeskéri 1970 cited in Buikstra and Ubelaker 1994) was assessed based on the presence of a pronounced right supraorbital margin (score=5), and nuchal lines of the occipital bone (score=4). This was also confirmed by a preserved right greater sciatic notch (score=4, Phenice 1969). Finally, the general morphology of the bone fragments indicates visible differences in robusticity between a male and a second individual interred in the discussed burial. The presence of a female individual was additionally confirmed and assessed based on the presence of gracile bone fragments and preserved left supraorbital margin (score=2), right mastoid process (score=1), and glabella (score=2). Based on the measurements, the malformed mandibular condyle was assigned to the male individual. Among these 1837.9 g of human cremains, there was not a single bone fragment indicating a distinctly different degree of development of the human osseous system, and significant number of cranial bones with obliteration of sutures in the endocranial surface making it unreasonable to conclude that a non-adult individual was deposited in this burial.

Macroscopic evaluation

A deep and oval groove is present in the middle of the BMC, separating it into two, nearly equal in size heads in the sagittal plane (Fig. 4a, 4b). The pitting is visible within the mentioned medial groove. Lateral and medial views of the affected mandibular condyle present the

morphology of the groove and its depth in the additional perspectives (Fig. 4c, 4d). The maximum mediolateral diameter of the groove is 3 mm and the maximum anterioposterior diameter of the groove is 8 mm This lesion caused the characteristic Y-shaped BMC (Fig. 4e). No osteophytes, tumors, or alternations on the articular surfaces have been observed on the BMC.

Radiographic evaluation

CT image of the BMC under discussion presents the normal cancellous bone presence without any signs of remodelling, fracture lines or bone microstructural disturbances (Fig. 5a, Fig. 5b, Fig. 5c, Fig. 5d). Furthermore, these images offer additional documentation of the BMC's morphology, confirming the symmetrical sagittal condyle separation by a curved groove.

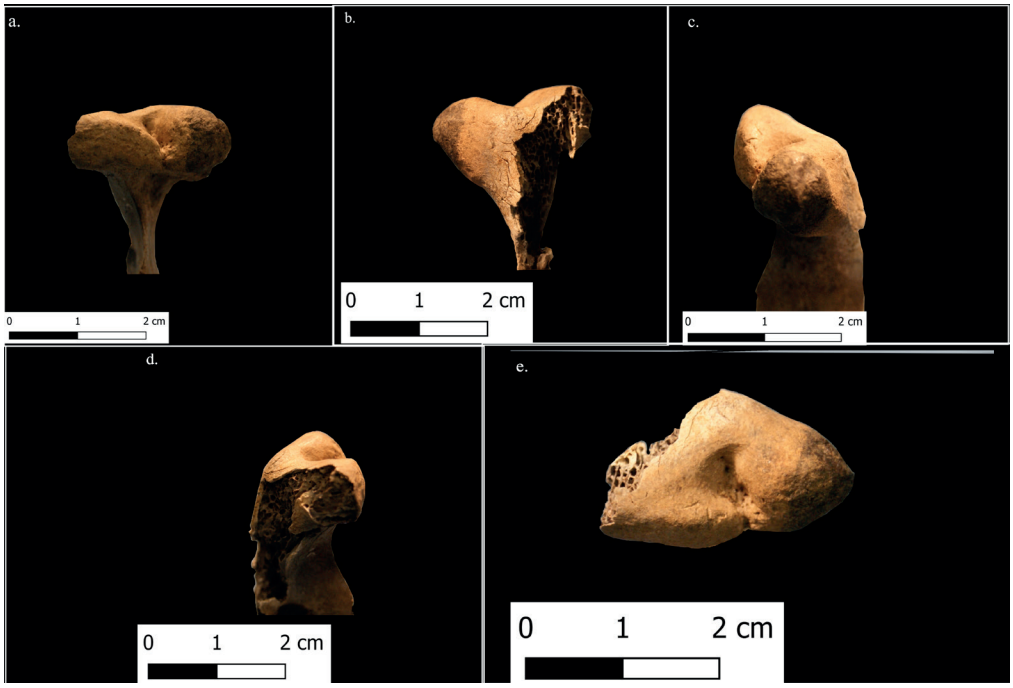

Fig. 4. BMC from the funerary urn 75 from Paprotki Kolonia site 1. **A.** The mandibular condyle from the anterior view. **B.** posterior view**. C.** medial view. **D.** lateral view. **E.** superior view

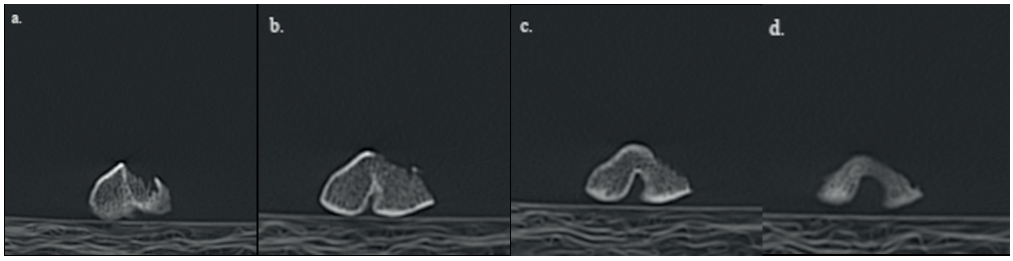

Fig. 5. Series of CT scan images of BMC (a–d), displaying a series of cross sections through the condyle for the visualization of internal bone structure

Discussion

Differential diagnosis

Bifid and multi-headed mandibular condyles are considered rare conditions and are often described as developmental traits with an unknown etiology (Hrdlička 1941). Publications addressing these lesions in archaeological contexts frequently rely on clinical medical reports and echo the etiological conclusions drawn therein. The following section provides observations grounded in the most frequently cited symptoms found in the literature to establish the etiology of the discussed lesion (Table 1).

Among the various etiological mechanisms proposed for the BMC, the case from Paprotki Kolonia aligns most closely with developmental or trauma-induced instances. The absence of osteoarthritic changes, osteophytes, osteochondroma, and lobulation on the condyle surface justifies the exclusion of degenerative or tumor etiology.

Currently, trauma is the most frequently cited etiological mechanism of the BMC in the clinical literature (Antoniades et al. 2004; Cornwall et al. 2015; Cowan and Ferguson 1997; Daniels and Ali 2005; Ertas et al. 2013; González-Garrido et al. 2020; Güven 2018). Szentpétery et al. (1990) were the first to suggest a distinction between sagittal separation of the condyle because of traumatic etiology and coronal separation as characteristics of developmental origin. However, cases of coronal separation of the condyle with confirmed trauma record were also reported in multiple studies (Almăşan et al. 2011; Cowan and Ferguson 1997; Daniels and Ali 2005; Lund 1974; Hersek et al. 2004; Shriki et al. 2005). Moreover, sagittal separation, both unilateral and bilateral, is often recorded in individuals with no known history of trauma (Antoniades et al. 1993; Cornwall et al. 2015; Cowan and Ferguson 1997; Daniels and Ali 2005; Güven 2018; Hersek et al. 2004; Jordana et al. 2004; Kahl et al. 1995; Loh and Yeo 1990). Severe trauma cases in clinical records involve condylar dislocation or dysplasia accompanied by flattening of the mandibular condyle, osteoarthritic changes, and temporomandibular joint (TMJ) ankylosis (Cornwall et al. 2015; Daniels & Ali 2005; Güven 2018).

Clinical records often associate BMC with symptoms such as trismus, clicking, deviation toward the affected side, and pain during mouth opening, although this condition does not consistently hinder TMJ motion or functionality (Almăşan et al. 2011; Ertas et al. 2013; Espinosa-Femenia et al. 2006; Gundlach et al. 1987; Hersek et al. 2004; Loh and Yeo 1990; Lysell and Öberg 1975). Conversely, post-traumatic cases of bifid and trifid mandibular condyles often result in significant restriction of joint functionality and movement (Jha et al. 2013; Moraes Ramos et al., 2006), particularly when osteoarthritis accompanies BMC (Rando and Waldron 2012). Further progression of degenerative lesions can gradually decrease the ability to open the mouth (Antonidades et al. 2004; Cowan and Ferguson 1997; Daniels and Ali 2005; Espinosa-Femenia et al. 2006; Hersek et al. 2004). This can hinder food consumption or create discomfort during eating, especially when biting harder foods. In severe cases, particularly those associated with dislocation of the mandibular condyle and fracture of the condylar neck, these injuries may lead to visible facial asymmetry (Dimitroulis 1997; Ertas et al. 2013; Hersek et al. 2004; Kahl et al. 1995; Shriki et al. 2005; Zachariades et al. 2006).

On the other hand, non-traumatic cases of BMC are commonly not associated with any symptoms or incidents of moderate pain and clicking during the activity of TMJ (Almăşan et al. 2011; Daniels and Ali 2005).

Table 1. Summary of differential diagnosis of BMC from Paprotki Kolonia with possible etiological mechanisms

Symptom	BMC from Paprotki Kolonia	Childhood trauma	Adulthood trauma	Developemental origin	Degenerative conditions	Tumor
Osteoarthritis	-	-	+[a, d, e]	-	+[g]	-
Medial groove	+	+[a, b, c]	+[a, e]	+[a, c, e]	-	-
Flattening of mandibular condyle	-	-	+[a, e]	-	-	-
Lobulation of manidublar condyle	-	-	-	-	+[g]	+
Signs of bone healing	-	+[a]	+[a, d, e]	-	+[g]	-
Condyle dislocation	-	-	+[a]	-	-	-
Sagittal separation of mandibular condyle	+	+[a, b]	+[a, d, e]	+[a, c, e]	-	-
Coronal separation of mandibular condyle	-	+[a, b, c]	-	+[c, e]	-	-
Osteochondroma	-	-	-	-	-	+[h, i]
Ankylosis	-	+[a, b]	+[a, e]	-	+[g]	-
Separated mandibular fossa	-	-	-	-	-	-
Condylar neck separatation	-	-	+[a, d, e]	-	-	-

+ Lesions consistent with condition.

- Lesions inconsistent with condition.

a Cowan, D.F., Ferguson, M.M., 1997. "Bifid mandibular condyle". Dentomaxillofac. Radiol. 26, 70–73.

b Daniels, J.S.M., Ali, I. 2005. "Post-traumatic bifid condyle associated with temporomandibular joint ankylosis: Report of a case and review of the literature". Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology, 99(6), 682–688.

c Blackwood, H.J.J., 1957. „The Double-Headed Mandibular Condyle". *American Journal of Physical Anthropology* 15 (1): 1–8.

d Dennison, J., Mahoney, P., Herbison, P., & Dias, G., 2008. „The False and the True Bifid Condyles". *HOMO* 59 (2): 149–59.

e Szentpétery, A., Kocsis, G., & Marcsik, A. 1990. "The problem of the bifid mandibular condyle". *Journal of Oral and Maxillofacial Surgery*, *48*(12)

g Açikgöz, A. 2006. "Bilateral bifid mandibular condyle: A case report". Journal of Oral Rehabilitation, 33(10), 784–787.

h González-Garrido, L., Gómez-González, S., Gonzalo-Orden, J.M., & Wasterlain, S.N., 2022. „Multi-headed (bifid and trifid) mandibular condyles in archaeological contexts: Two posttraumatic cases". *Archives of Oral Biology* 134: 105326.

i Hersek, N., Özbek, M., Taşar, F., Akpınar, E., Fırat, M., 2004. „Bifid Mandibular Condyle: A Case Report". *Dental Traumatology* 20 (3): 184–186.

Conclusion

Despite the increasing number of recorded cases of BMC in both archaeological and medical contexts, its etiology remains poorly understood (Dennison et al. 2008; Loh and Yeo 1990; Moraes Ramos et al. 2006). In the discussed case, the fragmentation caused by the cremation process hampers our ability to precisely estimate the impact of BMC on the individual's quality of life. However, based on both macroscopic features and radiographic depiction, we suggest that this variation is of developmental origin, most similar to the Blackwood (1957) theory of the early development disturbance in the condylar cartilage, due to the lack of any macroscopic or radiographic signs of bone healing or remodeling of bone structure, which would indicate traumatic origin (Cowan and Ferguson 1997; Loh and Yeo 1990).

This report thus presents another early example of BMC, from Central Europe, dating back to the Iron Age. Moreover, to our knowledge, this is the first reported case of BMC from a prehistoric cremation burial.

Ethics statement

The research procedures undertaken during the analysis published in this report were performed following the BABAO Codes of Ethics and Practice. This article has not been previously published or concurrently submitted to an editorial office of another journal, and it is approved by all authors and the institutions.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study

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Declaration of interest: none.

Authors' contribution

AB was responsible for conceptualization, methodology, formal analysis, writing the original draft, review and editing, and visualization. MK was responsible for data curation, investigation, providing resources, writing the original draft, and review and editing.

Corresponding authors

Adam Budziszewski, University of Warsaw, Faculty of Archaeology, Krakowskie Przedmieście 26/28, 00-927 Warsaw, Poland, e-mail: a.budziszews@uw.edu.pl; Maciej Karczewski, University of Bialystok, Faculty of International Relations, Konstantego Ciołkowskiego Str. 1K, 15-245 Białystok, Poland, e-mail: m.karczewski@uwb.edu.pl

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Mismeasurement of the virtual human body: analyzing error of landmark acquisition

Dominik Černý, *Petra Urbanová*

Department of Anthropology, Faculty of Science, Masaryk University

Abstract: Modern physical anthropology increasingly employs non-invasive methods that use 3D models representing the human body. Frequently, these are 3D models of a person's physical appearance, i.e., face or body. A traditional approach to analyse these records is to process discrete points (landmarks, feature points) collected manually on the model surface. The digitization of landmarks and associated errors have been sufficiently studied in the context of the human face, due to its functional and aesthetic importance. However, other parts of the human body have not received the same level of attention.

The aim of the present study was to quantify the error of body landmarks when collected in 3D full-body models and to explore how it relates to other model properties, such as a demographic and somatic indicators.

The study tested two datasets of 10 body landmarks acquired in 60 models (32 males and 28 females). The data acquisition was carried out during the time span of 14 days. The magnitude of the digitization error for each point was acquired and tested between groups defined according to their anatomical location (shoulders, arms, legs; torso and limbs or body side), sex, age, height and body type.

The results of this study showed that the error of digitising landmarks in a 3D model was greater compared to the error reported in the literature when acquiring landmarks on the human body. The digitization error was independent of participants' age, sex, height, and body type but was correlated with the anatomical location, where the upper chest, neck, and back on the knee yielded the highest digitization errors. In addition, this study showed that landmarks located on the shoulders and arms exhibited an error which was correlated negatively with the volume of the lower and upper half of the body and positively with the body depth.

Key words: digitization, landmarks, 3D model, digitization error, morphology, morphometry.

Original article
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Introduction

The rapid development of imaging and information technologies in the last two decades has enabled to extend the study of the human body into a digital environment. The key prerequisite for conducting a virtual body assessment is the accurate transfer of the human body properties, such as size, shape, colour, to the virtual workspace. Generally, the result of such a transfer (via 3D optical or laser scanning, or single-camera photogrammetry) is a three-dimensional model, also referred to as a polygonal model or 3D mesh (Daanen and Ter Haar 2013). Unlike traditional approaches, such as 2D images, photographs, or conventional measurements, three-dimensional models encompass complex morphological details about the human body, which also includes the depth information which is, otherwise, lost when using the traditional two-dimensional imagery. As an additional benefit, three-dimensional body models can be easily shared in the manner which is identical to any digital data. Importantly, their qualitative and quantitative properties may be explored, once or repeatedly, without requiring direct human contact or sometimes tedious and time-consuming repeated interactions with the subject under study (Kullmer 2008; Craik and Collings 2022).

