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FULL LENGTH ARTICLE

First genome-wide association study of 99 body measures derived from 3-dimensional body scans

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Abstract Body height, body mass index, hip and waist circumference are important risk factors or outcome variables in clinical and epidemiological research with complex underlying genetics. However, these classical anthropometric traits represent only a very limited view on the human body and other traits with potentially higher functional specificity are not yet studied to a larger extent. Participants of LIFE-Adult were assessed by three-dimensional body scanner VITUS XXL determining 99 high-quality anthropometric traits in parallel. Genotyping was performed by Axiom Genome-Wide CEU 1 Array Plate microarray technology and imputation was done using 1000 Genomes phase 3 reference panel. Combined phenotype and genetic information are available for a total of 7,562 participants. Largest heritabilities were estimated for height traits (maximum heritability with $h^2 = 44\%$ for neck height) and 61 traits achieved values larger than 20%. By genome-wide analyses, we identified 16 loci associated with at least one of the 99 traits. Ten of these loci were not described for association with classical anthropometric traits so far. The strongest novel association was observed for 7p14.3 (rs11979006, $P = 2.12 \times 10^{-9}$) for the trait *Back Width* with *ZNRF2* as the most plausible candidate gene. Loci established for association with classical anthropometric traits were subjected to anthropometric phenome-wide association analysis. From the reported 709 loci, 211 are co-associated with body scanner traits (enrichment: $OR = 1.96$, $P = 1.08 \times 10^{-61}$). We conclude

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that genetics of 3D laser-based anthropometry is promising to identify novel loci and to improve the functional understanding of established ones.

Introduction

Anthropometric traits are important in clinical and epidemiological research either as risk factors or as outcome variables. Traits of classical anthropometry often show a considerable heritability and large genome-wide meta-analyses with sample sizes of hundreds of thousands of individuals were performed for a few ubiquitously available traits, namely body height,[1] body mass index,[2] hip circumference, waist circumference, and waist-to-hip ratio.[3] Causal relationships of anthropometric traits towards other clinical phenotypes were established, e.g. hypertension,[4] type 2 diabetes mellitus,[5] or overall cancer risk.[6] However, molecular mechanisms behind the established loci are often unclear. Moreover, is has not yet been systematically investigated whether these loci are specific for a certain anthropometric trait or associated with several possibly correlated ones.

Since classical anthropometric assessments in the framework of epidemiologic studies are time-consuming, only a limited number of parameters are typically assessed and analyzed. Innovative three-dimensional laser-based anthropometry overcomes this limitation allowing assessing a virtually unlimited number of anthropometric parameters in seconds. However, this technique was not used widely in epidemiologic studies so far. In our LIFE-Adult study, we performed three-dimensional laser-based anthropometry and showed that 99 meaningful traits could be retrieved with good quality.[7]

In the present study, we performed the first genome-wide association analysis of these traits with the aim (1) to better understand which anthropometric traits are effected by established genetic loci of classical anthropometric traits, (2) to detect novel loci associated with anthropometric traits, and (3) to analyze the common genetic origin of classical anthropometric traits and body scanner traits by genetic correlation analysis.

Materials and methods

Study sample

All analyses were performed in participants of LIFE-Adult. LIFE-Adult is a population-based study which collected more than 10,000 inhabitants from the city of Leipzig (Saxony, Germany) by random sampling in an age- and sex-stratified manner between 2011 and 2014.[8] Age ranged from 19 y to 82 y with a median of 60 y (IQR: 48 y—69 y). Weight classification according to Body mass index (BMI[9]) yielded 0.5% underweight (BMI$<$18.5 kg/m^2), 33.0% normal weight (18.5 kg/m^2$\leq$BMI$<$25.0 kg/m^2), 41.6% overweight (25.0 kg/m^2$\leq$BMI$<$30.0 kg/m^2), and 24.9% obese subjects (30.0 kg/m^2$\leq$BMI).

Informed consent was obtained in written form from all subjects before enrolment. The study protocol adheres to the principles laid out in the Declaration of Helsinki. The study was approved by the ethics committee of the Medical Faculty of the University of Leipzig (263-2009-14122009).

3D laser-based anthropometry and quality control

The ANTHROSCAN VITUS XXL SYSTEM (Human Solutions, Kaiserslautern, Germany) was used for three-dimensional (3D) laser-based anthropometry. The system includes the 3D body scanner (BS) VITUS XXL (laser class 1 — safe with open eyes) and the ANTHROSCAN BASIS software (version 2.9.9.b). The ANTHROSCAN VITUS XXL SYSTEM is in accordance to DIN EN ISO 20685 to ensure that predefined feature points determined by the software comply with existing standards. The assessment was performed at room temperature of about 22 °C with participants undressed down to underwear and stockings, and wearing a tight-fitting bathing cap not to distort body proportions while scanning. Instructions for the standing posture of the participants and the measurements were prescribed by a standard operation procedure. Adherence to standard operating procedure was regularly monitored.

Biometric quality control (QC) comprised visual inspection of measurement lines for key indicator measurements directly upon scanning, scoring of measurements derived by the scan software with high confidence, and visual inspection of suspicious scans for correct posture, loose clothing or disruptive incident light. Additionally, Grubbs' outlier test[10] was applied to each body scanner measurement to remove possible outlying values (applied significance threshold $\alpha = 1\%$).

By default of the scanning software, 155 traits were calculated. In a previous analysis, we showed that 12 of them yielded low intra- or inter-rater reliability.[7] These traits were removed from the present analysis *(Neck Height Front, Distance Buttock To Vertical, Upper Torso Torsion, Side Upper Torso Length* (left & right), *Shoulder Width* (left & right), *Shoulder Angle* (left & right), *Across Front Width, Width Armpits, and Distance Waistband High Hip Back)*. Further 17 single "to vertical"-traits were excluded due to their meaningless interpretation if not being combined with another "to vertical"-trait. For example, *Distance Abdomen To Vertical* and *Distance Buttock To Vertical* are meaningless if considered separately but their difference determines the length of puncture from abdomen to buttock. Left and right versions of traits were available for 27 of the remaining traits. These are typically strongly correlated and we decided to use their averages for genetic association analyses. Thus, a total of 99 traits of high

quality were considered in this study. Descriptive statistics of all considered traits for all individuals with both body scan and genotyping are provided in Table S1. A visual representation of all standard BS traits is included in supplementary file 1.