To date, the quantitative variation of the human body represented by three-dimensional virtual models have been examined by a variety of traditional as well as advanced approaches, such as traditional measurements, curves, or surface comparison (Ben Azouz et al. 2008; Urbanová 2016; Čuta et al. 2024). However, the most frequent are studies of 3D models by means of discrete points, i.e., landmarks, collected manually or automatically on the model surface (Bromiley et al. 2014; Urbanová et al. 2018). The exact position of the collected landmarks within the virtual workspace is traditionally expressed by the Cartesian x, y, z coordinates (Bookstein 1991). These coordinates are used as start and end points to calculate inter-landmark distances, compatible to linear measurements (Caple and Stephan 2016), or to determine ratios, indices, or angles (Sforza and Ferrario 2006). In more complex data processing, they function as registration points to align and superimpose three-dimensional models (Charlier et al. 2014). Subsequently, in post-registration analysis, they serve as variables related to shape and/or size (Zelditch et al. 2012).

The quantitative methods employed to study human variation in 3D virtual body features can be considered accurate and meaningful only on the condition that data are collected cautiously, reliably and without bias. Therefore, to ensure an optimal level of accuracy, repeatability and reproducibility of collected landmarks is paramount (Jones and Rioux 1997). There are four approaches to quantifying acquisition error when discrete points are collected – 1) superimposition-based method, 2) simplified residual method, 3) inter-landmark distance method, and 4) point-to-centroid method. The first approach involves the use of two or more sets of digitized landmarks aligned using a registration method, such as Generalized Procrustes Analysis (GPA), Generalized resistant-fit analysis or the three-point registration (Slice 1996). The registration minimizes the spatial differences between the corresponding points based on the selected measure of deviation, e.g., least-squares, medians etc. Then, direct distances between corresponding points are calculated. This determines the acquisition error at the given point, while the sum of in-

ter-point distances comprises the total error. Alternatively, under the condition that the sets of landmarks are aligned to three body axes, deviations relative to x, y, z axes can be calculated. This may further clarify the direction in which the error is imposed (von Cramon-Taubadel et al. 2007).

The second approach is an alternative of the first approach. It involves quantifying acquisition error from sets of landmark configurations collected repeatedly, while keeping the position of the 3D model unchanged and omitting the registration process (Arnqvist and Mårtensson 1998).

In the third approach, digitization error is quantified using modified methodology from an international standard (ISO 20685-1:2018), where two sets of measurements calculated from landmarks are confronted. The difference between the first and second measurement is calculated to determine the average measurement error and the measurement estimation error. Unlike the superimposition approach, this technique is more successful in localizing the source of error as superposition can dilute the error between landmarks (Ross and Williams 2008).

Ultimately, the fourth approach for error assessment uses the position of the centroid (i.e., the centre of a landmark configuration) and determines distances from the centroid to each point of the configuration. The digitization error is then expressed as the difference between the distances derived from the first and the second set of points (von Cramon-Taubadel et al. 2007; Navarro et al. 2019). This approach is particularly suited for determining the error of closely related landmarks, such as outlines (Chen et al. 2002). As distance-based approaches, both the third and fourth methods require no registration of landmarks.

While there ought to be maximum effort to achieve minimum measurement or data acquisition errors, there is little doubt that such intentions are frequently influenced by a number of external and internal factors. External factors include factors inherent to the digitization process. These include the software used to collect data, workplace, work schedule, or time restrictions. It has been shown that in a less intuitive virtual environment, working with digital data increases the time requirements, and when combined with time pressure it may result in errors (Jurda et al. 2019). Generally, acquiring experience and skills in digital data processing leads to increased accuracy (Kouchi and Mochimaru 2011).

In contrast, internal factors influencing data accuracy and reliability include the type, position, and definition of the landmark (or measurement) and the characteristics of the 3D model on which the data collection is conducted. These factors encompass demographic indicators, such as age and biological sex as well as body somatic indicators (Muehlenbein 2010). According to Bookstein's classification system (1991), type II and III landmarks are particularly sensitive to acquisition errors. These points are defined as the extremes of curvatures or points furthest along (or away from) some structure or the standard anatomical axis (Benfer, 1975; Zelditch et al. 2012). In traditional caliper-based anthropometrics, these landmarks are identified tentatively by tracing the vicinity of anatomical spots until the maximum distance is reached and registered. Consequently, "instrumentally determined" or "maximum width" landmarks, such as the zygion or the vertex, often exhibit the greatest error in only one direction (Katina et al. 2016).

Studies examining the association between the error of landmark placement and body characteristics are scarce,

despite potential interference from sex-related variations in body posture and composition, fat distribution, muscle development, or the tendency toward lower limb swelling. Among the few published studies, Hara et al. (2016) found no influence of participants' age and sex on digitization error in two-dimensional records. Similarly, for faces, the influence of sex (Daboul et al. 2018) and age (Ferrario et al. 2022) was investigated providing negative results. The effect of body type has primarily been quantified for automatic digitization systems, where automatically digitized landmarks exhibited errors correlated with different or atypical body shapes (Devarajan and Istook 2004).

There is a wide range of digitization error that is generally tolerated without questioning the integrity of the published studies. Similarly, there is no consensus on how large the error is acceptable (Ulijaszek a Kerr 1999; Ryan-Stewart et al. 2022). The published work agree that the threshold of acceptable error varies with the size of the body or body parts for which the error is quantified (Ruescas-Nicolau et al. 2024). While a larger error is acceptable for the gross anatomical parts, the same error for the finer body elements has a significant effect on acquired results. In traditional somatometrics, such relevance is underlined by expressing the measurement error relative to the taken measurement. Of the human body parts, the human face is the most frequent anatomical site to quantify acquisition error. Fourie et al. (2011) reported a tolerated acquisition error of 1.5 mm when collecting standard facial points. Sukno et al. (2015) obtained an overall error of 2.3 mm, with averages per landmark below 3.4 mm for 14 tested points and within 2 mm for half of them. In addition to the extent of an error, identifying its direction provides insights into data variation. For instance, Utermohle and Zegura (1982) highlighted directional trends in quantitative data acquisition, observing that in traditional craniometrics, the second set of repeated measurements tended to yield larger values than the initial measurements.

One of the principles related to point accuracy was outlined by Prokopec published in Fetter et al. 1967. Here, an error of 10 mm is reported as tolerable for measuring person's height, 5 mm for measuring dimension on body and 1 mm for measuring on human face. In this case, the limits refer to when the body measurement is taken directly on the participants without the use of 3D models. Conversely, Ulijaszek and Kerr assessed the acquisition error on 3D models, revealing a tolerance of 3% for smaller measurements (e.g., lengths of limbs and head) and 5% for larger dimensions (e.g., stature). Alternatively, standards, such as ISO 7250-1 establish benchmarks for basic human body measurements in technological design with a tolerable measurement error limit of 5 mm. Similarly, ISO 20685-2:2015, which sets standards for 3D scanning and dimensional measurements on 3D models representing the human body, where a measurement error of 9 mm for long measurements over 10 cm (body height, torso height, limb length) is tolerated, while for small measurements up to 10 cm (wrist width, ankle width, finger length), an error of 1 mm is acceptable.

The aim of this study is three-fold: 1) quantify the accuracy of collecting 10 landmarks on the 3D models representing the human body and compute contributions of each landmark to the total error, 2) explore the effect of demographic factors, such as age and sex, of the participants on the acquisition error, 3) assess the extent of somatic factors

(e.g., body type, body size, landmark location, shape and size and influence to measurement of dimensions) on the acquisition error.

Material

The study sample consisted of 60 volunteers, 32 males and 28 females aged from 25 to 76 years (with the average of 47 years) at the time of data acquisition. For males, the average age was 45 years (median = 44 years), while for females, the sample averaged at 49 years (median = 48 years). An analysis of age differences between sexes was performed to assess the sample's demographic balance, and no statistically significant differences were found across the age categories 20–29, 30–39, 40–49, 50–59, and 60–76 (Chi-squared test, p= 0.06).

All participants were recruited from the CardioVision Brno 2030 project at the International Clinical Research Centre (ICRC), St Anne's University Hospital in Brno (FNUSA), Czech Republic. The study was approved by the Ethics Committee of St. Anne's University Hospital in Brno.

Methods

Scanning

Three-dimensional digital body models were obtained using a full-body scanner [TC]^2. The full-body scanner [TC]^2 consists of a booth with an entrance covered with a curtain. Inside the booth, there are 16 sensors with a total of 32 cameras, i.e., two cameras per sensor. In order to ensure maximum accuracy, the scanner was calibrated and checked for errors daily. The participants were scanned in uniform underwear in a standing position with their lower limbs apart and upper limbs spread out. The standardized body posture was achieved using marks placed on the floor indicating the position of feet and height-adjustable handles for gripping and setting of the correct position of the hands.

The pointing accuracy of the scanner is less than 6 millimetres, and the circumferential accuracy is less than 1 cm. The density of the grid of points of the scanner is smaller than 2 by 2 millimetres. The density of data per square centimetres is 75 points, and the density of points throughout a scan is from 600 000 up to one million points (www.tc2.com, 2021). The primary output from the scanner is a point cloud representing a three-dimensional body model in Virtual Reality Modelling Language (.wrl) format.

Scan post-processing

In total, 60 three-dimensional body models were recorded. Final adjustments were carried out in the GOM Inspect and Meshlab program. The primary model in wrl format consisted of 8 separate, unconnected parts (head, torso, both arms, upper parts of both legs, and ankles) with a number of holes present between these parts. The format was first converted to a point cloud (xyz format) in GOM Inspect and then triangulated into a mesh (stl format and finally the obj format) in Meshlab. This ensured that the eight separate parts were connected into one model and all holes were closed properly.

Due to the lower quality of the mesh in the head area, the meshes were manually processed by cutting out the heads with necks in the virtual environment. They were checked for errors (function: Eliminate Mesh Errors) and holes, caused by mesh error (function: Close Holes) and reduced to the final resolution of 45k – 50k vertices. In areas where originally separate parts of the model

overlapped, different densities of vertices emerged, therefore, a reorganization of polygons (GOM Inspect) was performed. This achieved a consistent distribution of vertices within the polygonal mesh.

Landmarks

For each model, a set of 10 landmarks (2 unilateral, 8 bilateral) was collected following definitions as described in Table 1 and Figure 1.

Table 1. Landmarks tested in this study

Name		Definition
Acromiale dx	ACR_R	The points located at the superior and external border of the acromion process with the subject standing erect with arms relaxed.
Acromiale sn.	ACR_L	
Suprasternale	SPS	The point located on the upper edge of the sternum in the mid-sagittal plane.
Radiale dx.	RAD_R	The point located at the tip of the elbow.
Radiale sn.	RAD_L	
Lateral part of the popliteal fossa dx.	GEN_R	The points located on the lateral part of the shallow depression located at the back of the knee.
Lateral part of the popliteal fossa sn.	GEN_L	
Outer ankle dx.	MALL_EX_R	The points located on the tip of the outer ankle.
Outer ankle sn.	MALL_EX_L	
Cervicale	CVR	Protrusion of the 7th cervical vertebra.

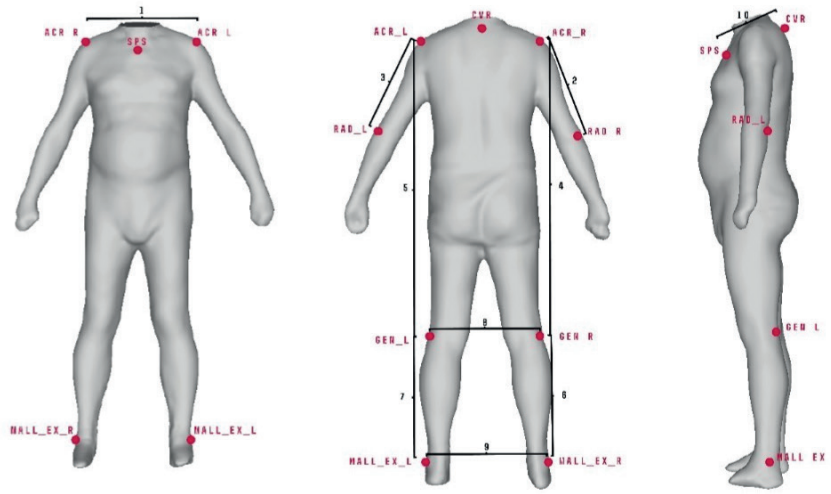

Fig. 1. Landmarks: right and left acromiale (ACR_R, ACR_L), suprasternale (SPS), right and left radiale (RAD_R, RAD_L), right and left lateral part of the popliteal fossa (GEN_R, GEN_L), right and left outer ankle (MALL_EX_L, MALL_EX_R and cervicale (CVR). Linear distances between landmarks: ACR_R-ACR_L (1), ACR_R-RAD_R (2), ACR_L-RAD_L (3), ACR_R-GEN_R (4), ACR_L-GEN_L (5), GEN_R-MALL_EX_R (6), GEN_L-MALL_EX_L (7), GEN_R-GEN_L (8), MALL_EX_R-MALL_EX_L (9), CVR-SPS (10)

Landmarks were selected based on several criteria: 1) clear definition with a supposedly high level of repeatability, 2) distribution throughout the entire body, allowing for a comprehensive description of the human body (Simmons and Istook 2003; Atamtürk et al. 2019), and 3) the clarity of the landmark on the model without texture.

Methods of digitization error analysis

The dataset of 10 landmarks was digitized twice for each model. Data digitalisation was conducted with a 14–day interval between the first and second session. Digitalisation error was quantified from the sets of landmark configurations collected repeatedly while the 3D model position remains unchanged. The error was calculated as the difference, i.e., direct distance between the first and second set of digitized landmarks corresponding to each other and obtained on one identical model. In addition, the landmark displacement according to the x, y, and z axes was determined. The x-axis corresponded to the anterior-posterior body direction, the y-axis aligned with the medial-lateral direction, and the z-axis matched the up and down direction.

Normality of data distribution was tested using the Shapiro-Wilk test and a normal probability plot. Descriptive statistics including mean, maximum, minimum, and standard deviation were calculated. Alternatively, the median, maximum, minimum, and quartile range were used for the results when the data distribution did not meet normality requirements.

A digitization error was detected for each landmark and landmark location. To test the effects of the landmark location, the data set was divided into groups according to anatomical location: those located on the 1) torso and 2) limbs, and in concordance with the right and left side of the body (Fig. 1). In addition, individual's sex, height, body type, body shape, and body size were tested for their influence on data digitalisation. For each 3D model, body type was assessed visually by classifying the 3D model into one of three pre-defined classes. To create categories for body type assessment, BMI was calculated from height and weight of 208 individuals from an independent dataset (archived at the home institution). These individuals were further grouped into three categories, and 3D models representing individuals with the lowest and highest BMI for a given category were used as templates, built separately for men and women (Fig. 2). The pair of templates per category defined the range within which each individual with unknown BMI was assessed. To test repeatability of the approach, intra-observer and interobserver errors were determined. When testing an intra-observer error, only one individual was assigned to a different category. When interobserver error was determined, five individuals were classified differently.

In contrast, body size was described as the volume of a prism calculated from: 1) the height of the individual (cm), measured on the day of the scan at CardioVision (ICRC, FNUSA); 2) the width of the body at the abdomen and hips, defined as the dimension between the two most lateral points in this area (cm), measured on the model; and 3) the anteroposterior dimension at the abdomen, defined as the distance between the most ventral point on the abdomen and the most dorsal point on the back, in a plane parallel to the imaginary ground on which the individual is standing (cm), measured on the model (Fig. 3).