Genotyping, quality control and imputation

Axiom Genome-Wide CEU 1 Array Plate (Affymetrix, Santa Clara, California, USA) micro-array technology was used as genotyping platform comprising a total of 587,352 single nucleotide polymorphisms (SNPs). $N = 8048$ samples of LIFE-Adult were genotyped in batches of $N = 96$. Genotype calling was performed with Affymetrix Power Tools (APT) software (version 1.20.6) with standard settings.[11]

Sample and SNP QC were performed using the software R (version 3.6.0). During sample QC, samples were excluded if one or more of the following filtering criteria were fulfilled: Dish QC (signal to noise ratio) < 0.82, call rate $<97\%$, differences between submitted and genotyped sex, and implausible relatedness. Genetic heterogeneity was assessed by principal components analysis (PCA). Outlier values were excluded if six standard deviations away from mean. A panel plot for the first ten principal components is provided in Figure S1. For SNP QC, we excluded SNPs with a call rate $<97\%$, Fisher's Linear Discriminant (FLD) < 3.6, Heterozygous Cluster Strength Offset (HetSO) < 0.1, Homozygote Ratio Offset (HomRO) < -0.9 (for three clusters), violation of Hardy–Weinberg equilibrium (HWE) ($P \leq 10^{-6}$ in exact test), and plate association ($P \leq 10^{-7}$ in χ^2-test). After QC, a total of $N = 7{,}669$ samples and $M = 541{,}977$ SNPs were available.

IMPUTE2 software (version 2.3.2) was used for imputation along with the 1000 Genomes Project reference data base (phase 3, version 5).[12] Imputation increased the number of SNPs to 85,063,807.

Genome-wide association analysis

Combined high-quality genotype and phenotype data were available for $N = 7{,}562$ samples. Associations between the 3D-based traits and SNPs were analyzed by an additive linear regression model adjusted for sex using software PLINK (v2.00a2LM AVX2 Intel (28 Oct 2018)). X-chromosomal markers were analyzed assuming total X-inactivation (i.e. male genotypes are coded as 0, 2 and female genotypes are coded as 0, 1 and 2). We considered associations for SNPs with MAF$\geq$0.01 and imputation info score$\geq$0.8 resulting in $M = 8{,}975{,}313$ markers. P-values less than or equal to 5×10^{-8} were considered genome-wide significant. Suggestive SNPs are defined by P-values larger than 5×10^{-8} but less than or equal to 1×10^{-6}. Top-hits were priority pruned by applying an LD cut-off of $r^2 \geq 0.3$ according to the 1000 Genomes Project reference data base (phase 3, version 5).[12]

SNPs were annotated by nearby genes (nearest three genes within $\pm$ 250 kilo base pairs, kb) using Ensembl,[13] with other trait associations by LD-based lookup ($r^2 \geq 0.3$) in the GWAS Catalog,[14] and with expression quantitative trait loci (eQTLs) by LD-based lookup ($r^2 \geq 0.5$) based on the data resources Genotype-Tissue Expression (GTEx)[15] and (updated) own data.[16]

Loci were defined as non-overlapping blocks of length of 1 mega base pairs (Mb) with the top-SNP centered in the block. Overlapping blocks were combined in favor of the top SNP with the lower P-value.

Sex-specific analyses

We performed sex-specific analyses of top-SNPs of loci showing genome-wide significance. Effect sizes of males and females were formally compared using an interaction test as suggested by Shungin D et al.[17]

Selection and analysis of candidate SNPs

We used the GWAS catalog[14] for a lookup of SNPs for which genome-wide significant associations with classical anthropometric (CA) traits were reported. Relevant traits were extracted script-based by the following search terms: *Arm*, *Back*, *Belly*, *BMI*, *Body Mass Index*, *Breast*, *Calf*, *Head*, *Height*, *Hip*, *Knee*, *Leg*, *Neck*, *Shoulder*, *Thigh*, *Waist*, and *Weight*. Since our study had considerably smaller sample size than current GWAS of CA traits, we matched associations with BS traits to these associations applying the 5% quantile of minimum P-values from the genome-wide analysis as significance threshold, i.e. $P_{5\%} \approx 0.0011$.

Surprise analysis

In addition to the above-mentioned lookup of the GWAS Catalog, we aimed at identifying BS associations which are not obvious in view of the reported associations with CA traits (called surprising associations), i.e. situations in which the co-associated BS trait is only weakly correlated with the originally reported CA trait. For this purpose, we applied the following locus-wise procedure:

1. For each CA locus, we determined the list of all BS phenotypes associated ($P \approx 0.0011$) with one of the SNPs reported for this locus.
2. For each BS phenotype identified at step 1 we calculated the maximum absolute correlation with the CA traits reported for this locus.
3. From step 2, we chose the BS trait with the lowest maximum absolute correlation to those CA traits representing the most surprising BS association for that locus.

Genetic correlation analysis

To analyze the degree of correlation between pairs of the 99 BS traits driven by their shared genetic backgrounds, we performed linkage disequilibrium score regression (LDSR).[18] Using our GWAS summary statistics, we calculated heritabilities and genetic correlations[19] for all BS traits using the software "ldsc" from GitHub using the LD reference from the 1000 Genomes Project.[12] Genetic correlation estimates outside the interval from -1 to 1 or missing values were set to -1, 1, and zero, respectively. Using one minus the absolute genetic correlation

as distance measure, BS traits were clustered by hierarchical clustering. Accordingly, perfect genetic correlation (positive or negative) indicates zero distance while genetic non-correlation corresponds to maximum distance.

Data access

Summary statistics of analysis data is provided under the following link: https://www.health-atlas.de/studies/42.

Results

Genome-wide association analysis of 3D anthropometric traits in LIFE-Adult

GWAS analysis revealed 316 genome-wide significant associations, which could be summarized to 16 loci. 45 BS traits were involved in these associations. Genomic control factors for all BS traits lay in between 1.001 and 1.050. A visual overview is given as Manhattan plot across all BS traits (see Fig. 1, S2). Corresponding regional association plots for a more detailed insight into the respective loci are provided in Figure 2 (for novel loci) and in Figure S3.

Loci are listed and annotated in Table 1 (for further details see Table S2). Ten of the 16 loci were not reported for associations with anthropometric traits so far. Two of them were in linkage disequilibrium (LD) with other non-anthropometric trait associations found in the GWAS Catalog.

Six loci are already reported for association with anthropometric traits

For six of the 16 identified loci, we found associations with other anthropometric traits in the literature. These loci comprised the three strongest associations of our GWAS (loci #16, #15, and #10 from Table 1).

The strongest association was found for rs6038571 at 20p12.3 for *Knee Height* ($P = 4.99 \times 10^{-11}$). This locus was already reported to be associated with the CA traits height, waist-to-hip ratio (WHR), and BMI.[20] The candidate gene was *BMP2* due to its involvement in bone development.[21]

The second strongest association was rs113935429 at 16q12.2 with *Bust Chest Girth* ($P = 9.01 \times 10^{-10}$). This is the well-established FTO locus of type-2 diabetes[22] for which associations with BMI,[20] waist circumference (WC), WHR, and hip circumference (HC)[3] were also reported.

The third strongest association was found for rs151161179 at 6p22.2 with *Belly Circumference Height* ($P = 1.33 \times 10^{-9}$). This locus was already reported for association with the CA traits height,[1] WC, and HC.[3]

Novel loci

For the other 10 loci, no associations with anthropometric traits were reported in the literature. Thus, we considered them as novel.

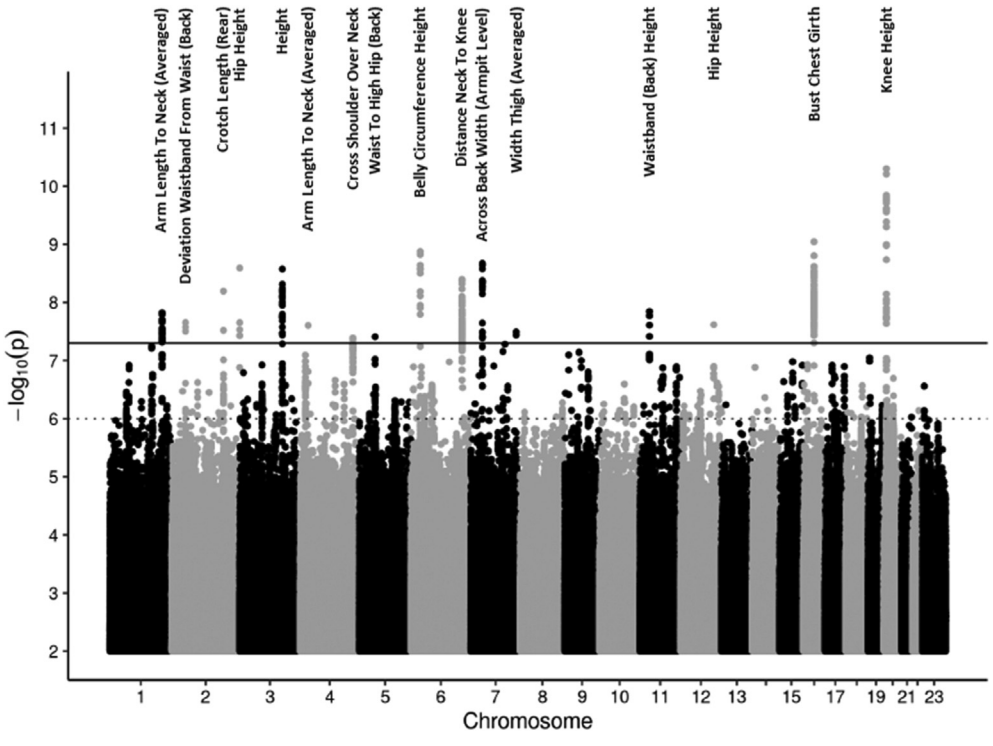

Figure 1 Manhattan plot showing associations with the 99 considered BS traits. For each SNP the maximum negative log-*P*-value with respect to all BS traits is shown. The solid line corresponds to the genome-wide significance threshold (5×10^{-8}). The dotted line indicates suggestive associations with a *P*-value less than or equal to 1×10^{-6} for one of the BS traits. Associations could be summarized to 16 distinct loci. Genome-wide significant hits are annotated by their best associated BS phenotype. Manhattan plots of single traits are provided as Figure S2.