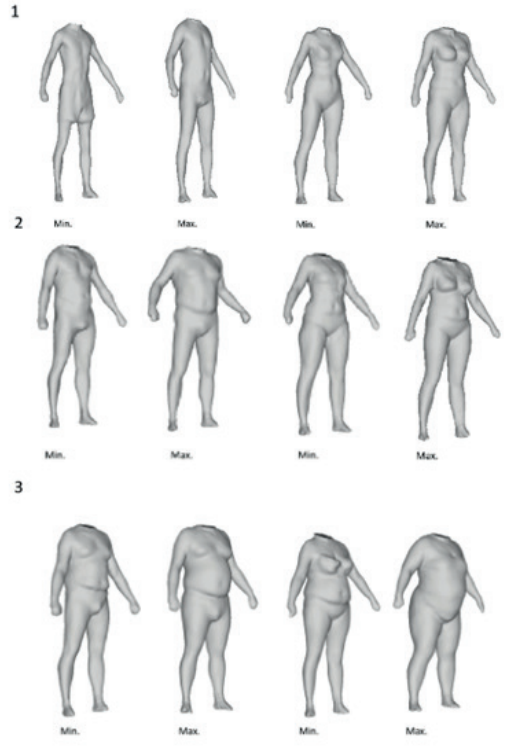

Fig. 2. Model examples representing 3 categories of body types for both males and females: Normal range (1), Overweight (2), Obese (3)

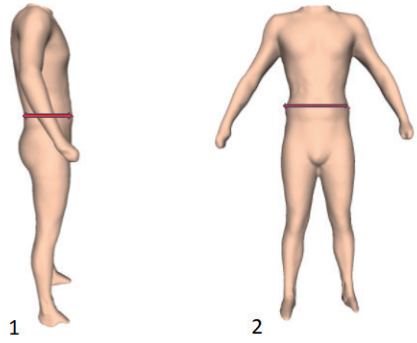

Fig. 3. Two dimensions of body type, the largest anteroposterior dimension of the body in the abdomen (1) and the largest width of the body in the hips (2)

To examine the impact of body shape, the set of landmarks collected at the first session underwent alignment process via Generalized Procrustes Analysis (GPA)

while the size standardization was first omitted (i.e., shape and size variables were acquired), and then included (i.e., only shape variables were acquired). Principal component analysis was performed on both registered data sets (size-present, size-invariant), from which the 4 first components were selected and tested against the digitization error.

In addition, the impact of errors on linear inter-landmark distances were explored. A total of 10 linear distances (Fig. 1) were computed for both sets of collected landmarks and absolute differences between the first and the second set were computed. The error of measurements was expressed in terms of mean absolute difference (MAD), median absolute difference (MedAD), and technical error of measurement (TEM).

Effects of the position of landmarks, sex and somatotype based on BMI were tested with the nonparametric Kruskal-Wallis test and median test, and the Mann-Whitney U test. The relationship between the error and quantitative parameters (body height, body size, error of linear measurements, shape and size principal components) was expressed in terms of the non-parametric Spearman's rank correlation coefficient. Principal component analysis and visual outputs were created in R Studio software using the morpho package (v2.12; Schlager 2017) and geomorph (v3.3.2; Adams et al. 2021).

To test the effect of symmetry, the difference in digitization error between the right and left landmarks at paired points was calculated and tested using the Wilcoxon pairwise test. Difference in symmetry, between the landmarks on right and left side of the body in the digitization error was also tested for its association with shape and size using the Spearman's rank correlation coefficient.

Results

Digitization error

The errors of the digitized landmarks averaged between 11.88 and 18.65 mm (with medians ranging from 10.21 to 16.41 mm) (Tab. 2). The maximum digitization errors were observed for landmarks located on the neck (CVR), the back of the knee joint (GEN_R, GEN_L), and the upper chest (SPS). Landmarks with the highest variability were those on the upper chest (SPS) and the back of the knee joint (GEN_R, GEN_L). Descriptive statistics of digitization error for landmarks by each anatomical axis in absolute values are displayed in Table 3. Here, displacement in the superior-inferior direction often dominated.

Table 2. Descriptive statistics of distances between the landmarks digitised in the first and second batches (in mm)

Landmark	Median	Mean	Minimum	Maximum	SD
ACR_R	11.1	13.26	0.45	36.29	8.44
ACR_L	11.04	13.2	1.69	32.37	8.33
SPS	15.52	18.65	2.98	50.25	12.11
CVR	11.17	13.54	0.98	51.15	9.11
RAD_R	11.89	14.23	2.38	42.7	9.05
RAD_L	11.99	14.25	3.16	39.97	8.74

Landmark	Median	Mean	Minimum	Maximum	SD
GEN_R	16.41	18.91	1.4	44.33	9.7
GEN_L	13.44	15.90	2.27	46.18	9.50
MALL_EX_R	10.5	12.65	1.11	50.65	8.51
MALL_EX_L	10.21	11.88	1.43	30.98	6.5

Table 3. Descriptive statistics of digitalisation error in absolute values (mm)

Landmark	Axis	Median	Minimum	Maximum	Quartile margin
ACR_R	x	5.90	0.19	28.05	7.70
	y	6.56	0.17	24.00	8.04
	z	4.83	0.01	23.41	5.69
ACR_L	x	5.12	0.32	26.01	7.78
	y	6.59	0.02	26.32	7.99
	z	4.16	0.33	19.51	7.96
SPS	x	6.14	0.17	24.47	10.81
	y	5.95	0.04	23.16	6.46
	z	11.08	1.04	39.92	15.55
CVR	x	4.77	0.04	28.64	4.89
	y	4.86	0.41	32.98	5.54
	z	6.71	0.10	36.64	5.11
RAD_R	x	1.94	0.06	28.14	3.61
	y	6.74	0.21	33.02	9.03
	z	7.57	0.06	25.72	8.55
RAD_L	x	2.45	0.03	25.85	3.92
	y	6.72	0.38	25.76	7.01
	z	7.46	0.06	37.52	8.26
GEN_R	x	6.67	0.01	28.56	7.66
	y	5.44	0.19	16.90	6.24
	z	12.63	0.06	40.36	17.69
GEN_L	x	5.62	0.04	37.18	7.42
	y	4.82	0.06	22.99	5.85
	z	8.96	0.60	35.84	10.64
MALL_EX_R	x	4.05	0.12	43.48	5.07
	y	2.40	0.02	22.56	3.97
	z	6.68	0.38	23.39	7.96
MALL_EX_L	x	4.27	0.06	23.01	6.52
	y	1.76	0.07	24.21	1.83
	z	7.83	0.04	24.17	9.06

Digitization error between landmark groups

Based on the values of standard deviation, the groups with the largest variations were landmarks on the upper part of the chest (SPS and CVR) and landmarks on the lateral part of the back of the knee (GEN_R and GEN_L). Kruskal-Wallis test showed statistically significant differences between landmark groups ($H = 21.94$, $p = <0.001$). For landmarks located on the torso or limbs, Mann-Whitney U Test showed no statistically significant difference ($U = 19688$, $p = 0.15$). For landmarks grouped according to the right and left body side, Wilcoxon pairwise test showed significant differences only for the landmarks located at the back of the knee (GEN_L and GEN_R) ($T = 61.0$, $p = 0.02$).

Effect of participant sex, age, body height, body size and body type

The Mann-Whitney U Test showed no statistically significant differences between males and females for any of the tested landmarks. Spearman's correlation coefficient testing the effect of somatic factors (body height and estimated body size) on digitization error was found to be statistically insignificant for the total data set as well as separately for males and females. Similarly, no correlation was found while testing the error against age.

The Kruskal-Wallis and median tests showed no statistically significant differences between all body type groups, except for the landmark cervicale (Kruskal-Wallis test $H = 21.71$, $p = 0.02$) (Tab. 4). In this case, the 3D models of individuals with normal weight produced the largest errors, while the overweight group showed relative consistency in data acquisition.

Table 4. Landmarks according to body type (in mm). Significant differences are marked with asterisk

	Normal weight (N 14)			Overweight (N 25)			Obesity (N 21)		
Landmark	Median	Mean	SD	Median	Mean	SD	Median	Mean	SD
ACR_R	12.66	13.1	8.92	9.38	12.05	6.44	12.93	14.02	6.83
ACR_L	10.92	11.25	7.8	15.01	10.32	7.39	10.66	11.5	9.57
SPS	15.36	15.85	9.12	14.02	16.2	10.19	16.12	17.71	10.65
CVR*	16.48	17.02	10.96	9.54	10.86	9.03	13.01	14.02	7.62
RAD_R	15.41	16.22	8.02	11.01	12.1	8.97	12.04	13.52	8.38
RAD_L	16.42	17.12	10.44	10.59	12.5	8.33	11.4	13.1	6.44
GEN_R	19.2	20.08	9.38	16.5	18.8	10.09	18.27	20.22	9.98
GEN_L	16.2	17.5	9.16	11.95	13.13	9.74	12.93	15.01	10.31
MALL_EX_R	12.28	13.38	8.92	11.13	12.44	9.01	10.48	12.82	7.43
MALL_EX_L	13.07	13.95	7.03	10.59	12.6	7.62	9.05	10.9	7.97

Effect of shape and size variables

Spearman's correlation coefficient testing the effect of shape, size, and symmetry variables on digitization error was found to be statistically significant for several landmarks. Correlations were

observed for the right acromiale point and shape-and-size PC3 associated with subtle arm and leg position and robusticity, and for the left acromiale point together with the left radiale with PC4, which describes arm and leg position. (Fig. 4). Left acromiale and left radiale points revealed a relationship with shape-based PC3 and PC4, which describe the upper and lower body robusticity and the ventrodorsal body dimension respectively.

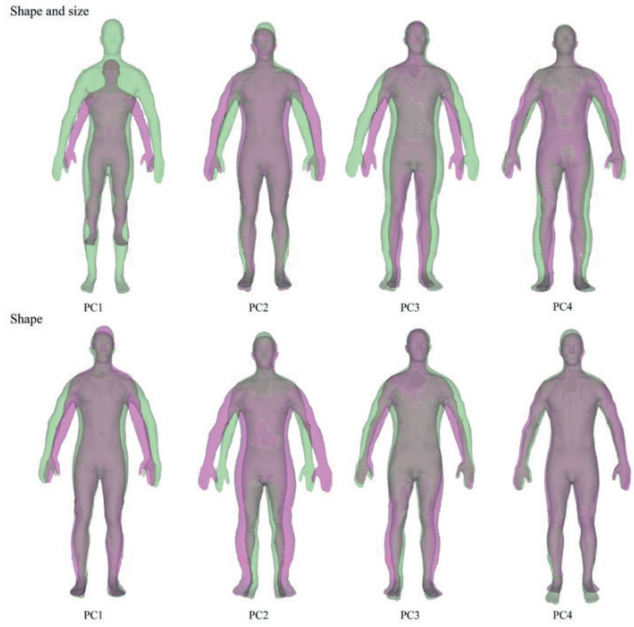

Fig. 4. Description of 4 principal components expressing the most variability for shape and size (green corresponds to positive PC scores, purple corresponds to negative PC scores): PC1 overall size (67.1% variability), PC2 body width and arms position (8.7% variability), PC3 body width knee distance (4.8% variability) and PC4 knee distance (3.5% variability) and for shape: PC1 body position and strength of the upper half of the body (61.3% variability), PC2 body width (10.3% variability), PC3 robusticity of the lower and upper half of the body (5.6% variability) and PC4 anteroposterior body dimension (4.9% variability). Statistically significant correlations between digitalisation errors and principal components for both shape and shape and size are described by landmarks names with positive/negative correlation are market with plus or minus signs

Effect of error on linear distances

The error of inter-landmark distances computed from the two sets of landmarks is displayed in Table 5. The largest error, regardless of evaluation statistics, was recorded for the right-sided length of the shin (GEN_R-MALL_EX_R), while the smallest was observed for the distance between the right and left ankles (MALL_EX_R-MALL_EX_L). When compared to the landmark error, Spearman's correlation coefficient showed that the

strongest correlation with the absolute error was for the suprasternale point and the upper chest measurement (CVR-SPS) ($\rho = 0.85$, $p = 0.001$). This was followed by the knee joint points and their corresponding measurements (GEN_R vs GEN_R-GEN_L: $\rho = 0.31$, $p = 0.011$; GEN_L vs GEN_R-GEN_L: $\rho = 0.48$, $p = 0.001$; GEN_R vs ACR_R-RAD_R: $\rho = 0.62$, $p = 0.011$; GEN_L vs ACR_L-RAD_L: $\rho = 0.53$, $p = 0.001$; GEN_R vs GEN_R-MALL_EX_R: $\rho = 0.65$, $p = 0.001$; GEN_L vs GEN_L-MALL_EX_L: $\rho = 0.24$, $p = 0.06$). However, when considering the described differences, the correlation between the points and the measurements of the upper chest remained significant ($\rho = 0.60$, $p = 0.001$), but the lower limb relationships were not present.

Table 5. Error of inter-landmark distances (in mm) expressed as the mean absolute distance (MAD), the median absolute distance (MedAD) and technical error of measurement (TEM)

	MAD	MedAD	TEM
ACR_R-ACR_L	10.726	9.435	9.574
ACR_R-RAD_R	11.165	9.675	10.090
ACR_L-RAD_L	10.690	8.430	9.950
ACR_R-GEN_R	14.763	11.035	13.308
ACR_L-GEN_L	12.542	11.075	10.957
GEN_R-MALL_EX_R	16.681	14.220	14.701
GEN_L-MALL_EX_L	11.840	9.975	10.747
GEN_R-GEN_L	10.022	7.990	8.929
MALL_EX_R-MALL_EX_L	5.316	3.215	5.750
CVR-SPS	13.764	11.650	12.019

Discussion

Selection of variables is a key aspect of any morphological data processing. Typically, this selection process is influenced by field standards, the study's purpose, as well as traditions and lab protocols passed down through generations of professionals (Fetter 1967; Ben Azous et al. 2006). It is important to stress that most traditional anthropometric landmarks are defined relative to specific locations on the human body, often situated in areas with a solid bony base and minimal overlaying soft tissue. Similarly, it has also been pointed out that landmarks are defined for body dimensions, not locating a position on the body surface (Kouchi, Mochimaru 2011). In addition, these definitions generally pertain to taking linear measurements directly on the human body, assuming that the underlying skeletal structures ensure placement consistency (such as landmarks near joints or bone prominences) (Blaak 2001). However, they do not account for the possibility of collecting a landmark on a 3D model, where immediate feedback regarding the landmark's position relative to its surroundings is missing. Before selecting the final ten landmarks for further processing, additional landmarks located on the wrists, hips, and back of the pelvis area were considered

to ensure more thorough coverage of the entire human body. However, this pilot study revealed that landmarks on the wrists were unsuitable due to poor model quality in that area, and landmarks on the hips and lower back were inaccessible due to participants' underwear or the observer's inability to follow the original point definition, which often requires tactile assessment to confirm the location of the landmarks (e.g., iliospinale, trochanterion).

The present study showed that among the ten tested landmarks digitized on a 3D model representing the human body, the upper chest and both landmarks on the back of the knee joint had the highest digitization errors. The error in the chest area is understandable, as the region is relatively flat and lacks geometric characteristics that are easily distinguishable on 3D models. This is in agreement with the Harris and Smith (2009) study, which reported that surface curvatures affected the accuracy of landmark localization – sharper curves facilitate landmark placement, whereas more gradual curvatures tend to make placement more difficult.

In contrast, the large error in the knee joint region is more puzzling. It is worth noting that the major displacement of the knee joint points was observed in the up and down direction. Subsequently, this had a significant effect on the error registered for the length of the shin. Positions of joints are frequently traced manually or automatically on static or dynamic recordings for gait or movement analyses (Ruescas-Nicolau et al. 2024). In these instances, however, the joint is often in various degrees of flexion, which facilitates landmark placement. Similarly, for direct anthropometrics, the measured individual is often asked to facilitate point placement by changing the joint position (della Croce et al. 1999).

In addition to region specificity, significant differences were observed between right and left-sided landmarks. This was also very pronounced in the landmarks of the knee joint. Observer's handedness is often reported as a source of asymmetry in measurement error studies (Harris and Smith 2009) and was also previously recorded when landmarks were collected using handheld mechanical digitizers (such as MicroScribe) (Urbanová 2009, Urbanová 2011). It remains unclear whether such a bias is translated into the virtual workspace in a similar manner, although computer screens, mice, and other accessories tend to be arranged to accommodate the user's handedness and side preferences. It is worth noting that Kouchi and Mochimaru (2011) reported no right and left differences when landmarking a real-life subject.

Regarding external factors, our results showed that the digitization error of the analysed landmarks was not affected by the sex of the participants for whom the landmarks were digitized. Neither was the digitization error affected by the body type of the individuals. This indicates that sex-related variations in body size and morphology, particularly in fat distribution (Ruff 2002), had no significant impact on the accuracy of landmark placement for the ten landmarks we considered. This is logical given that none of the tested landmarks are located in regions generally associated with fat tissue deposition, which can cause morphological rounding and decrease landmark accuracy (Bouchard et al. 1990). Of the ten landmarks, only the suprasternale and cervicale points would be the logical choices. Here, the cervicale did indeed

showed statistically significant associations with BMI values. However, the observed trend was not straightforward as the largest error was associated with normally weighted individuals, while the most accurately acquired data were from the overweight group.

The literature on acquisition error suggests that for body dimensions, the errors in landmark placement are largely underestimated (Kouchi and Mochimaru 2011). Misplacement of landmarks significantly impacts both body dimensions and shape analysis based on these landmarks (Xi et al. 2007). In addition, most studies have evaluated body dimensions rather than the erroneous placement of landmarks, and the effects of point misplacement have not been considered separately (Aldridge et al. 2005), possibly because landmark placement depends heavily on human judgment. Sometimes there might be a tendency to deny or conceal the impact of the human factor in scientific procedures (Murrie et al. 2019). This leads to the wrongful impression that most landmarks are placed correctly. Meysam et al. (2021) demonstrated that the measurement error was generally smaller compared to the error in the landmarks themselves. This is logical, as the greatest effect on linear measurements comes from landmark misplacement that aligns with the direction of the inter-landmark distance, whereas side deviations of the same magnitude would be less pronounced.

Our results confirm that landmark misplacement was more pronounced than the measurement error associated with inter-landmark distances. In both cases, however, the errors were alarmingly large. While Kouchi and Mochimaru (2011) reported intra-observer errors for the cervicale, suprasternale, acromiale, and radiale points in landmarking a real-life subject in the range of 1.5 to 2.5 mm, and inter-observer errors of 3.3 to 11.5 mm, our study found intra-observer errors far exceeding these values. The lack of geometric details in 3D models, the absence of immediate feedback about the error magnitude, and the absence of texture guiding the landmark placement, can be cited as reasons for these results. Additional training, proper supervision and experience are often recommended to improve proficiency and accuracy in data acquisition. However, in our case, the landmarks were collected by a single, reasonably experienced operator (the first author), who had spent a significant amount of time on landmark selection and adjustment of definitions. We believe that it is important not to shy away from these results, as errors of 3D body landmarks have reported scarcely and can significantly alter the outcomes of 3D scan-based analyses.

Lately, automated landmark detection algorithms have been on the rise owing to the computational capabilities of machine learning algorithms, particularly the neural networks (Ruescas-Nicolau et al. 2024). While a deep insight into these approaches is beyond the scope of this study, it is important to stress that they may be the key to improving the accuracy of manually collected landmarks. Generally, there are two types of techniques: landmark-based and template-based (Kaashki et al. 2021). The major drawbacks of these approaches are that they require a large training dataset if based on state-of-the-art machine learning algorithms, and they are often incompatible with traditional anatomical or anthropometric points (Ruescas-Nicolau et al. 2024).

Conclusion

Our results indicate that digitizing landmarks to a 3D model representing the human body has its pitfalls. When digitizing landmarks, it is necessary to pay attention to the proper methodology of digitization so that the already high error does not increase. It is also important to select landmarks according to their location, so that a compromise between their digitization error and the requirement of the analysis is achieved.

Ethics Approval

The study was approved by the Ethics Committee of St. Anne's University Hospital in Brno 2 (reference number 2G/2012).

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Conflict of interests

The authors declare no potential conflicts of interest regarding the research, authorship, or publication of this article.

Author's contribution

DČ – data collection, data processing, methodology design, and manuscript drafting; PU – methodology design and manuscript drafting.

Corresponding author

Dominik Černý, Department of Anthropology, Faculty of Science, Masaryk University, Kotlářská 267/2, Brno 61137, Czech Republic, e-mail: dominikcerny@sci.muni.cz

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VDR gene polymorphism in susceptibility to urolithiasis among the Asian population: A systematic review and meta-analysis

Malvika Yumnam, Sanjenbam Yaiphaba Meitei

Department of Anthropology, Manipur University

Abstract: Urolithiasis is one of the most prevalent urinary diseases worldwide. Several studies have reported VDR gene polymorphisms to have a contributing genetic factor in susceptibility to urolithiasis and suggested its possibility of being a good candidate marker for urolithiasis. However, results across numerous studies centred on the relationship between the VDR gene polymorphism and urolithiasis have been inconclusive. Therefore, we performed a meta-analysis concerning the association between the risk of urolithiasis and VDR gene polymorphisms viz., ApaI, BsmI, FokI, and TaqI among the Asian population. A comprehensive electronic search was conducted to identify published studies that investigates the relationship between four polymorphisms (ApaI, BsmI, FokI and TaqI) in the VDR gene and the risk of urinary stone disease using electronic databases. VDR ApaI and FokI polymorphisms were found to be associated with urolithiasis risk. Results from pooled analysis indicated ApaI aa genotype to be associated with urolithiasis compared to AA or Aa genotypes. In addition, the minor f allele of FokI variant was identified to be the risk allele in susceptibility to urolithiasis while F allele to be protective. Moreover, from the subgroup analysis, the ff genotype of FokI and aa genotype of ApaI were associated with higher risk of urolithiasis among the East Asian but not among the Southwest Asians.

Key words: Vitamin D receptor, genetic polymorphism, SNPs, urinary stones disease, allele, genotype.

Original article
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Introduction

Urolithiasis is one of the most prevalent urinary diseases worldwide, causing a huge burden on healthcare systems. It is a complex disease that may result from various factors, such as environment, diet, age, genetic factors, metabolic disorders (Fallahzadeh et al. 2012). Urolithiasis is characterized by a high recurrence rate and its incidence continues to increase (Lee et al. 2002). Gene polymorphism has been reported to be an important factor associated with the disorder. A growing amount of epidemiological studies have highlighted the allelic variation in the Vitamin D Receptor (VDR) gene to be involved in the urinary stone disease.

The human VDR, which is a member of the steroid receptor family, is a product of a single gene and is located on chromosome 12 at 12q13-14, and it comprises 11 exons that, together with intervening 8 introns, span approximately 75 kb (Arababadi et al. 2011; Labuda et al. 1992; Miyamoto et al. 1997). Single nucleotide polymorphisms (SNPs) of the VDR gene, commonly ApaI (rs7975232), BsmI (rs1544410), FokI (rs2228570) and TaqI (rs731236) have been intensively studied to investigate associations between these polymorphisms and the risk of urolithiasis as they have been hypothesized to influence the expression and/or function of the VDR protein (Subaşı et al. 2017). These are the restriction enzymes widely used to study the VDR gene polymorphism. Among the four VDR variants, three of them (ApaI, BsmI and TaqI) occur in the intron sections, while only the FokI variant changes the codon (González-Castro et al. 2019; Ou et al. 2014), located at the translational start site of exon 2 of the VDR gene, has been reported to alter the VDR protein sequence and associated with a reduced response to vitamin D in target cells (Arai et al. 1997). Whereas, the SNPs ApaI and BsmI located in exon 8 and TaqI in exon 9 have also been proven to enhance messenger RNA (mRNA) stability or transcriptional activity, and therefore they may lead to an increase in vitamin D activity (Morrison et al. 1994). Several investigations have observed VDR gene polymorphisms to have a contributing genetic factor in susceptibility to urolithiasis and suggested its possibility of being a good candidate marker for urolithiasis (Bid et al. 2005; Chen et al. 2001a; Jawad and Awad 2020). In this light, a well-established genetic marker would have a profound influence in screening and preventing urolithiasis. However, results across numerous studies centred on the relationship between the VDR gene polymorphism and urolithiasis have been inconclusive.

Previous meta-analyses (Imani et al. 2020; Lin et al. 2011; Yang et al. 2019; Zhou et al. 2013) studied the Asian population as a subgroup and their conflicting results could have been due to the ethnic diversity across the region. Hence, our study aims to perform a meta-analysis looking at the the association between the risk of urolithiasis and VDR gene polymorphisms, viz., ApaI, BsmI, FokI, and TaqI among the Asian population specifically, and to further analyze by stratifying them based on regional variation into East Asians and the Southwest Asians. The present meta-analysis is expected to provide a better understanding and may clarify the association between the VDR gene polymorphism and urolithiasis among the Asian populations.

Materials and Methods

Search strategy: A comprehensive electronic search was conducted (from December 2023 upto March 2023) to

identify all published studies that have investigated the relationship between four polymorphisms (ApaI, BsmI, FokI and TaqI) in the VDR gene and the risk of urinary stone disease. Three electronic databases, Science Direct, PubMed and Google Scholar, were searched. The databases were searched using the combination of the following keywords: 'Urolithiasis', 'Nephrolithiasis', 'Kidney stones', 'VDR gene polymorphism', 'SNP'.

Selection criteria

Inclusion criteria: (1) The data supplied the frequency of each genotype or the raw data for computing the frequency of each genotype, which could calculate odd ratios and 95% confidence intervals (CIs). (2) Studies documenting the link between VDR polymorphisms and urolithiasis susceptibility. (3) Case-control studies

Exclusion criteria: (1) Studies with preliminary results not on VDR BsmI, Fok1, TaqI and ApaI gene polymorphism or outcome. (2) Duplicate data, case reports, book chapters, reviews, letters, and articles with no full text or detailed data were excluded. There was a language limit, and studies not available in English were excluded.

Data extraction and synthesis

Two investigators independently screened the literature search and retrieved the titles, abstracts, and full texts of articles that matched the search terms. Then, the same authors cross checked the selections made and any disagreement between the authors were resolved by consensus. The first author's name, journal and year of publication, country of origin, ethnicity, mean or range of age, and total sample size of cases and controls and for each gender separately, the VDR variant studied and genotype frequencies were extracted. The Newcastle-Ottawa Scale (NOS) was applied to assess the quality of relevant articles. The NOS evaluation criteria included three aspects: selection of research subjects (4 points), comparability of research subjects (2 points) and risk factor exposure (3 points) consisting of of nine points in total. The total score of each article could be rated from 0 (lowest) to 9 (highest). The quality of the article was considered to be low if the score was less than 5 points and high if the score was more than or equal to 5 points (Luchini et al. 2017). Quality assesments were performed by the two authors independently and any discrepancies in the evaluations were resolved by discussion or by the assistance of a third researcher if needed.

Statistical analysis

The association between the risk of urolithiasis and the gene polymorphisms of VDR ApaI, BsmI, FokI, and TaqI was determined by the calculation of pooled odds ratios (OR) and 95% confidence intervals (CI). For pooled OR to be statistically significant, $p<0.05$ was required. Between studies heterogeneity was estimated using Cochrane's Q test, significant at $p<0.05$. Besides, I^2 was used to quantitatively report the heterogeneity among the included studies. In absence of heterogeneity, the pooled statistic was performed using the fixed effects model, but a random effects model was conducted when the p-value of the heterogeneity test was <0.10. All data were analyzed using Metagenyo (Martorell-Marugan et al. 2017) to calculate the available data from each study. Seven statistical models were applied in this meta-analysis, viz. Allelic model which compares the minor allele to major allele (ApaI a vs. A; BsmI b vs. B; FokI f vs. F and Taq t vs. T); Recessive model (ApaI aa

vs. AA+Aa; BsmI bb vs. BB+Bb; FokI ff vs. FF+Ff; and TaqI tt vs. TT+Tt), Dominant model (ApaI Aa+aa vs. AA; BsmI Bb+bb vs. BB; FokI Ff+ff vs. FF; and TaqI Tt+tt vs. TT), Over-dominant model (ApaI Aa vs. aa+AA; BsmI Bb vs. bb+BB; FokI Ff vs. ff+FF and TaqI Tt vs. tt+TT), and three pair-wise comparison models viz. Homozygous model (ApaI aa vs. AA, BsmI bb vs. BB, FokI ff vs. FF, and TaqI tt vs. TT), heterozygous model (ApaI Aa vs. AA, BsmI Bb vs. BB, FokI Ff vs, FF and TaqI Tt vs.TT) and minor allele homozygote versus heterozygote model (Apa aa vs. Aa, BsmI bb vs. Bb, FokI ff vs. Ff and TaqI tt vs. Tt). In addition, subgroups based on the region in Asia, viz., East Asia and Southwest Asia were stratified.

We used Egger's test for an objective evaluation of the publication bias. If the P-value of Egger's test is greater than 0.05 and the funnel plot is symmetrical, it can be considered that there is no significant evidence of publication bias. We also performed a sensitivity analysis to assess whether individual studies affected the overall results by leave one out method. The analysis is repeated after removing one study each time, and it was found that the combined odds ratio (OR) of the remaining studies was within the 95% CI in the meta-analysis. The results showed that the combined OR of this meta-analysis had good stability.

Results

Study characteristics: Figure 1 outlines the study selection process. A total of 1362 articles were identified after the initial search from the electronic databases. After an initial screening of titles and abstracts using inclusion and exclusion criteria, 29 studies were identified for full-text review, and 17 articles were included in quantitative analysis.

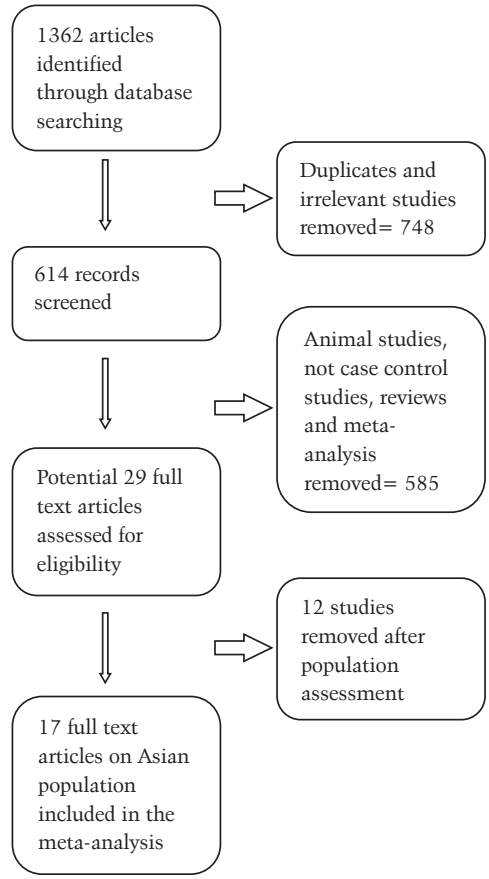

Fig. 1. Flowchart illustrating the study selection process

A total of 17 aticles reporting the relationship between VDR ApaI, BsmI, FokI, and TaqI gene variants and urolithiasis susceptibility were recruited through the search strategy. The required data from these studies were extracted (Tab. 1). Of these 17 articles, 6 articles studied the ApaI (rs7975232) variant, 4 articles for BsmI (rs1544410) variant, 11 articles for FokI (rs2228570) variant, and 10 articles for TaqI (rs731236) variant.