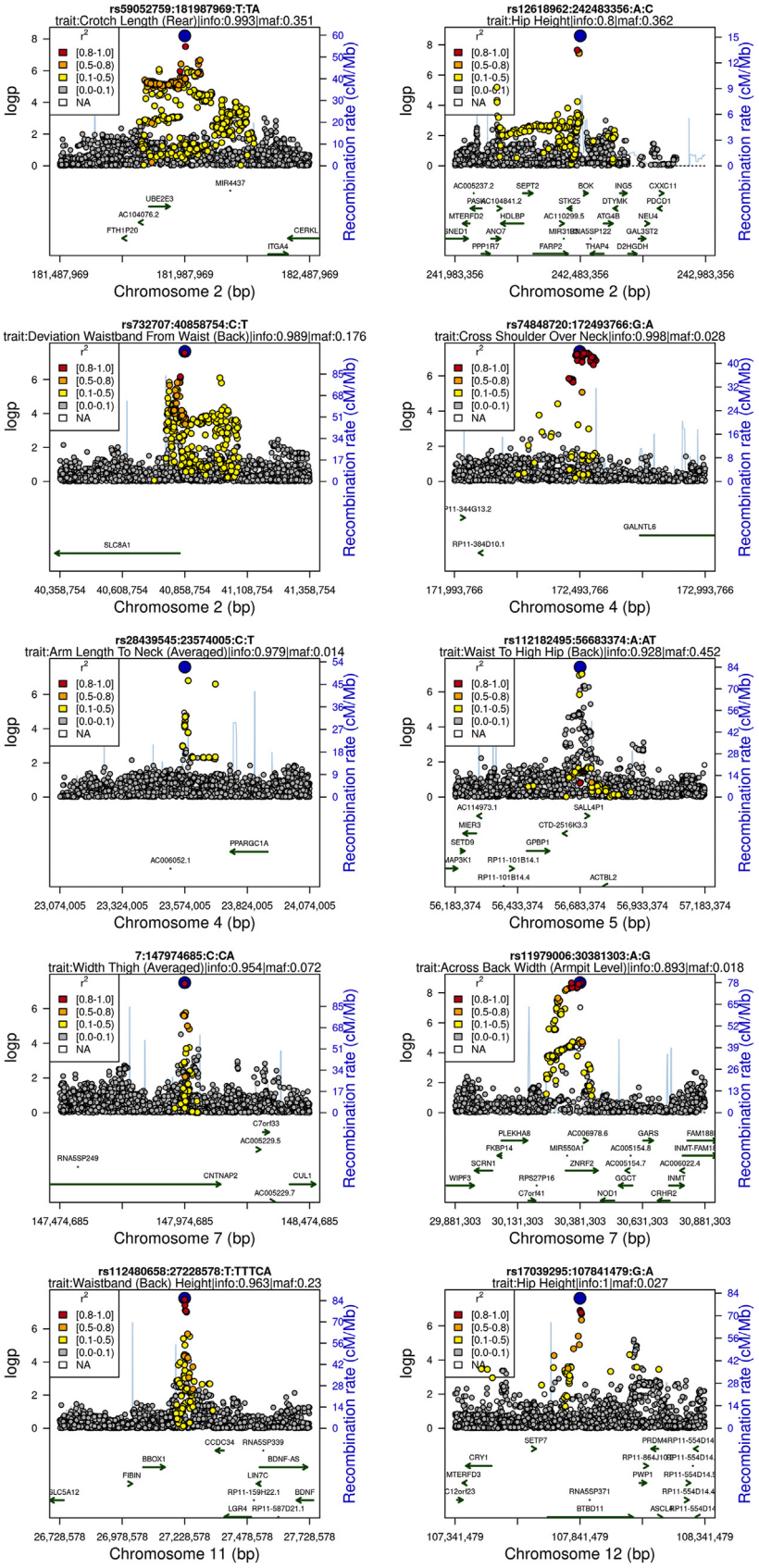

Figure 2 Regional association plot. The 10 novel loci are illustrated. Top associated BS trait, chromosomal position, *P*-value, recombination rate, SNPs in linkage disequilibrium (r^2), and annotated genes are given for a window size of 1 Mb of each locus.

The strongest of these associations was found at 7p14.3 for *Across Back Width (Armpit Level)* (rs11979006, $P = 2.12 \times 10^{-9}$). The SNP is located in the gene *ZNRF2* associated with osteosarcoma.[23]

The second strongest of these associations was found at 2q37.3 for *Hip Height* (rs12618962, $P = 2.56 \times 10^{-9}$). Reported other associations of this locus are inflammatory bowel disease, Crohn's disease[24] and red blood cell count.[20] The SNP is near *BOK* (15 kb). Plausible candidates are *FARP2* (49 kb) due to its involvement in osteoclast biology[25] or *STK25* (34 kb) known to be involved in adipose tissue biology.[26,27]

At 2p22.1 we found an association with *Deviation Waistband From Waist (Back)* (rs732707, $P = 2.21 \times 10^{-8}$). The SNP is near *SLC8A1* (21 kb). This gene is a mediator of sodium calcium exchange contributing to ossification and bone mineralization.[28]

Finally, an association was found at 11p14.1 (rs112480658, $P = 1.43 \times 10^{-8}$) with *Waistband (Back) Height*. A plausible candidate is *LGR4* (160 kb) due to its involvement in bone mesenchymal stem cell regulation.[29]

Sex-specific analysis of candidate SNPs from GWAS results

We performed association analyses for the subsets of males and females separately, in order to compare effect estimates between both sexes. We restrict this analysis to the top-SNPs of the loci showing genome-wide significance and their corresponding best associated phenotypes (see Table 1).

For the considered SNPs, direction of effect estimates for males and females were consistent throughout (see Fig. 3). No significant differences of effect sizes between sexes could be observed. Summary statistics with sex-specific effect estimates and standard errors as well as *P*-values for interaction tests are provided in Table S3.

Comparisons with published loci of classical anthropometric traits

We analyzed whether these loci are co-associated with our BS traits with at least nominal significance accounting for multiple testing of 99 BS traits. We extracted 709 loci associated with classical anthropometric traits with genome-wide significance ($P \leq 5 \times 10^{-8}$) from the recent GWAS Catalog. Indeed, for a total of 211 of these 709 loci we could identify such co-associations with the BS traits considered in our study (applying $P_{5\%} \approx 0.0011$, see methods). Thus, co-associations are strongly enriched ($OR = 1.96$, $P = 1.08 \times 10^{-61}$ in binomial test). A comprehensive overview of the 211 expressing co-associations with BS traits is provided in Table S4.

For 59 of the 211 loci, there was only one co-associated BS trait. In 26 of the loci with more than one co-association, the co-associated BS trait with the strongest correlation to the CA trait reported in the GWAS Catalog was also the best co-associated BS trait, i.e. these associations were not surprising. In contrast, we observed that for 39 of the 211 loci, the co-associated BS trait with the lowest correlation to the CA trait reported in the GWAS Catalog showed the strongest co-association among all co-associated BS traits.

We further identified 33 co-associations for which the best associated BS trait was only weakly correlated ($|r| \leq 0.3$) with the originally reported CA trait, which we considered "surprise associations". The 10 strongest of these co-associations are provided in Table 2.

We present the top three examples in more detail. Locus 1p36.13 (reported genes: *MFAP2*, *ATP13A2*, *KLHDC7A*, *RP1-37C10.3*) was reported with height. In our study, we observed much stronger association with *Distance Across Back Width (Armpit Level) To Waist* ($P = 4 \times 10^{-6}$) which is only weakly correlated with height ($r = 0.28$). The association with *Height* was smaller in our data ($P = 1 \times 10^{-4}$) so that we consider *Distance Across Back Width (Armpit Level) To Waist* as the better associated BS trait here. This BS trait is an operationalization of abdominal length, and therefore, might be more specific for the underlying genetic mechanism. Second strongest co-association was at locus 2q35 (reported genes: *IHH*, *DIRC3*, *TNP1*, *TNS1*, *NHEJ1*, *CCDC108/IHH*, *SLC23A3*, *PLCD4*, *TTLL4*, *CRYBA2*, *USP37*, *IGFBP5*). This locus was reported for height. In our data, *Hip Thigh Girth* showed strongest association ($P = 6 \times 10^{-6}$) at this locus and only weak correlation to height ($r = 0.25$). Third strongest co-association was observed at locus 6p24.3 (reported genes: *BMP6*, *RREB1*, *SNRNP48*, *C6orf218*, *TFAP2A*). This locus was reported for height and WHR. *Thigh Girth (Horizontal) (Averaged)* showed stronger association ($P = 7 \times 10^{-6}$) than *Height* ($P = 8 \times 10^{-5}$) even though correlations were low with both reported CA traits ($r = 0.16$ for height and $r = -0.05$ for WHR, respectively).