Table 1. Characteristics of studies included in the meta analysis

Reference	Age group	Stone composition	VDR polymorphic site	Cases	Controls	NOS
Amar et al., (2020)	NA	NA	BsmI,FokI, TaqI,	235	243	**7**
Bid et al., (2005a)	Adult	Calcium oxalate	FokI	138	166	6
Bid et al., (2005b)	Children	NA	FokI	50	60	8
Chen et al., (2001a)	Adult	Calcium oxalate	FokI	146	90	**5**
Chen et al., (2001b)	Adult	Calcium oxalate	BsmI	124	90	4
Guha et al., (2015)	Adult	Calcium Stones	FokI, TaqI	200	200	8
Huang et al., (2019)	Children	NA	FokI	142	238	**7**
Jawad & Awad, (2020)	All	Calcium Stones	TaqI	204	127	**5**
Liu et al., (2007)	Adult	Calcium Stones	FokI	235	231	8
Mittal et al., (2010)	Adult	NA	ApaI,FokI, TaqI	125	150	**7**
Nishijima et al., (2002)	Adult	Calcium Stones	ApaI, TaqI	83	86	6
Parvaresh et al., (2022)	Children	Calcium Stones	TaqI	90	90	**7**
Seo et al., (2010)	Adult	Calcium Stones (major)	ApaI,FokI, TaqI	273	525	**7**
Relan et al., (2004)	Adult	Calcium oxalate (major)	BsmI, FokI	150	100	**7**
Shaogang et al., (2003)	Adult	Calcium oxalate	ApaI,FokI, TaqI	150	80	6
Wang et al., (2012)	Adult	Calcium Stones	ApaI,BsmI, FokI, TaqI	464	450	8
Yang et al., (2019)	Adult	Calcium oxalate	ApaI, TaqI	943	975	8

NOS: New Castle Ottawa Scale
NA: Not available

Association of VDR ApaI gene polymorphism with urolithiasis

Six studies associating VDR ApaI gene polymorphism and urolithiasis risk were identified from the literature search. A total of 2074 cases and 2263 controls were included in our analysis. Between studies heterogeneity was detected in the allelic model and homozygous model but not in the dominant, recessive, over-dominant model and heterozygous model. In the pooled OR from overall studies, the ApaI variant showed no significant associations in any of the genetic models: allelic model (a vs. A: OR=1.04, 95% CI 0.89-1.23), dominant model (Aa+aa vs. AA: OR=1.06, 95% CI 0.89-1.26), recessive model (aa vs. AA+Aa: OR=1.14, 95% CI 1.00-1.30), over-dominant model (Aa vs. AA+aa: OR=0.91, 95% CI 0.81-1.03), homozygous model (aa vs. AA: OR=1.07, 95% CI 0.74-1.56), heterozygous model (Aa vs. AA: OR=1.00, 95% CI 0.83-1.21) or minor allele homozygote versus heterozygote model (aa vs. Aa: OR=1.14, 95% CI 0.99-1.30) (Tab. 2, Fig. 2). However, in the subgroup analysis, a significant association was found among the East Asian in the recessive model (aa vs.

AA+ Aa: OR=1.17, 95% CI 1.00-1.30) and pairwise minor allele homozygote versus heterzygote model (aa vs. Aa: OR=1.16, 95% CI 1.01-1.34) but not among the Southwest Asian. Funnel plot and Egger's test were used to detect publication bias. However, publication bias was not detected (p>0.05).

Table 2. Association analysis for ApaI variant with urolithiasis

ApaI Genetic contrasts	Subgroup	No. of studies	Q test P value	Model selected	OR (95% CI)	p value	Egger's p value
a vs. A	Overall	6	0.04	Random	1.04 (0.89-1.23)	0.60	0.24
	East Asian	5	0.02	Random	1.05 (0.87-1.26)	0.60	0.34
	Southwest Asian	1	-	Fixed	0.97 (0.69-1.37)	0.86	-
aa vs AA+Aa	Overall	6	0.07	Random	1.10 (0.88-1.38)	0.40	0.41
	East Asian	5	0.11	Fixed	1.17 (1.02-1.33)	0.02	0.75
	Southwest Asian	1	-	Fixed	0.62 (0.29-1.30)	0.21	-
Aa+aa vs. AA	Overall	6	0.07	Random	1.04 (0.79-1.38)	0.76	0.58
	East Asian	5	0.04	Random	1.00 (0.72-1.41)	0.96	0.59
	Southwest Asian	1	-	Fixed	1.17 (0.0.71-1.92)	0.54	-
Aa vs. AA+aa	Overall	6	0.35	Fixed	0.91 (0.81-1.03)	0.14	0.79
	East Asian	5	0.73	Fixed	0.88 (0.78-1.00)	0.06	0.52
	Southwest Asian	1	-	Fixed	1.42 (0.88-2.28)	0.15	-
aa vs. AA	Overall	6	0.03	Random	1.07 (0.74-1.56)	0.71	0.15
	East Asian	5	0.03	Random	1.13 (0.76-1.70)	0.54	0.28
	Southwest Asian	1	-	Fixed	0.72 (0.32-1.62)	0.43	-
aa vs. Aa	Overall	6	0.12	Fixed	1.14 (0.99-1.30)	0.07	0.64
	East Asian	5	0.26	Fixed	1.16 (1.01-1.34)	0.03	0.83
	Southwest Asian	1	-	Fixed	0.55 (0.25-1.20)	0.14	-
Aa vs. AA	Overall	6	0.14	Fixed	1.00 (0.83-1.21)	0.98	0.71
	East Asian	5	0.13	Fixed	0.96 (0.78-1.18)	0.71	0.62
	Southwest Asian	1	-	Fixed	1.31 (0.78-2.19)	0.31	-

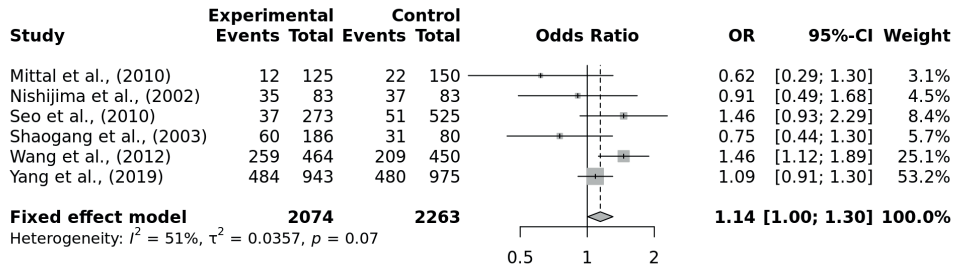

Fig. 2. Association analysis of ApaI variant with urolithiasisna

Association of VDR BsmI gene polymorphism with urolithiasis

A total of 4 papers consisting of 959 cases and 870 controls were included to determine the correlation between BsmI and the risk of urolithiasis. Between studies heterogeneity was not detected. From the pooled OR in this meta-analysis we observed that the BsmI variant had no association with urolithiasis risk in the allelic comparison (b vs. B: OR=1.13, 95% CI 0.95-1.35), dominant model (Bb+bb vs. BB: OR=1.17, 95% CI 0.85-1.61), recessive model (bb vs. BB+Bb: OR=1.16, 95% CI 0.91-1.47), over-dominant model (Bb vs. BB+bb: OR=0.95, 95% CI 0.75-1.19), homozygous model (bb vs. BB: OR=1.23, 95% CI 0.83-1.81), minor allele homozygote versus heterzygote model (bb vs. Bb: OR=1.13, 95% CI 0.88-1.45) or heterozygous model (Bb vs. BB: OR=1.12, 95% CI 0.79-1.60) (Tab. 3). Moreover, subgroup analysis also rejected any significant association between VDR BsmI variant with urolithiasis under any genetic model in East and Southwest Asian. Funnel plot and Egger's test were performed to estimate the publication bias, and no publication bias was observed (p>0.05).

Table 3. Association analysis for BsmI variant with urolithiasis

BsmI Genetic contrasts	Subroup	No. of studies	Q test P value	Model selected	OR (95% CI)	p value	Egger's p value
b vs. B	Overall	4	0.66	Fixed	1.13 (0.95-1.35)	1.16	0.60
	East Asian	2	0.60	Fixed	1.02 (0.75-1.39)	0.88	-
	Southwest Asian	2	0.41	Fixed	1.19 (0.96-1.47)	0.11	-
bb vs. BB+Bb	Overall	4	0.86	Fixed	1.16 (0.91-1.47)	0.23	0.63
	East Asian	2	0.88	Fixed	1.08 (0.76-1.54)	0.65	-
	Southwest Asian	2	0.48	Fixed	1.23 (0.88-1.70)	0.22	-
Bb+bb vs. BB	Overall	4	0.22	Fixed	1.17 (0.85-1.61)	0.33	0.62
	East Asian	2	0.85	Fixed	0.80 (0.38-1.69)	0.56	-
	Southwest Asian	2	0.07	Random	1.30 (0.69-2.44)	0.41	-
Bb vs. BB+bb	Overall	4	0.07	Random	0.99 (0.68-1.45)	0.96	0.69
	East Asian	2	0.80	Fixed	0.89 (0.63-1.24)	0.48	-
	Southwest Asian	2	0.01	Random	1.14 (0.49-2.68)	0.76	-
bb vs. BB	Overall	4	0.84	Fixed	1.23 (0.83-1.81)	0.31	0.30
	East Asian	2	0.80	Fixed	0.83 (0.26-2.66)	0.76	-
	Southwest Asian	2	0.58	Fixed	1.29 (0.85-1.94)	0.23	-
bb vs. Bb	Overall	4	0.39	Fixed	1.13 (0.88-1.45)	0.35	0.69
	East Asian	2	0.93	Fixed	1.11 (0.78-1.59)	0.56	-
	Southwest Asian	2	0.08	Random	1.03 (0.53-2.04)	0.92	-
Bb vs. BB	Overall	4	0.09	Random	1.09 (0.61-1.97)	0.77	0.77
	East Asian	2	0.83	Fixed	0.75 (0.32-1.74)	0.50	-
	Southwest Asian	2	0.02	Random	1.31 (0.53-3.27)	0.56	-

Association of VDR FokI gene polymorphism with urolithiasis

For the association between FokI polymorphism of VDR gene and the risk of urolithiasis, a total of 11 papers consisting of 2143 cases and 2454 controls were included in our analysis. Heterogeneity between the studies was detected in the allelic, dominant, over-dominant and heterozygous models. The ff genotype of the FokI recessive model presented a significantly higher risk of urolithiasis by 1.27 fold (ff vs. FF+Ff: OR=1.27, 95% CI 1.07-1.51), by 1.24 fold in the homozygous model (ff vs. FF: OR=1.24, 95% CI 1.02-1.52) and by 1.26 fold in the minor allele homozygote versus heterzygote model (ff vs. Ff: OR=1.26, 95% CI 1.04-1.51) (Tab. 4, Fig. 3, 4 and 5). However, the allelic (f vs. F: OR= 1.06, 95% CI 0.88-1.28), dominant (Ff+ff vs. FF: OR= 1.01, 95% CI 0.72-1.40), over-dominant (Ff vs. FF+ff: OR= 0.88, 95% CI 0.64-1.22) and heterozygous model (Ff vs. FF: OR= 0.96, 95% CI 0.68-1.35) showed no significant association. In the subgroup analysis ff genotype among the East Asian are found to have 1.32 fold significantly higher urolithiasis risk than Ff genotype (OR=1.32, 95% CI 1.08-1.60). Egger's test was performed to estimate the publication bias. Publication bias was not observed (p>0.05).

Table 4. Association analysis for FokI variant with urolithiasis

FokI Genetic contrasts	Subgroup	No. of studies	Q test P value	Model selected	OR (95% CI)	p value	Egger's p value
f vs. F	Overall	11	0.00	Random	1.06 (0.88-1.28)	0.51	0.54
	East Asian	6	0.01	Random	1.13 (0.92-1.38)	0.24	0.82
	Southwest Asian	5	0.00	Random	0.96 (0.65-1.41)	0.83	0.33
ff vs. FF+Ff	Overall	11	0.11	Fixed	1.27 (1.07-1.51)	0.01	0.52
	East Asian	6	0.06	Random	1.32 (0.99-1.77)	0.06	0.91
	Southwest Asian	5	0.55	Fixed	0.90 (0.52-1.55)	0.70	0.65
Ff+ff vs. FF	Overall	11	0.00	Random	1.01 (0.72-1.40)	0.97	0.54
	East Asian	6	0.06	Random	1.06 (0.82-1.36)	0.66	0.73
	Southwest Asian	5	0.00	Random	0.88 (0.40-1.93)	0.74	0.38
Ff vs. FF+ff	Overall	11	0.00	Random	0.88 (0.64-1.22)	0.45	0.48
	East Asian	6	0.49	Fixed	0.87 (0.76-1.01)	0.07	0.46
	Southwest Asian	5	0.00	Random	0.88 (0.38-2.03)	0.77	0.36
ff vs. FF	Overall	11	0.15	Fixed	1.24 (1.02-1.52)	0.03	0.50
	East Asian	6	0.02	Random	1.29 (0.89-1.88)	0.18	0.97
	Southwest Asian	5	0.97	Fixed	0.94 (0.54-1.65)	0.84	0.68
ff vs. Ff	Overall	11	0.10	Fixed	1.26 (1.04-1.51)	0.02	0.59
	East Asian	6	0.21	Fixed	1.32 (1.08-1.60)	0.01	0.94
	Southwest Asian	5	0.17	Fixed	0.83 (0.47-1.46)	0.53	0.53
Ff vs. FF	Overall	11	0.00	Random	0.96 (0.68-1.35)	0.80	0.47
	East Asian	6	0.28	Fixed	0.98 (0.84-1.16)	0.79	0.90
	Southwest Asian	5	0.00	Random	0.88 (0.38-2.02)	0.76	0.36

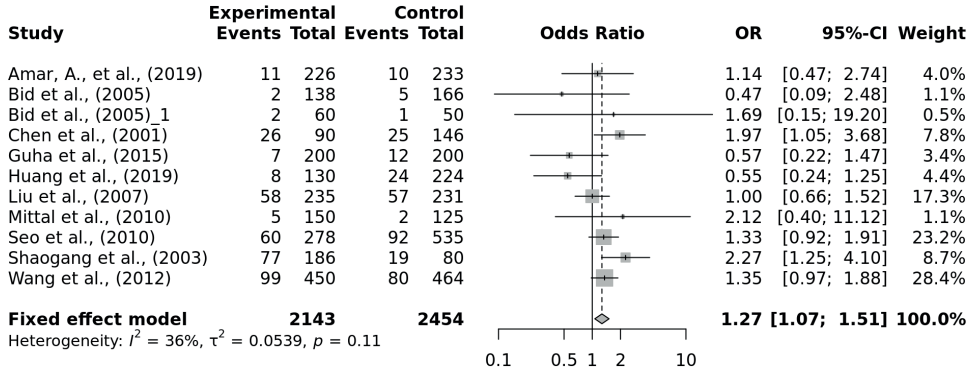

Fig. 3. FokI ff vs. FF+Ff forest plot

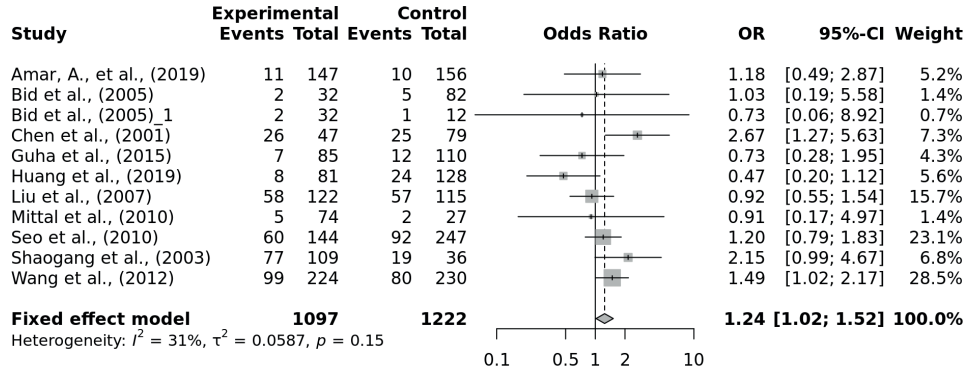

Fig. 4. FokI ff vs. FF forest plot

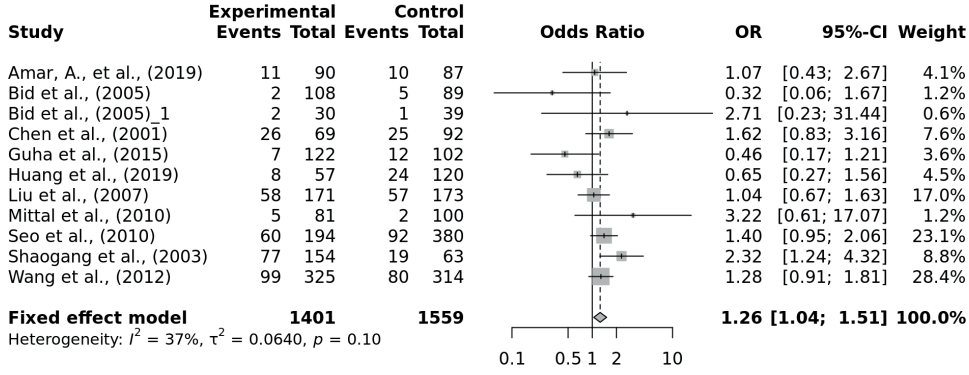

Fig. 5. FokI ff vs. Ff forest plot

Association of VDR TaqI gene polymorphism with urolithiasis

Ten studies associating VDR TaqI gene polymorphism and urolithiasis risk were included in our analysis comprising of a total of 2811 cases and 2920 controls. Between studies heterogeneity were detected in the dominant, overdominant and heterogyzous model. The pooled OR from this meta-analysis showed no significant association of the TaqI variant with urolithiasis risk in the allelic comparison (t vs. T: OR=1.09, 95% CI 0.97-1.23), dominant model (Tt+tt vs. TT: OR=1.09, 95% CI 0.86 -1.37), recessive model (tt vs. TT+Tt: OR=1.47, 95% CI 1.09-2.00), over-dominant model (Tt vs. TT+tt: OR=0.97, 95% CI 0.78-1.20), homozygous model (tt vs. TT: OR=1.48, 95% CI 1.07-2.04), pairwise minor allele homozygote versus heterozygote model (tt vs. Tt: OR=1.47, 95% CI 1.07-2.03) or heterozygous model (Tab. 5: Tt vs. TT: OR=1.03, 95% CI 0.81-1.31).

Table 5. Association analysis for TaqI variant with urolithiasis

TaqI Genetic contrasts	Subgroup	No. of studies	Q test P value	Model selected	OR (95% CI)	p value	Egger's p value
t vs. T	Overall	10	0.08	Random	1.09 (0.93-1.26)	0.29	0.05
	East Asian	5	0.36	Fixed	1.08 (0.91-1.32)	0.38	0.11
	Southwest Asian	5	0.03	Random	1.14 (0.83-1.55)	0.56	0.25
tt vs. TT+Tt	Overall	10	0.20	Fixed	1.47 (1.09-2.00)	0.34	0.29
	East Asian	5	0.74	Fixed	1.12 (0.63-2.01)	0.70	0.93
	Southwest Asian	5	0.04	Random	1.63 (1.14-2.34)	0.25	0.02
Tt+tt vs. TT	Overall	10	0.03	Random	1.09 (0.86-1.37)	0.40	0.06
	East Asian	5	0.38	Fixed	1.09 (0.89- 1.33)	0.40	0.03
	Southwest Asian	5	0.01	Random	1.03 (0.64-1.67)	0.78	0.34
Tt vs. TT+tt	Overall	10	0.01	Random	0.97 (0.78-1.20)	0.76	0.33
	East Asian	5	0.61	Fixed	1.07 (0.88-1.31)	0.49	0.01
	Southwest Asian	5	0.00	Random	0.81 (0.54-1.22)	0.84	0.82
tt vs. TT	Overall	10	0.44	Fixed	1.48 (1.07-2.04)	0.09	0.51
	East Asia	5	0.66	Fixed	1.24 (0.67-2.28)	0.49	0.96
	Southwest Asia	5	0.16	Fixed	1.58 (1.08-2.31)	0.12	0.10
tt vs. Tt	Overall	10	0.07	Random	1.19 (0.80-1.78)	0.39	0.42
	East Asia	5	0.83	Fixed	1.00 (0.54-1.83)	0.99	0.93
	Southwest Asia	5	0.01	Random	1.71 (1.17-2.51)	0.35	0.06
Tt vs. TT	Overall	10	0.01	Random	1.03 (0.81-1.31)	0.52	0.12
	East Asian	5	0.49	Fixed	1.09 (0.89-1.33)	0.43	0.01
	Southwest Asian	5	0.00	Random	0.91 (0.55-1.51	0.92	0.36

Additionally, the subgroup analysis also indicated no signgificant association of urolithiasis risk with TaqI variant among the East and Southwest Asian subgroup. Publication bias ($p<0.05$) was detected among the East Asian subgroup

in the dominant model, over-dominant model and heterozygous model and in the recessive model among the South-west Asian subgroup.

Sensitivity Analysis and Potential Publication Bias

Several sensitivity tests were performed to evaluate the robustness of our findings by sequentially removing one study in turn. The analysis is repeated excluding one study each time in order to visualize if any study has a significantly greater contribution to overall statistics than the other studies. However, the pooled ORs of the significantly associated genetic models were not substantially altered and was within the 95% CI, indicating that no single study influenced the stability of the results obtained in this meta-analysis (Fig. 6, 7, 8, and 9). Egger's test with p value of <0.05 defined as having potential publication bias was used to evaluate potential publication bias. However, in this meta-analysis, except for TaqI polymorphism, no publication bias was observed both in overall and subgroup analyses. The funnel plots of the significantly associated genetic models also shows to be symmetrical (Fig. 10, 11, 12 and 13).

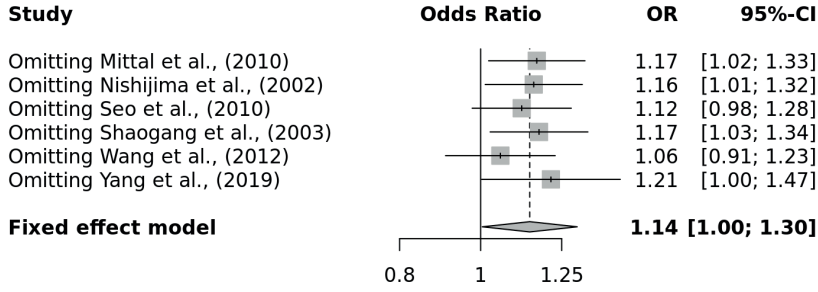

Fig. 6. Apa aa vs. AA+Aa sensitivity plot

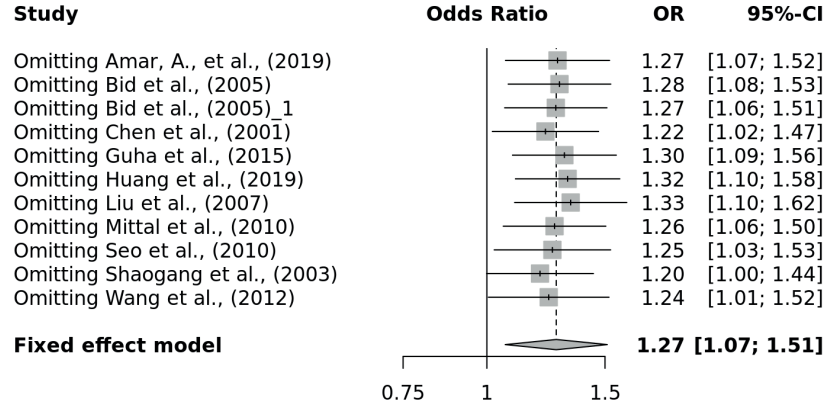

Fig. 7. FokI ff vs. FF+Ff sensitivity plot

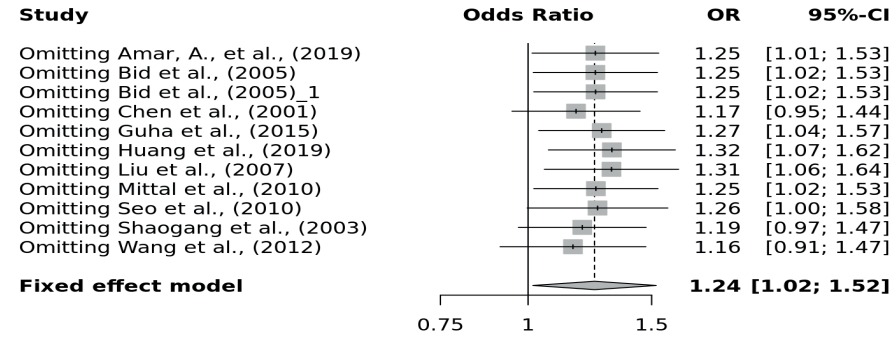

Fig. 8. FokI ff vs. FF sensitivity plot

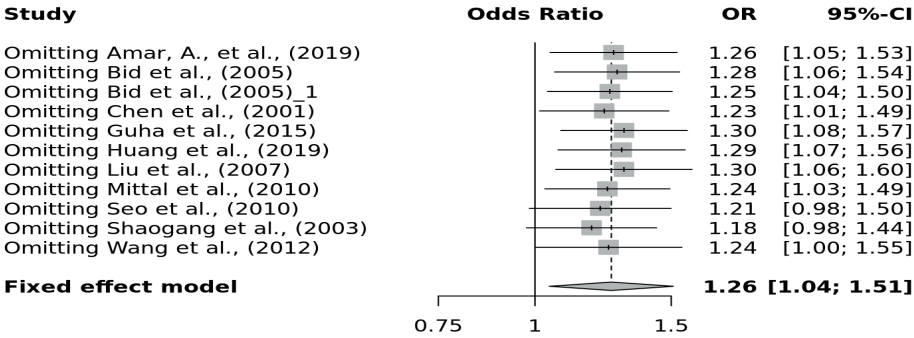

Fig. 9. FokI ff vs. Ff sensitivity plot

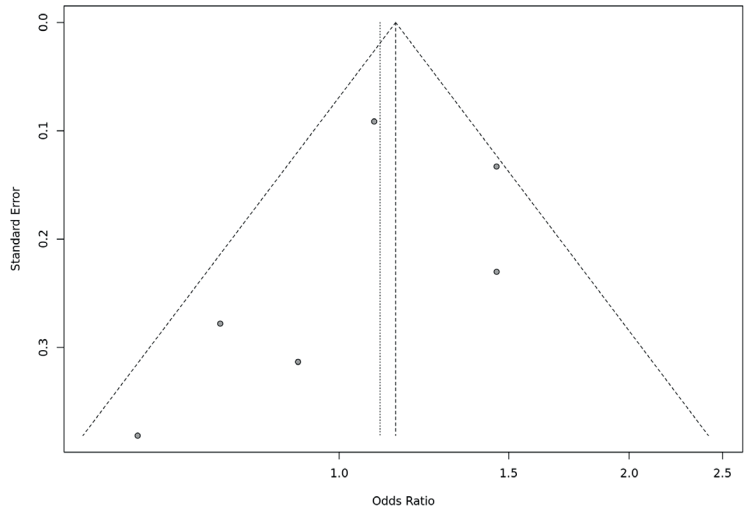

Fig. 10. ApaI aa vs. AA+Aa funnel plot

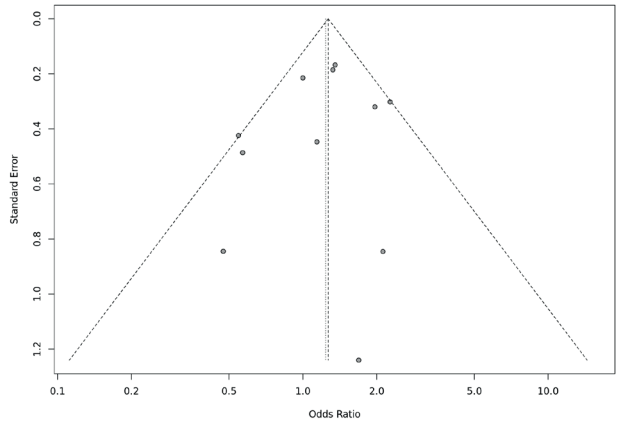

Fig. 11. FokI ff vs. FF+Ff funnel plot

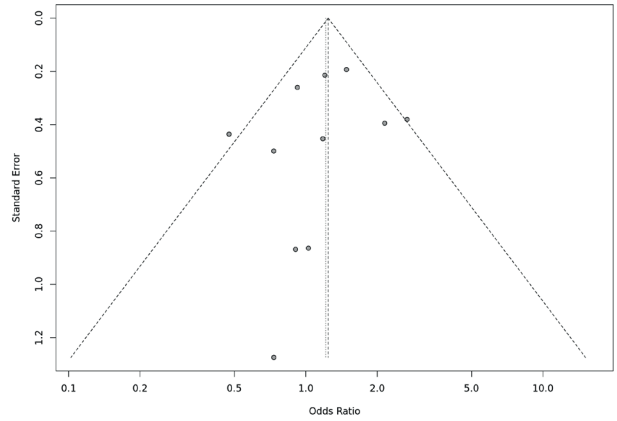

Fig. 12. FokI ff vs. FF funnel plot

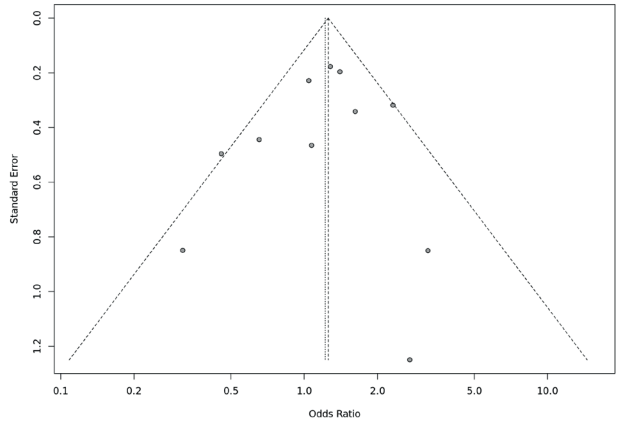

Fig. 13. FokI ff vs.Ff funnel plot

Discussion

In this meta-analysis, a total of 17 articles reporting the relationship between VDR ApaI, BsmI, FokI, and TaqI gene variants and urolithiasis susceptibility in the Asian population were analyzed. In addition to the earlier allelic, recessive, dominant, over-dominant, pair-wise homozygous and heterozygous genetic models, one new pair-wise genetic model, which compares minor allele homozygote to the heterozygote (aa vs. Aa; bb vs. Bb; ff vs. Ff; tt vs. Tt), has been included in this meta-analysis. The results of the pooled analysis revealed that VDR gene polymorphism was significantly associated with urolithiasis risk in the Asian population. Six studies were included for evaluating the association of ApaI variant, with urolithiasis risk, and was found that ApaI aa genotype had a 1.17 fold increased risk of urolithiasis in the recessive model (aa vs. AA+Aa: OR=1.17, 95% CI 1.02-1.33) and 1.16 fold increased risk in the pair-wise aa vs. Aa model (OR=1.16, 95% CI 1.01-1.34) among the East Asian population but not among the Southwest Asian. Similar findings of positive significant association of ApaI polymorphism with urolithiasis risk in the East-Asians has also been reported by Imani et al. (2020), where the 'a' allele showed a significant association with a higher urolithiasis risk compared to A allele. According to their result, the aa genotype in recessive model had a higher risk of urolithiasis compared to AA and Aa genotypes (OR=1.20, 95% CI 1.05-1.37, p<0.001), a allele in allelic model had 1.15 fold increased risk of urolithiasis (OR=1.15, 95% CI 1.05-1.26, p<0.001) and aa genotype in the homozygous mode was at 1.40 fold higher risk of urolithiasis than AA genotype (OR=1.40, 95% CI 1.12-1.75, p <0.001). However, our finding is in contrast with Zhang et al. (2013), in which the AA or Aa genotypes of ApaI variant to have been reported to have an increased risk compare to aa genotype. This contrasting finding could have arised due to difference in number of studies included as we had language restricition and included only those studies available in English.