Heritability and genetic correlation analysis

To evaluate the potential of future GWAS of BS traits, we estimated heritability for each of the 99 considered traits for the first time. Overall, highest heritability estimates were observed for height measurements, namely *Neck Height* ($h^2 = 0.44$) followed by *Belly Circumference Height* ($h^2 = 0.42$) and *Buttock Height* ($h^2 = 0.42$). These estimates are in the same order of magnitude as that for the CA trait *Height* ($h^2 = 0.39$). A complete list of heritability estimates can be found at Table S5.

To assess the possible common genetic background of BS traits, we estimated the correlation between each pair of traits explained by genetics, i.e. the genetic correlation and subjected these data to hierarchical clustering. Nine clusters of anatomically related BS traits were identified. Detailed information with cluster memberships of BS traits, cluster labels, and average genetic correlations within clusters are provided in Table S5. The hierarchical clustering (dendrogram) is provided as Figure S4.

To illustrate the clusters, the genetic correlations between the clusters, and the heritabilities, we provide Figure 4.

We briefly summarize these results: Cluster 2 (Waist/hip heights and leg lengths) and cluster 6 (Torso lengths and arm lengths) showed highest average heritabilities for the corresponding BS traits (average heritability $h^2 = 0.34$ for both clusters). Clusters 5 (Torso circumferences and circumferences of extremities), 9 (Torso distances), 7 (Torso circumferences and leg lengths), and 3 (Waistband) showed moderate heritabilities with averages $h^2 = 0.25$, $h^2 = 0.23$,

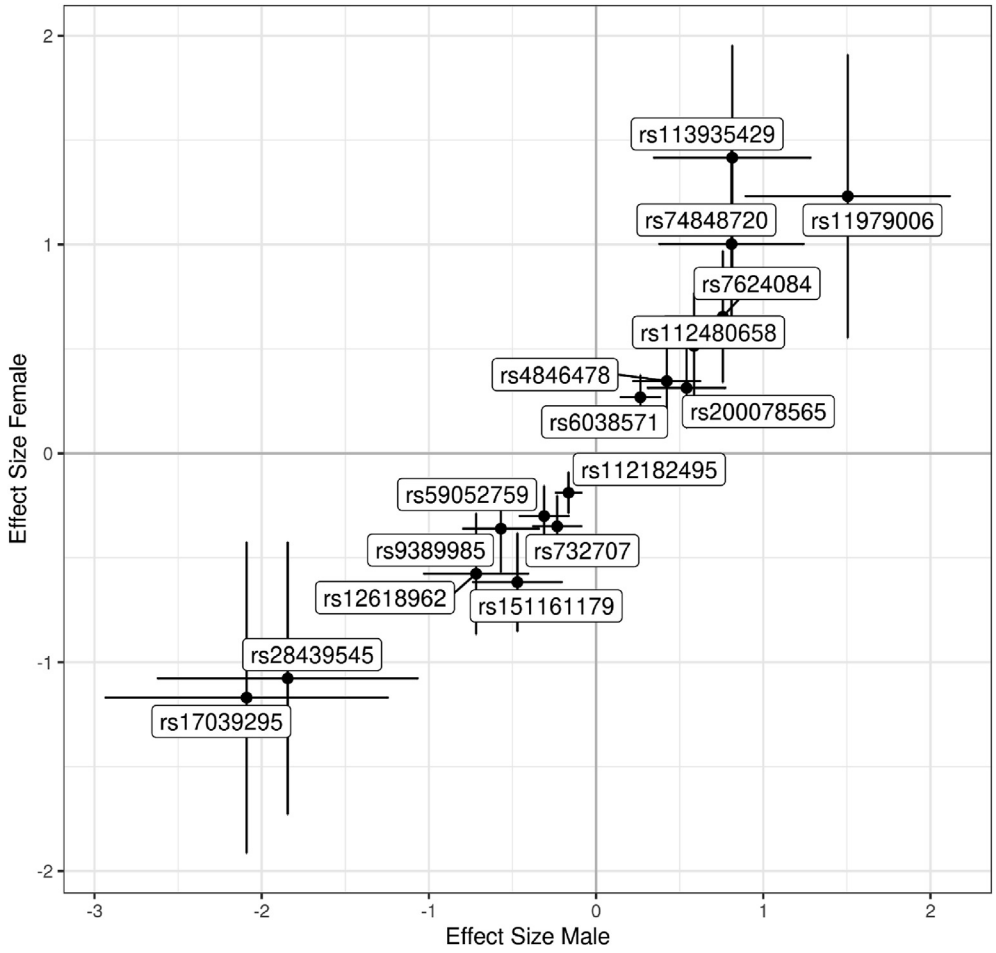

Figure 3 Comparison of genetic effects between sexes for the 16 candidate SNPs and their best associated phenotypes. No significant differences of effect sizes were observed.

$h^2 = 0.21$, and $h^2 = 0.20$, respectively. However, cluster 9 showed the strongest heterogeneity of heritability estimates. For cluster 4 (Waist/hip circumferences and arm circumferences), cluster 1 (Waist/hip circumferences and distances to crotch), and cluster 8 (Waist/hip distances) low average heritabilities were observed ($h^2 = 0.18$, $h^2 = 0.15$, and $h^2 = 0.14$, respectively).

Cluster 7 (Torso circumferences and leg lengths) showed strongest absolute within-cluster correlation with an average absolute genetic correlation of $r = 0.49$. Lowest absolute within-cluster correlation was observed for cluster 8 (Waist/hip distances) with an average genetic correlation of $r = 0.33$. For each BS trait with heritability greater than or equal to 20%, we determined the strongest positive and negative genetic correlation with BS traits not in the same cluster (see Fig. 4).