The outcome of this meta-analysis showed no significant association of BsmI polymorphism with urolithiasis risk across all the seven genetic models: allelic (OR=1.13, 95% CI 0.95-1.35), dominant model (OR=1.17, 95% CI 0.85-1.61), recessive model (OR=1.16, 95% CI 0.0.91-1.47), over-dominant model (OR=0.95, 95% CI 0.75-1.19), homozygous model (OR=1.23, 95% CI 0.83-1.81), minor allele homozygote versus heterozygote model (OR=1.13, 95% CI 0.88-1.45) or heterozygous model (OR=1.12, 95% CI 0.79-1.60). The subgroup analysis also did not show any association of BsmI variant with urolithiasis in the East Asian and the Southwest Asian subgroup. However, the results are less robust since there is an inadequate number of a primary study included in this meta-analysis. Nonetheless, the insignificant association between BsmI variant and urolithiasis risk are still consistent with other meta-analysis (Chen et al. 2020; Daryanto et al. 2020; González-Castro et al. 2019; Imani et al. 2020; Lin et al. 2011; Zhang et al. 2013). According to the literature, the minor f allele of the FokI variant introduces a start codon leading to a three amino acid longer VDR protein (Gross et al. 1998),which in turn influences the VDR protein activity and results in less effective transcriptional activator (Cakir et al. 2016; Dastani et al. 2013).

However, from our analysis, the overall finding of the FokI variant reported ff genotype in the recessive model presents a higher risk of urolithiasis by 1.27 fold (ff vs. FF+Ff: OR=1.27, 95% CI 1.07-1.51), by 1.24 fold in the homozygous model (ff vs. FF OR=1.24, 95% CI 1.02-1.52) and by 1.26 fold in the minor allele homozygote versus the heterozygote model (ff vs. Ff: OR=1.26, 95% CI 1.04-1.51) suggesting a protective association of F over f allele. Moreover, subgroup analysis also revealed ff genotype to be at 1.32 fold increased risk of urolithiasis than Ff genotype (ff vs. Ff: OR=1.32, 95% CI 1.08-1.60) among the east Asian population. Previous meta-analysis had also reported the ff+Ff genotype in the dominant genetic model and f allele presented with a marginally positive relationship to susceptibility for urolithiasis in the Asian subgroup (Lin et al. 2011). On the other hand, Zhou et al. (2015) found FF genotype is associated with increased urine calcium levels in urolithiasis but not with ff or Ff genotypes. However, association of FokI variant with urolithiasis risk among Asians has been conflicting as number of studies rejected any significant association (Chen et al. 2020; Imani et al. 2020; Yang et al. 2019; Zhang et al. 2013).

As per literature, the TaqI variant does not modify the VDR protein structure but can influence the translation efficiency and/or stability of the RNA, which might in turn affect the development of urolithiasis (Jurutka et al. 2001; Uitterlinden et al. 2004). Furthermore, it has also been found that individuals with tt genotype had significantly higher VDR mRNA levels compared to those with TT genotype (Carling et al. 1998), which suggests that the t allele has an increased susceptibility. However, from our analysis, the TaqI polymorphism was not found to be associated with urolithiasis risk among the Asian population under any of the genetic models considered. Further, subgroup analysis also did not result in any significant associations. However, earlier meta-analysis by Yang et al. (2019) reported that TaqI polymorphism of the VDR gene is associated with urolithiasis risk in theAsian population. Their result indicated the TT genotype has a protective association with urolithiasis risk while the heterozygote Tt genotype has a significantly higher risk of urolithiasis over the homozygotes. Similar findings by Zhang et al. (2013) reported the tt or Tt genotypes with 1.39 fold increases the risk of urolithiasis compared to the TT genotype. Also, according to Chen et al. (2020), significant urolithiasis risk with TaqI variant was identified among Asians where the Tt genotype had 1.33 fold increased risk and TT genotype had a protective association with urolithiasis. Nonetheless, our analysis did not result in any significant association of TaqI variant with urolithiasis risk.

In summary, findings from our meta-analysis supports the fact that some of the VDR gene polymorphisms are associated with an increase in probability of urolithiasis among the Asian population under certain genetic models. Our results indicated that VDR ApaI and FokI polymorphisms are associated with risk of urolithiasis. The results from our pooled analysis indicated ApaI aa genotype are associated with urolithiasis compared to AA or Aa genotypes. Additionally, the minor f allele of FokI variant was indicated to be the risk allele in susceptibility to urolithiasis while F allele to be protective. Moreover, from the subgroup analysis, the ff genotype of FokI and aa

genotype of ApaI were associated with higher risk of urolithiasis among the East Asian while the same was not the case among the Southwest Asian.

Efforts have been made to test the publication bias and conducting sensitivity analysis to acquire a more accurate estimate based off the available studies. However, there were heterogeneities in some of the included studies and it may affect the accuracy of the analysis. Many more detailed and well-designed case-control studies needs to be carried out to validate the role of VDR gene polymorphisms in susceptibility to urolithiasis. This review highlights the varied association of VDR gene polymorphism with urolithiasis among the Asian population, which provides the importance of population stratification in designing future association studies among the Asian population with respect to VDR gene polymorphisms or any other genetic trait.

Authors' contribution

Sanjenbam Yaiphaba (SY) originated the idea/concept of the study. Malvika Yumnam (MY) and SY acquired and organised the data. MY performed statistical analysis, interpreted data, and drafted the manuscript. SY revised the manuscript. Both authors read and approved the final version of the manuscript.

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Declaration of competing interest

The authors declare no conflict of interest related to this publication.

Corresponding Author

Malvika Yumnam, Department of Anthropology, Manipur Univesity, Canchipur-795003, Imphal, Manipur, India, e-mail: malvikayumnam96@gmail.com

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Mind-body medicine and altered states of consciousness in *Homo*

Kazhaleh Mohammadi[1], *Arthur Saniotis*[2,3]

[1] Department of Anesthesia, Cihan University-Erbil, Erbil, Kurdistan Region, Iraq
[2] School of Biomedicine, Faculty of Health and Medical Sciences, The University of Adelaide, Australia
[3] Bachelor of Doctor Assistance Department, DDT College of Medicine, Gaborone, Botswana

Abstract: The mind-body relationship has long been a subject of inquiry from both philosophical and scientific perspectives. Ancient Greek philosophers such as Pythagoras and Plato posited dualistic models, where the mind and body are distinct substances. In contrast, modern approaches in Mind-Body Medicine (MBM) offer integrative models that emphasize the interconnectedness of mental and physical states and the proactive role of the patient in their own healing process. This review examines the evolutionary roots of altered states of consciousness (ASC) as a precursor to current MBM techniques. By tracing ASC to early hominins and their cognitive development, it posits that the ability to enter various ASC—such as those used in rituals, meditation, and other mind-body practices—provided evolutionary advantages, influencing both individual fitness and social cohesion. Moreover, this review discusses tonic immobility in animals as a survival mechanism and explores parallels in human and non-human primate behaviors involving ASC. Additionally, neurochemical pathways that govern ASC, such as serotonergic and dopaminergic regulation, are explored for their roles in promoting social behaviors, cognitive flexibility, and emotional regulation. Furthermore, the role of the default mode network is investigated in relation to psychotropic and mood altering substances and altered states of consciousness. This integrated perspective offers new insights into the origins of MBM and underscores the significance of ASC in both evolutionary and contemporary contexts.

Key words: Mental representations, tonic immobility, great apes, neurochemical regulation, serotonergic and dopaminergic systems, default mode network, primary and secondary states, psychotropics.

Original article
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Introduction

The mind-body relationship has been theorised over millennia from philosophical and scientific perspectives (Viretta 2019). The ancient Greeks proposed dualistic and monist approaches in understanding the mind-body connection. Both Pythagoras and Plato believed the body and soul were comprised of different substances. In particular, Plato's dualistic model which was based on his theory of archetypes and forms, had a profound influence on western and Islamic philosophical and scientific thought (Uner 2007). Plato's theory was influenced by Anaxagoras who considered Mind (*nous*) as a unique and universal substance – eternal, infinite, self-subsistent and directing all cosmic processes (Hergenhahn 2009; Baloyannis 2018). In his doctrine, Mind pervades and controls all cognitive and limbic functions, directing the 'inner' life of humans (Baloyannis 2016; 2018). Other thinkers such as Alcmaeon, Galen, Hippocrates and Hierophilus considered the brain as the principal organ of cognitive functions (*hegemonicon*) and sensation (Kirk and Raven 1957). Their ideas assisted our understanding on the influence of psychic processes in regulating physiological activities, thus, setting the stage for mind-body techniques.

The field of Mind-Body Medicine (MBM) has grown considerably over the last generation, heralding various interventions and psycho-clinical approaches that are gaining credence in the medical community (Dunne and Schubert 2021). Indeed, beneath the umbrella of MBM is a broad range of interventions which may include complementary and alternative medicine. These interventions are based on an integrative model which views the individual as a physical and spiritual being; second, they emphasise the patient being pro-active in their own healing process via fostering life-style changes (Lemley 2012; Moura 2012). Although, this integrative model demarcates from western biomedicine in some areas, it is being recognised by a growing number of health care and public health professionals for its potential salutogenetic aspects (Wallach et al. 2012). The central proposition of MBM is that humans are able to manipulate mental states which influence neuro-endocrinological regulation with subsequent psycho-physical well-being (Saniotis 2016; Wahbeh et al. 2009). On this theme, Saniotis and Henneberg (2011) note that, "By altering the chemical environment in which the brain operates and relations to external world, the nature of consciousness can be altered".

Mind-Body interventions include various 'western' (bio-feedback, hypnosis) and 'eastern techniques (vipassana meditation, transcendental meditation, yoga, tai chi, chi kung) (Wahbeh et al. 2008). While the aforementioned techniques attempt to induce a parasympathetic response via modulating physiological processes, only bio-feedback utilises medical instruments such as EEG and EMG which are displayed to the patient where he/she can modulate a desired physiological response (Wahbeh et al. 2008; Schwartz and Andrasik 2005). Advances in neuroimaging and neuroscience in the last 25 years have provided a framework for improving our understanding of psychoneuroimmunological mechanisms. Ongoing research in mind-body techniques, as well as their clinical applicability, will further enhance psychotherapeutics, especially in the area of personalised medicine.

Since the human brain is a product of evolution it is crucial that researchers study the evolutionary antecedents that

have shaped it. For instance, the human ability for entering into various kinds of altered states of consciousness (ASC) which are incorporated in MBM, can be better appreciated through the lens of evolution that conferred ancestral hominins with a suite of unique cognitive abilities (Saniotis et al. 2014). Anthropological studies note that ASC would have been utilised by ancestral hominins in various contexts (i.e. healing, religious rituals, art) which increased human cultural complexity and had fitness value (Saniotis and Henneberg 2011).

In this paper, ASC will be examined within the evolutionary context in order to identify important evolutionary precursors of current MBM. This is an area that has hitherto received minimal theoretical focus. The fact that humans are able to enter into various types of altered/dissociative states, with identifiable salutogenic effects, demands greater attention regarding the evolutionary origins of such states.

Mental representations in early homo

Numerous anthropological studies have detailed the human propensity of ASC in diverse cultures (Bourguignon 1977; Dinges 1990; Saniotis 2001; Ebon 1966; Eliade 1964, Krippner 2000; Winkelman 1992; 2000a, 2000b). The anthropologist Erika Bourguignon has noted that 90% of human societies use at least one technique for inducing ASC. Laughlin states that the human brain has evolved to experience manifold phases. Similarly, Henneberg and Saniotis (2009) have argued that by the time of *H. erectus* humans had become adept in mental imagery that would have been used in several ways, from tool development to the creation of imaginary entities which triggered certain behaviours that had fitness value. Interestingly, this ability to create and retain mental images may have involved the integration of cortical and sub-cortical areas, leading to "greater control of mind psychodynamics" and altering consciousness (Henneberg and Saniotis 2009; Winkelman 2000). For instance, the symmetrical nature of Acheulian axes (1.5 mys) which are attributed to *H. erectus*, required a high degree of cortical control in the repeated flaking of the initial stone at different angles, as well as, holding a mental representation of the desired appearance of the object as it was being shaped.

Importantly, the increasing ability in ancestral hominins in creating and sustaining mental representations was part of an evolving cognitive and behavioural kit of culturally based behaviours, informing and shaping each other via self-amplifying feedback mechanisms (Henneberg and Ekhardt 2022). Several feedback mechanisms became positively selected, thereby, generating self-amplifying properties in behavioural and morphological features in early homo: increasing social co-operation and reduction in aggression, extended childhood rearing, tool-making, complex procurement practices, and aesthetic consciousness (Henneberg and Ekhardt 2022).

Winkelman (2013), proposes that cultural activities such as early rituals informed changes in consciousness and novel kinds of self experience – these altered kinds of experience evolved from much older "cognitive modules", becoming a template for symbolic dependent imagination which could be shared with other group members. Enhanced motor control – due to humans possessing increased cortical, cerebellar and basal ganglia inhibition, smaller muscle units and higher levels of cortical and spinal grey

matter enabled the evolution of precise motor patterns, facilitating ASC within collective rituals, chanting and dancing (Winkelman 2013).

Altered states of consciousness in the animal kingdom: Tonic immobility

Over evolutionary history, animals have developed different types of strategies in order to reduce predation. Apart from the sympathetic nervous system mediated "flight or fight" a third existential strategy involves an animal entering into a disassociative state of tonic immobility (TI) also referred to death feigning, (*thanatosis*), freezing, "playing possum", or "playing dead" in response to predatory threat (Humphreys and Ruxton 2018; Damas-Moreira 2021). Tonic immobility has been widely reported in mammals (Francq 1969), reptiles (Lipinski et al. 2021; Burghardt and Greene 1988; Muscat et al. 2016), amphibians (Sanchéz et al. 2016; Sazima 1974, Toledo et al. 2010), birds (Sargearnt and Eberhardt 1975), fish (Tobler 2005), and insects (Allen 1990; Oliver 1996; Cassill et al. 2008).

Tonic immobility has been postulated as an adaptive behaviour that may be employed as a last line of defence, following detection from a predator (Humphreys and Ruxton 2018). Various authors note that TI may cause a predator to pause or to lose interest in the prey animal, thereby providing an opportunity for the latter to escape (Bertoluci et al. 2006; Rogers and Simpson 2014; Lipinski et al. 2022). Furthermore, Roelefs (2017) claims that tonic immobility triggers altered somatic processes, including slowing down of heart rate (bradycardia) and changes in body temperature, respiration and in somatic posture. For instance, when threatened the American possum may undergo tonic immobility where its body becomes curled and stiff with eyes half closed and with bared teeth. During this time, its anal glands may secrete a foul smelling liquid that is a characteristic feature of post-mortem putrefaction. The American possum can subject itself in this altered state for up to four hours after which its somatic processes return to normal.

It is noteworthy that tonic immobility activates the sympathetic and parasympathetic systems. The initial act of predator/prey confrontation activates a sympathetic response in the latter (characterised by increased arterial pressure and cardiovascular output, long distance optic acuity, bronchial vasodilation, hypothothalamic-pituitary-adrenal axis, increased muscle tone and glucose output from the liver) triggering a parasympathetic response with subsequent cardiac deceleration and entering into a state of tonic immobility. In *homo*, this switching between the two autonomic systems can be self-induced in order to enter into a desired ASC, which will be discussed later.

Like non-human animals, humans also have the ability to undergo a "freeze" response which amplifies inhibition response. This kind of response is often triggered during a violent or sexual assault, enabling the assailant to accomplish their illicit act. It has been postulated that in humans the "freeze response" involves subcortical areas such as the reticular formation and the locus coeruleus which are involved in arousal, alertness and modulating psychoneuroendocrine responses. During a traumatic/emergency event these brain structures may activate a "network reset" characterised in tonic immobility (Bouret and Sara 2005).

Altered states of consciousness in the great apes

Apart from tonic mobility there has been little theoretical work done in other ASC in non-human animals. The exception to this is Samorini's seminal work (2002) on the widespread use of hallucinogenic plants and ethanol in the animal kingdom. According to Samorini, ASC produced by plants may enable fixed instincts to be circumvented, enabling for new kinds of behaviours and techniques to be learned by individual animals. Kelley (2004) also notes that several animal species conduct exploratory behaviours in order to access wild plants with hallucinogenic properties. In short, the findings of various authors reveal a pan universal proclivity in vertebrates and invertebrates to induce ASC mainly via the consumption of natural hallucinogenic substances, and that this "psychonautic" tendency may have evolved over hundreds of millions of years (Kelley 2004; Samorini 2002; Kehoe and Blass 1986; Panksepp and Huber 2004).

Being phylogenetically nearest to *homo*, an examination of non-human primates may provide insight regarding the evolutionary origins of ASC in the hominin clade. Non-human primates in the wild have been observed to identify and consume specific plants for their hallucinogenic properties. For example, Gorillas have been seen to search and consume the Iboga plant for its hallucinogenic effects (Samorini 2002). Gorillas in Equitorial Africa also seem drawn to eating the leaves of Caffea liberica (*Rubiaceae*) and Theobroma cacao (*Sterculiaceae*) (Pi 1977), which which contain caffeine and theobromine respectively (Cousins and Huffman 2002). Other studies show that wild primates will consume fermented plants/fruits containing alcohol (Amato et al. 2021; Hockings et al. 2015). What these studies show that consumption of alcohol and subsequent "drunkard" like behaviours may be an unescapable result of their frugivorous diet (Hockings et al. 2015). Within experimental conditions, monkeys have self administered ethanol to the point of reduced motor co-ordination (Deneau et al. 1969).

Apart from substance induced ASC, apes also seek other types of ASC that derive from movements that alter somatic equilibrium. A recent study reveals that captive gorillas engage in the act of high speed rope spinning in order to induce ASC. Due to their vestibular homology, gorillas are capable of inducing similar neurophysiological after-effects of rope spinning as humans do (Lameira and Perlman 2023). This apparent shared tendency to induce ASC in apes and humans provides an important window for understanding the evolutionary adaptive value of ASC in the hominin lineage (Lameira and Perlman 2023). It can be argued, that this proclivity in self inducing ASC in humans and great apes had probably existed by the time of the last common ancestor of hominin and great ape lineages.

Interestingly, spinning in both apes and humans transitions from the initial active sympathetic stage to a parasympathetic finale. In apes, the latter is characterised by lying down, probably as a response of subsequent vertigo after experiencing euphoria. Alternatively, spinning in humans can be both spontaneous or ritualised. A recent study shows that the Sufi Whirling Dervishes of the Mevleviye Sufi order located in Konya, Turkey and founded in 1273 (Smeets 2006), perform a whirling meditation without experiencing balance or vertigo problems. This could be due to structural

alterations to the default mode network (DMN) coordinating perception and motion (Cakmak et al. 2017). Surprisingly, the vigorous and prolonged nature of the whirling meditation (approximately one hour) achieves a high meditative state of awareness in line with other studies on experienced meditators that showed the deactivation of the DMN (Cakmak et al. 2017; Brewer et al. 2011).

Ritual healing hypothesis and the disassociative aptitude in homo

For several decades anthropologists have extensively examined ASC from mainly non-western and traditional cultures. Their investigative peregrinations have been invaluable in formulating our current understanding of MBM. One of the foremost anthropologists of the 20th century was Victor Turner who expanded upon van Gennep's theory of ritual. Much of Turner's work focussed on transition periods of ritual which van Gennep had earlier referred to "limen", which in Latin means "threshold". Turner (1969, 1974) further refined this idea and retitled it "liminal" – a ritual state in which participants undergo a symbolic transformation that is antithetical to that experienced in the everyday life. In this state, temporal and social boundaries are temporarily cessated and supplanted by the realm of myth, that confounds the boundary between the real and the imaginary (Krippner 2005).

In this sense, liminality transcends ritual forms and includes the realm of mind, of Jung's "collective unconscious", that boundless and ineffable storehouse of symbols whose antecedents derive from a time long before the advent of *homo*. Colin Turnball's re-analysis of liminality warns us against limiting this concept to a "transitory in-between state of being" (1990:80). This realm also extends itself to hypnotic induction and trance states, where Paleolithic shamanism derives its tradition. Krippner (2005) speculates that hypnotic induction is a form of self-hypnosis, a dissociative state engaging the mythic imagination whereby the individual is disconnected from their ordinary state of awareness and enters into an altered experience that is indeterminate and fluid. For Krippner, hypnosis blurs "psychological boundaries".

The apparent universal nature of ASC brought Paul McClenon (2004) to suggest that human hypnotic aptitude was developed during the Upper Paleolithic period. Even if human hypnotic/disassociative ability had been increasingly improved from this period onwards, it was based on much earlier evolutionary mammalian antecedents as was previously discussed. He further notes that disassociative genotypes in *homo* were positively selected over evolutionary history because they conferred fitness value. According to McClenon, disassociative states would have enabled individuals for coping with trauma, reducing stress response and cohesifying group ties. Rituals were developed over a long time period where cortical areas (mythopoietic ideations) synchronised with limbic and sub-cortical regions (affective states), generating a fusion of emotion, behaviour and thought (Winkelman 2002). In humans as in other mammals limbic activation is biased towards parasympathetic dominance as discussed earlier. Similarly, Krippner (2000:96) notes that ASC involve cortical synchronisation with slow wave emissions from the limbic system. Next, it has been shown that shamanic based ritual techniques trigger the release endogenous opiates, thereby eliciting physiological responses to ritual of symbolic manipulation (Winkelman 2002: 1881). Third, long attention span is

a signature feature of *homo*. Human ability to remain in attention states for long time periods, important in many meditational techniques such as Vipassana – the precursor of modern mindfulness meditation, would have been crucial in other cultural areas such as tool production, development of art and parental rearing. These cultural modes of production in early *homo* would have informed each other via amplification feedback mechanisms (Henneberg and Ekhardt 2022), primarily under neuro-hormonal regulation of dopaminergic and serotonergic systems (Saniotis et al. 2021).

Raghanti et al. (2010) have proposed that the prefrontal cortex in humans and chimpanzees have a high density of serotonergic afferents that may provide greater social inhibition and impulse control. The neurochemical hypothesis posits that serotonergic activation of limbic structures such as the amygdala may have altered striatal serotonin levels in ancestral hominins due to selective pressures favouring pro-social behaviours, impulse control, language development, "cooperative subsistence activities" and problem solving (Raghanti et al. 2018; Lew et al. 2019, Hare et al. 2007; Saniotis et al. 2021). It is well known that the human hippocampus has dense amounts of serotonergic receptors and cortical regions – the latter being the most recently developed. Additionally, the 5-HT2AR serotonin receptor may have facilitated eusocial activities in ancestral hominins and improved neuroplasticity.

Dopaminergic regulation has had no less importance in the evolution of human cognition. Previc (1999; 2009) informs us that dopamine is involved in several motor and cognitive functions including memory, neuromodulation and motivation (Klein et al. 2019; Salamone and Correa 2012; Raghanti et al. 2010). Previc also states that humans have approximately 30% higher T4 (thyroxine) levels than found in chimpanzees (Previc 2002). Thyroxine is central in the conversion of tyrosine to dopamine. Higher levels of T4 in humans facilitate higher cognitive abilities in *homo* (Previc 2002). In humans, structures which form the basal ganglia such as the medial caudate nucleus are more influenced by the control of dopamine secretion than in non-human primates. It has been postulated that increased dopamine activity in this region improves cognitive and behavioural plasticity (Raghanti et al. 2016). Additionally, a correlation has been shown between reduced motivation inclination and increased secretion of striatal dopamine and lessened willingness for action (Kjaer et al. 2002).

Behaviours requiring fine and precise motor movements such as tool making, language production, music and artistic creation require both dopaminergic and serotonergic activity. Both systems also inform body proprioception during rhythmic motor sequences (Rodriguez-Fornells et al. 2012; Clark and Tamplin 2016). Furthermore, the creation and maintenance of rhythmic motor sequences as manifested in dance or walking meditation activates endorphins under the control of dopaminergic and serotonergic regulation (Clark and Tamplin 2016; Rodriguez-Fornells et al. 2012).

Use of psychotropic and mood-altering substances, ASC and the default mode network

Hitherto, there has been a plethora of anthropological and evolutionary research on the use of psychotropic and mood-altering substances in hominins (Nesse

1997; Winkelman 2000, 2002, 2004, Saniotis 2010; Saniotis and Henneberg 2012; Sullivan and Hagen 2002). Both Winkelman (2001) Winkelman (2001) and Saniotis and Henneberg (2012) note that ancestral hominins probably had an innate predilection towards ingesting psychotropic and mood-altering substances in order to experience ASC. Winkelman (2004) further claims that the use of psychotropic plants may have influenced neurotransmitter regulation in ancestral hominins, as well as being sources of neurotransmitters, thereby, informing human brain evolution. Whatever the motivation for using psychotropic and mood altering substances in the evolutionary past, it seems likely that their use became a feature in many shamanistic societies, and still play a part of religious rituals in various cultures (Grob 1998). By the time of the late Neolithic period the use of psychotropic and mood altering substances in order to experience ASC had become a feature of various religions and esoteric *cults (i.e. Eleusinian Mysteries, Dionysian Mysteries*, the use of cannabis in Vedic based cultures).

It is only in the current generation that neurobiological explanations for ASC and psychotropic and mood altering substances have been increasing. For example, psychedelics such as Ayahuasca and psilocybin (which contain N,N-dimethyltryptamine (DMT)) are attracted to subtypes of serotonin (5-HT) receptors (Alonso et al. 2015; Halberstadt et al. 2011). These psychedelics' affinity with 5-HT receptors have been shown to induce ASC including alterations in affectivity, sensory perception and sense of self (Gattuso et al. 2023; Nichols 2016; Speth et al. 2016). Recently, neuroimaging techniques have indicated specific brain regions which psychedelics influence – these include the anterior and posterior cingulate cortex, medial frontal cortex and various areas of the parietal lobe (Cahart-Harris et al. 2012; Palhano-Fontes et al. 2015; Alonso et al. 2015). Of increasing interest is the influence of psychedelics on the Default Mode Network (DMN) – an interconnected regional network consisting of four functional hubs: angular gyrus, posterior cingulate cortex (PCC), precuneus and the prefrontal gyrus (mPFC); these hubs show elevated blood flow and metabolic activity even when at rest (Greicius et al. 2009; Gattuso et al. 2023; Cahart-Harris and Friston 2010). The DMC is also deactivated when an individual is immersed in a goal orientated task (Raichle et al. 2001). However, the DMN is unique in that it has been shown to be involved in the "attentional system" (Cahart-Harris and Friston 2010).

Modern theorists have developed a theory of the function of the DMN based elaborated on Freud's classic theory of the ego (Cahart and Friston 2010). Freud had considered two basic processes which inform human consciousness – secondary or waking state within which the ego operates and non-ordinary, primary state; the former state inhibits limbic and paralimbic activity, whereas the latter mode is characterised as being free and unconstrained of cultural bound behaviour (Freud 1940; Cahart and Friston 2010). Victor Turner's hypothesis of structure and anti-structure (1969, 1974) elaborates on Freud's two processes. Cahart and Friston (2010) argue that DMN functions to suppress and subordinate the anarchic impulses of the limbic influenced primary process. Second, they speculate that the processes of the DMN are cognate to "high levels of and inferential hierarchy" that functions to control

the free flowing energy of the primary process. Psychosis, or in this instance, drug induced ASC often to a breakdown of top-down control. Importantly, a reduction of top-down control may increase sensory excitation of the auditory and visual systems (often noted in individual experiences when taking Ayahuasca and LSD) (de Araujo et al. 2012). Muthukumaraswarmy et al. (2013) further posit that posterior cingulate desynchronization is due to the excitability of pyramidal neurons that have abundant 5HT2A receptors. Thus, the posterior areas of the limbic system influence the flow of information from the prefrontal cortex, with subsequent relaxing of executive control (Alonso et al. 2015).

Although, some ASC may involve reduced activity in certain brain regions which have been associated with advanced tool making, our understanding of this process is unclear. For example, many types of ASC incorporate the autonomic system and control network (use of "behavioral synchrony", "attentional distraction", "automatic imitation of scripted sequences", evocation of the limbic system) (Hobson et al. 2018) producing a sensory and affective overload. This often triggers a deep parasympathetic response often associated with hypnotic, catatonic and psychotic states. Second, by its nature toolmaking demands the creator to form a picture in their mind of the desired product, which informs the tool's construction. This ability to form a picture of the tool in mind – that includes attention to planned movements, motivation and decision making in real time, incorporates the mpFC (part of the DMN) and the mid dorsolateral prefrontal cortex (dlPFC) (part of the control network) (Stout et al. 2015).

However, some caution is warranted especially in the use of psychedelics for psychiatric therapy. Although, psychedelics can potentially alter gene expression (Martin and Nichols 2017) and neuroplasticity, it is difficult in gauging to what extent the benefits of psychedelic therapy result from neuroplastic modifications on either cellular or network (DMN) levels (Gattuso et al. 2023).

Conclusion: Implications for MBM in medicine

Over the last generation there has been increasing interest in exploring altered states of consciousness in relation to MBM. During the 20th century, anthropologists conducted exhaustive ethnic studies on healing rituals where altered states of consciousness were employed by ritual healers. For example, Bourguignon (1973) notes that 90% of 430 societies still employ at least one type of mind-body technique for inducing ASC. There are now a plethora of research studies on MBM for treating both physiological and psychological disorders. Consequently, MBM is now becoming an acceptable part of western medical practice. Scientific studies have identified that the use of MBM (i.e. music therapy, muscle relaxation, guided imagery, hypnosis) in conjunction with pharmacotherapy and cognitive-behavioural therapy may facilitate pain management and increase mental well-being in cancer patients (Astin 2002; Richardson et al. 2007; Carlson and Bultz 2008). Furthermore, the lifting of the decades long ban of the use of Lysergic acid diethylamide (LSD) in psychiatric practice will provide an important adjunct to cognitive-behavioural therapy. Lysergic acid diethylamide is a non-addictive psychedelic drug and played an invaluable part in psychiatric

therapy during the 1950s–1960s before being proscribed by the Nixon administration. It has been shown that LSD had for years manipulated ASC in patients during psychotherapy for the treatment of anxiety, depression, cancer and addiction (Saniotis 2020).

In light of research into the DMN and ASC the authors speculate that the "task-sensitive coupling" (Hobson et al. 2015) between the control network and DMN has implications for MBM. At this stage, we still do not have sufficient knowledge of the DMN and its correspondence with the reticular system which also co-ordinates different states of consciousness. However, Cahart-Harris et al. (2014) have highlighted that the primary state has greater connectivity, as well as being poised between order and chaos. Thus, the human brain has greater affinity with disordered psychological states than the brains of other animals. These authors further claim that during evolution human consciousness underwent increasing disorder (entropy-expansion) followed by increasing reorganisation and relaxing (entropy-suppression), and that the adult brain exhibits the latter (Cahart-Harris et al. 2014). Yet, greater entropy means an increasing range of possible mental states (Cahart-Harris et al. 2014) which provides more opportunities for mind-body therapies (i.e. meditation, visualisation, psychedelic therapy, biofeedback), since these use a repertoire of cognitive processes. What MBM may provide is a temporary retrieval of the primary state – a release from the cognitive dictates of the control network with subsequent freedom to experience states of consciousness that are culturally inhibited, albeit, psychologically beneficial.

Conflict of interests

Authors declare no conflict of interests.

Authors' contribution

KM – conceptualized the initial scope of the paper and designed the study protocol. Conducted a comprehensive literature review and analyzed neurochemical pathways discussed in the manuscript. Wrote the initial draft, focusing on historical and philosophical perspectives of the mind-body relationship and evolutionary aspects of ASC; AS –collaborated on refining the paper's concept and scope. Conducted in-depth analyses of the evolutionary psychology aspects and the neurobiological mechanisms associated with ASC. Reviewed and edited the manuscript, providing critical revisions for sections discussing tonic immobility and its parallels in human and non-human primate behaviors. Supervised the overall development of the manuscript.

Corresponding author

Kazhaleh Mohammadi, Department of Anesthesia, Cihan University-Erbil, Erbil, Kurdistan Region, Iraq, e-mail: Kazhaleh.enayat@cihanuniversity.edu.iq

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