For example, several BS traits from cluster 5 (Torso circumferences and circumferences of extremities) show strong positive genetic correlation with *Belly Circumference*, *High Hip Girth*, and *Weight* of cluster 4 (Waist/hip circumferences and arm circumferences) and a negative genetic correlation with *Forearm Length (Averaged)* of cluster 6 (Torso lengths and arm lengths). Several BS traits from clusters 2 (Waist/hip heights and leg lengths), 4 (Waist/hip circumferences and arm circumferences), 5 (Torso circumferences and circumferences of extremities), 6 (Torso lengths and arm lengths), and 7 (Torso circumferences and leg lengths) show strong negative genetic correlation with *Deviation Waistband From Waist (Side)* of cluster 8 (Waist/hip distances), which is a measurement of lower torso length.

For a complete overview of genetic correlations, we refer to Table S6.

Discussion

Large genome-wide association meta-analyses of hundreds of thousands of individuals identified hundreds of genetic associations for anthropometric traits.[1–3] However, only a handful of anthropometric traits ubiquitously available in epidemiologic studies were considered so far, namely height, body mass index, hip circumference, waist circumference, waist-to-hip ratio, and weight. Thus, genetics of the human shape is by far not resolved. Three-dimensional laser-based anthropometry greatly improves the situation making a virtually unlimited number of anthropometric measurements available for scientific research.

In our study, we considered 99 high-quality body scanner traits showing good reliability[7] and investigated these traits regarding genetic associations for the first time. The major

Table 1 Results of genome-wide SNP association analyses. The table includes all 16 loci (defined by lead SNP ± 500 kb) with genome-wide significant associations (threshold 5×10^{-8}). For each locus, lead SNP, corresponding cytogenetic and physical position, physical nearby genes (within ± 250 kb), best associated trait, effect allele, other allele, effect allele frequency, beta estimate with standard error and *P*-value for the top associated trait are shown. Rows with dark grey background indicate loci for which associations with CA traits were already reported. Rows with light grey background indicate loci for which other non-anthropometric associations were reported. Rows with white background indicate loci for which no associations with other traits were reported so far. Loci are presented in the order of their chromosomal position.

Locus	Lead SNP	Cyto-genetic position	Physical position	Physical nearby genes (Distance to 'Lead SNP' [kb])	Best associated trait	Effect A.	Other A.	Allele freq.	Beta	SE	p value
#1	rs4846478	1q41	218598328	*TGFB2 (0), C1orf143 (85), RRP15 (87)*	Arm Length To Neck (Averaged)	G	C	0.26	0.38	0.07	1.51 E-8
#2	rs59052759	2q31.3	181987969	*AC104820.2 (0), UBE2E3 (47), MIR4437 (180), FTH1P20 (250)*	Crotch Length (Rear)	T	T A	0.35	-0.31	0.05	6.38 E-9
#3	rs12618962	2q37.3	242483356	*BOK-AS1 (0.46), BOK (15), STK25 (34), THAP4 (40), RNA5SP122 (41), FARP2 (49)*	Hip Height	C	A	0.36	-0.65	0.11	2.56 E-9
#4	rs732707	2p22.1	40858754	*SLC8A1 (21)*	Deviation Waistband From Waist (Back)	C	T	0.18	-0.30	0.05	2.21 E-8
#5	rs7624084	3q23	141093285	*ZBTB38 (0), ACPL2 (80), KRT18P35 (96), RASA2 (110)*	Height	C	T	0.41	0.70	0.12	2.66 E-9
#6	rs74848720	4q34.1	172493766	*GALNTL6 (240)*	Cross Shoulder Over Neck	A	G	0.03	0.91	0.17	4.09 E-8
#7	rs28439545	4p15.2	23574005	*RP11-380P13.1 (0), RFPL4AP3 (57), PPARGC1A (180)*	Arm Length To Neck (Averaged)	T	C	0.01	-1.40	0.26	2.49 E-8
#8	rs112182495	5q11.2	56683374	*SALL4P1 (35), ACTBL2 (92), GPBP1 (120)*	Waist To High Hip (Back)	A	A T	0.45	-0.18	0.03	3.89 E-8
#9	rs9389985	6q24.1	142653898	*GPR126 (0), VTA1 (110), GJE1 (200), NMBR (240)*	Distance Neck To Knee	G	A	0.30	-0.46	0.08	4.01 E-9
#10	rs151161179	6p22.2	26202931	*HIST1H4E (1.9), HIST1H2BF (2), HIST1H3D (3.4), HIST1H2AD (3.5), HIST1H1PS1 (6.9), HIST1H2BG (13), HIST1H4D (14), HIST1H2AE (14), HIST1H2BE (18), HIST1H3E (22), HIST1H2APS3 (30), HIST1H2BD (31), HIST1H1D (32), HIST1H4F (38), LARP1P1 (38), HIST1H4G (44), HIST1H1E (46), HIST1H3F (47), HIST1H2BH (49)*	Belly Circumference Height	T	T A A	0.31	-0.55	0.09	1.33 E-9
#11	rs200078565	7q36.1	147974685	*CNTNAP2 (0), RN7SL72P (160)*	Width Thigh (Averaged)	C A	C	0.07	0.42	0.08	3.22 E-8
#12	rs11979006	7p14.3	30381303	*ZNRF2 (0), MIR550A1 (52), NOD1 (83), GGCT (150)*	Across Back Width (Armpit Level)	G	A	0.02	1.40	0.23	2.12 E-9
#13	rs112480658	11p14.1	27228578	*RP11-1L12.3 (0), BBOX1 (79), CCDC34 (120), LGR4 (160)*	Waistband (Back) Height	T T T C A	T	0.23	0.55	0.10	1.43 E-8
#14	rs17039295	12q23.3	107841479	*BTBD11 (0), RNA5SP371 (39), SETP7 (180), PWP1 (240)*	Hip Height	A	G	0.03	-1.60	0.29	2.42 E-8
#15	rs113935429	16q12.2	53822169	*FTO (0), RPGRIP1L (84)*	Bust Chest Girth	A	A T	0.38	1.10	0.18	9.01 E-10
#16	rs6038571	20p12.3	6634566	*BMP2 (110), CASC20 (130)*	Knee Height	A	C	0.48	0.27	0.04	4.99 E-11

aim was to gain a more detailed insight into genetics of the human body shape both by performing hypotheses-free genome-wide search and by hypothesis-driven anthropometric phenome-wide association study across loci previously reported for association with classical anthropometric traits.

The new body scanner traits showed heritabilities in the range of 3—44%. *Neck Height* showed the highest heritability. A total of 60 (61%) traits showed values greater than 20% making genome-wide association studies a worthwhile endeavor. The traits shared common genetic background as revealed by genetic correlation analyses. Nine distinct clusters of traits could be identified, which are characterized by length and circumference measurements of common body parts.

Body scanner traits from torso circumferences and circumferences of extremities showed strong genetic correlation with *Belly Circumference*, *High Hip Girth*, *Weight*, and *Forearm Length (Averaged)*. In contrast, *Deviation Waistband From Waist (Side)* showed strong genetic

Table 2 Table of loci reported for associations with CA traits taken from GWAS Catalog ($P \leq 5 \times 10^{-8}$) and showing nominal associations ($P \approx 0.0011$) with at least one of our BS traits. For each locus represented by its cytogenetic position, associated CA traits (summary statistics shown for trait in bold, if multiple traits were reported for this locus; "-" indicates value not available), best co-associated BS trait and best correlated BS trait showing at least nominal association are provided. We also provide (strongest) Pearson correlation (r), beta estimate with standard error (SE) and corresponding *P*-value for each (co-)association. The ten strongest associations of BS traits showing only low correlation ($|r|<0.3$) to the originally reported CA traits are reported. Superscripts provide matching of reported CA traits at this locus and respective correlations with the co-associated BS trait.

Cytogenetic position	Associated classical trait	Beta (SE)	*P*- value	Best co-associated BS phenotype	Beta (SE)	*P*- value	Best correlated co-associated BS phenotype	Beta (SE)	*P*- value
1p36.13	**Buttock Girth**,[1] Height,[2] Waist Girth,[3] Waist-to-hip Ratio,[4] Body Mass Index[5]	0.03 (−)	4E-18	Distance Across Back Width (Armpit Level) To Waist ($r = -0.02^1$, $r = 0.28^2$, $r = 0.01^3$, $r = 0.03^4$, $r = -0.11^5$)	−0.28 (0.06)	4E-6	Height ($r = 1.00^2$)	1.20 (0.30)	1E-4
2q35	Height	−(−)	2E-23	Hip Thigh Girth ($r = 0.25$)	1.60 (0.35)	6E-6	Calf Girth (Averaged) ($r = 0.3$)	0.73 (0.19)	8E-5
6p24.3	**Waist-to-hip Ratio**,[1] Height[2]	0.06 (−)	3E-8	Thigh Girth (Horizontal) (Averaged) ($r = -0.05^1$, $r = 0.16^2$)	−1.20 (0.26)	7E-6	Height ($r = 1.00^2$)	0.45 (0.11)	8E-5
13q33.1	Body Mass Index	−(−)	3E-8	Deviation Waistband From Waist (Back) ($r = 0.06$)	0.23 (0.06)	2E-5	Deviation Waistband From Waist (Side) ($r = -0.12$)	0.23 (0.06)	5E-5
16q24.3	Body Mass Index	−(−)	2E-8	Neck To Waist (Center Back) ($r = 0.22$)	0.41 (0.10)	2E-5	Neck To Waist (Back) (Averaged) ($r = 0.25$)	0.44 (0.11)	8E-5
13q22.3	Body Mass Index	−(−)	2E-9	Head Circumference ($r = 0.27$)	−0.12 (0.03)	4E-5	Head Circumference ($r = 0.27$)	−0.12 (0.03)	4E-5
17q11.2	Body Mass Index	0.01 (−)	8E-12	Distance Across Back Width (Armpit Level) To Waist ($r = -0.11$)	−0.27 (0.07)	5E-5	Distance Across Back Width (Armpit Level) To Waist ($r = -0.11$)	−0.27 (0.07)	5E-5
7q34	Height	0.03 (−)	4E-8	Distance Across Back Width (Armpit Level) To Waist ($r = 0.28$)	−0.25 (0.06)	6E-5	Distance Across Back Width (Armpit Level) To Waist ($r = 0.28$)	−0.25 (0.06)	6E-5
Xq26.3	Body Mass Index	0.02 (−)	1E-8	Arm Length (Averaged) ($r = -0.02$)	−0.20 (0.05)	6E-5	3D Waistband (Front) Height ($r = -0.29$)	−0.28 (0.08)	2E-4
5q15	Height	−(−)	5E-14	Waist-To-Hip Ratio ($r = 0.22$)	−2.40 (0.60)	7E-5	Waist-To-Hip Ratio ($r = 0.22$)	−2.40 (0.60)	7E-5

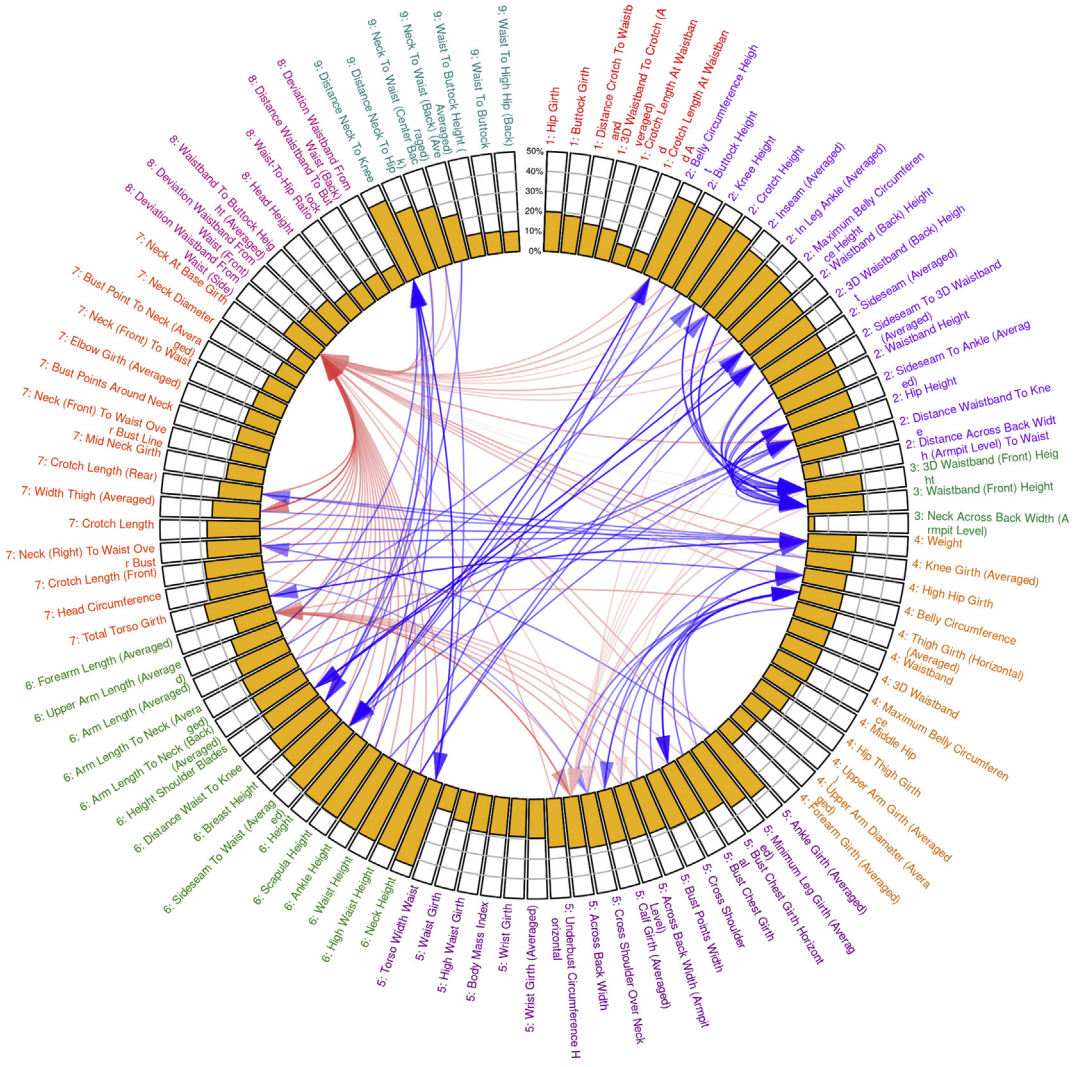

Figure 4 Circos plot with BS traits arranged due to annotated clusters from hierarchical clustering of their underlying genetic correlation structure (trait label consists of cluster number and trait name) and ordered cluster-wise in descending order of their estimated heritability (orange circular bar plots). For each BS trait with estimated heritability greater than or equal to 20%, the strongest positive (blue) and the strongest negative (red) genetic correlation to another BS trait not in the same cluster were displayed. Since this annotation is not symmetric, we also provided arrows indicating the directions of the assignments.

correlation with body scanner traits from length and girth measurements from torso and extremities.

In our GWAS analysis, we identified 316 genome-wide significant associations involving 45 body scanner traits and corresponding to 16 different genetic loci. Here, we applied the common threshold of genome-wide significance of 5×10^{-8}, i.e. we refrained from correction of multiple phenotype testing. We therefore consider our results as first genome-wide screening of these novel phenotypes requiring further validations in independent cohorts.

Of the identified 16 loci, six loci were already reported for associations with classical anthropometric traits. These six loci comprise the three strongest associations and could be assigned to well-established anthropometric loci, namely BMP2, FTO and the 6p22.2 locus containing several histone genes. Additionally, we could refine the set of corresponding trait associations for the known loci: At 20p12.3 *Knee Height* showed strongest association next to height, waist-to-hip ratio, and body mass index. For 16q12.2, best associated body scanner trait *Bust Chest Girth* could be added to the known associations with the classical anthropometric traits body mass index, waist circumference, waist-to-hip ratio, and hip circumference. *Belly Circumference Height* showed strongest association at 6p22.2 beyond the known associations with height, waist circumference, and hip circumference.

The remaining 10 loci were not reported so far and could therefore be considered as novel anthropometric loci. Strongest novel associations were found for *Across Back Width (Armpit Level)* (7p14.3), *Hip Height* (2q37.3), *Deviation Waistband From Waist (Back)* (2p22.1), and *Waistband (Back) Height* (11p14.1). Corresponding SNPs were associated with osteosarcoma, inflammatory bowel

disease, sodium calcium exchange, and bone mesenchymal stem cell regulation, respectively, i.e. functionally plausible genes could be assigned.

We performed sex-specific association analysis for the top-SNPs of our 16 genome-wide significant loci only, since the power of our study is too small for a hypothesis-free search for gene—sex interactions. No significant effects were found. Larger sample sizes are required to unravel the genetic basis of sex dimorphisms of the analyzed body scanner traits.

In our phenome-wide association analysis of 709 reported loci for associations with classical anthropometric traits, we searched for improved associations among the newly assessed body scanner traits. By this analysis we aimed at complementing the efforts to understand the underlying molecular mechanisms behind the identified loci by providing better co-associated body scanner traits. Moreover, this analysis complements general phenome-wide association approaches of classical anthropometric traits.[30—32] We identified co-associations with body scanner traits at 211 of these loci representing a strong enrichment with an odds ratio of 1.96 and a *P*-value of 1.08×10^{-61}.

Moreover, we performed a "surprise analysis" of these results in order to select unexpected co-associations. For 39 of these loci (more than 18%) we found that the lowest correlated co-associated body scanner trait showed stronger association than the best correlated co-associated BS trait.

The major limitation of this study is the relative small sample size compared to published genome-wide meta-analyses of classical anthropometric traits. Moreover, a replication cohort is not available since three-dimensional laser-based anthropometry was not introduced to epidemiologic practice to a larger extent so far, although this measurement is feasible in epidemiologic research. We therefore consider this study as starting point for a more refined analysis of the genetics of the human shape. Larger genome-wide analyses and meta-analyses of these traits are promising and should be performed when additional study data will become available in the future.

Conclusions

We conclude that genetics of three-dimensional laser-based anthropometry is promising to identify novel loci and to improve the functional understanding of established anthropometric loci. Larger studies and meta-analyses are required to fully unleash the power of this approach, and with it, to improve our understanding of the genetics of human body shapes.

Conflict of interests

The authors have declared that no conflict of interest exists.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2021.02.003.

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